National Collaborating Centre for Cancer

Suspected cancer:

recognition and management of suspected cancer in children, young people and adults

Clinical Guideline

Full guideline

November 2014

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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This guidance is a partial update of NICE clinical guideline 27 (published June, 2005) and will replace it.

New and updated recommendations have been included on the recognition, management and referral of suspected cancer in children, young people and adults in primary care.

Where recommendations are shaded in grey and end **[2005]** the evidence has not been reviewed since the original guideline. We will not be able to accept comments on these recommendations.

Where recommendations are shaded in grey and end **[2011]**, the recommendation has been incorporated from the NICE guideline on ovarian cancer (NICE guideline CG122). We will not be able to accept comments on these recommendations.

You are invited to comment on the new and updated recommendations in this guideline only. These are marked as **[2015]** if the evidence has been reviewed but no change has been made to the recommendation or **[new 2015]** if the evidence has been reviewed and the recommendation has been added or updated.

Appendix J4 contains recommendations from the 2005 guideline that NICE proposes deleting in the 2015 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where there are replacement recommendations, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given. You are invited to comment on the deleted recommendations as part of the consultation on the 2015 update.

The original NICE guideline and supporting documents are available from www.nice.org.uk/guidance/CG27

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Methodology

What is a clinical guideline?

Guidelines are recommendations for the care of individuals with specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Updating a NICE clinical guideline

Guidelines developed by NICE are published with the expectation that they will be reviewed and updated as is considered necessary. In February 2011 the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to update CG27 in accordance with the NICE guideline development process outlined in the 2012 edition of the guidelines manual (NICE 2012).

This guideline updates and replaces CG27. Any sections of CG27 that have not been amended are integrated within this updated document. Recommendations are marked **[2005]**, **[2015]** or **[new 2015]** to indicate the year of the last evidence review:

- **[2005]** indicates that the evidence has not been updated and reviewed since 2005
- **[2015]** indicates that the evidence has been updated and reviewed but no changes to the 2005 recommendation has been made
- **[new 2015]** indicates that the evidence has been reviewed and a new recommendation has been made.

Where recommendations are shaded in grey and end **[2011]**, the recommendation has been incorporated from the NICE guideline on ovarian cancer (NICE guideline CG122).

All supporting text from updated and new topics presented in this guideline have been highlighted. Data on incidence and survival rates were sourced from Cancer Research UK, National Cancer Intelligence Network and ONS.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the recognition and management of children, young people and adults with suspected cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on ‘Developing clinical evidence based questions’.

This guideline is relevant to all primary healthcare professionals who come into contact with people suspected of having cancer, as well as to the people with suspected cancer themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of people.

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The remit of the guideline

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2012). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the suspected cancer guideline can be found in Appendix E.

The guideline development process – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix E), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG
- developing clinical questions
- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

The scope

The scope was drafted by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategies

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and

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revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a four week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix D. During the consultation period, the scope was posted on the NICE website. Comments were invited from registered stakeholder organisations and NICE staff. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed and signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The suspected cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed by telephone prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix E). Individual GDG members were selected for telephone interview by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, research funding (either in the form of programme or project grants or personal research awards), fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix E).

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Guideline Development Group Meetings

Seventeen GDG meetings were held between 19-20 June 2012 and 3-4 February 2015. During each GDG meeting (held over either 1 or 2 days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before the evidence and draft recommendations were presented to the GDG. These recommendations were then discussed and agreed by the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Representatives

Individuals with direct experience of suspected cancer services gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

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Expert Advisers

During the development of the guideline the GDG identified two areas (oral cancer and clinical decision support tools) where there was a requirement for expert input . Experts were identified by the NCC-C (Appendix E) and invited to advise the GDG in their consideration of these areas.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

The GDG considered the use of clinical decision support tools for the assessment of cancer risk early in the development process of this guideline. Based on input from expert advisors, it was clear that very little implementation or evaluation work had been published for these tools, no trials had been undertaken, and none were planned. It was also clear that there were cancer sites to be covered in this guideline that were not covered by these tools. In addition, the role of clinical decision support tools in the process of referral for suspected cancer was not explicit in the scope of this guideline. The GDG, in agreement with NICE, therefore, decided their use would not be covererd in this guideline. However, data from research papers describing the development and validation of clinical decision support tools could be relevant to the GDG deliberations.

Method

From each of the key clinical issues identified in the scope, the GDG formulated a clinical question. For the clinical questions, the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study), I – the index test, or sign/symptom (what is being done; for the signs and symptoms questions, a patient presenting with a sign/symptom was considered to be test positive), C – the comparison (other main test options; in this case the reference standard), O – the outcomes (the measures of how effective the tests have been).

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: NHS Evidence, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), Health Economic Evaluations Database (HEED), Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how

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the review was to be carried out (Table 1) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the evidence review.

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG
Rationale	Using the PICO (population, intervention, comparison and outcome) framework for questions about treatment, or other suitable framework for questions about diagnosis or prognosis. Including the study designs selected.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The method that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

A specific filter was developed by the NCC-C to identify only primary care based studies, as people with symptoms in primary care were the population of relevance to this guideline. Prior to use, the accuracy of this filter was tested by using it to run searches for symptoms of colorectal cancer (a common cancer) and for symptoms of bladder cancer (a less common cancer). The results of these searches were then compared against the list of papers included in two published systematic reviews of symptoms of bladder and colorectal cancer in primary care. All of the papers in the systematic reviews, except one per review, were identified by the searches run with the primary care filter. The two papers that were not identified by the searches using the primary care filter were investigated further and it was established that they had not been found due to issues with the indexing of the paper. This information was presented to the GDG during a GDG meeting and they agreed that the primary care filter was accurate and appropriate for use.

No language restrictions were applied to the search.

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards
- Web of Science (all databases 1899 onwards)

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- Psychinfo 1806 onwards

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From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

The evidence was searched by cancer site because symptoms may represent several different cancers; furthermore, symptoms are often not included in the title or abstract of research outputs, so relevant publications could have been lost from our searches if we had searched by symptom alone.

Searches were updated and re-run 8-10 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, August 2014 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained, the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was provided. The quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting et al., 2011). A modified version of this tool (including three extra items specifically aimed at diagnostic case-control studies) was used to assess the quality of the evidence for the questions about signs and symptoms of the individual cancers. The QUADAS-2 tool is not designed to provide an overall quality of the evidence, but was used to identify potentially important areas where there was a high risk of bias or high concerns about applicability of the evidence, which in turn, were used to inform the overall estimates of the evidence quality in the Linking Evidence to Recommendations (LETR) sections. The same reviewer rated the overall quality of the evidence for all the clinical questions with input from the GDG. The aim of these ratings was to be as consistent as possible, but without them being too specific when that was clearly not possible (for example by using "not high" when not able to clearly make an overall rating of moderate, low or very low). The specific issues with the evidence are detailed in the QUADAS-2 figures and "Risk of bias in the included studies" sections and in the evidence section. GRADE was not used for the overall evidence quality ratings because it was still under development for diagnostic studies at the start of this guideline.

Meta-analysis was undertaken when it was feasible to do so, i.e. when there were at least three studies with study populations and symptoms that were considered similar enough to combine. Case-control studies were never included in these meta-analyses due to the different nature of the data, compared to the studies employing consecutive patient series. A minimum of three studies were required to perform the meta-analysis due to the need for a minimum number of data points relative to the number of parameters that were estimated during the analysis. In cases were sufficient data were available, secondary analyses were performed that excluded papers with particular quality or applicability concerns. Although we sought to perform meta-analyses for different age groups/genders, the data were never available for consistent age groups, or the two genders, in a sufficient number of studies for the same symptoms. This meant that the meta-analyses received less weight by the GDG

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than the individual studies that provided positive predictive values split by age and gender because age is such an important risk factor of cancer.

In addition to positive predictive values, the incidence of symptoms observed in cases and controls were sometimes reported in the results tables for case-control studies. This was because corresponding positive predictive values were not always available for these symptoms but the information was deemed to be potentially relevant to the GDG, especially in cancers where little other evidence was available. However, the GDG tended not to use this additional information when considering the evidence. Confidence intervals were included whenever possible for the reported positive predictive values. The GDG mainly used the point estimates to make decisions about the individual symptoms or symptom combinations, but where they did consider the confidence intervals (usually where the point estimate was above the pre-specified PPV threshold but based on a low number of patients and therefore subject to high levels of uncertainty) this has been explicitly documentd in the LETR sections.

At what value should the risk threshold be?

Previous guidance used a disparate range of percentage risks of cancer in their recommendations. Few corresponded with a PPV of lower than 5%. The GDG felt that, in order to improve diagnosis of cancer, a PPV threshold lower than 5% was preferable. Patient viewpoints were central to the decision about where the risk threshold should be. The GDG aspired to broaden recommendations to try and improve the timeliness and quality of cancer diagnosis. The lower the threshold could reasonably be set, the more patients with cancer would have expedited diagnoses, with accompanying improvements in mortality and morbidity.

Also germane to the selection of a risk threshold are the resource implications of change. At the time of setting the threshold figure, there were no strong quality health-economic reports which could help with the decision. Many reports could describe the costs involved in expanding cancer diagnostics. The benefits from expedited diagnosis were much less clear. It was, however, clear that broadening of recommendations would bring economic and clinical costs. The clinical costs include potential harms to the patient through the side effects of investigations performed and also through increased anxiety. The lower a threshold is set, the more likely people are to be exposed to these potential harms.

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Taking all of this into account, the GDG agreed to use a threshold value of 3% PPV to underpin their recommendations. This value represented a considerable liberalisation of the estimated PPVs of previous recommendations, but the GDG agreed that this change would not overwhelm clinical services, nor greatly increase the possible harms to patients from over-investigation. This 3% PPV governed recommendations for suspected cancer pathway referrals. The GDG also resolved to apply the same 3% PPV threshold to urgent direct access investigations in secondary care; such as brain scanning or endoscopy. The exception to this was where it was clear that appropriate investigation using tests previously unavailable to primary care could replace specialist referral. The implied economic advantages of this allowed the GDG to make recommendations below the 3% level. The GDG discussed these on a case by case basis. In instances where patients would not normally be referred on an urgent cancer pathway but would be referred routinely for specialist opinion, the 3% PPV threshold does not apply. The same is true where a non-urgent direct-access test was considered to be more resource efficient.

Two exceptions to the 3% PPV threshold for urgent action were agreed. The first relates to children and young people. As children and young people have longer to live than adults, a successful cancer diagnosis leading to cure should yield more years of life gained. Thus it was agreed that the GDG should make recommendations for children and young people significantly below the 3% PPV threshold, although no explicit threshold value was set.

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The second exception relates to tests routinely available in primary care, which can help to refine the underlying risk of cancer - this is the case whether the investigation is being carried out on an urgent basis or otherwise. These include blood tests such as PSA or imaging such as chest x-ray.

Symptoms present in multiple cancers but of low risk for each cancer site

There are a number of generic symptoms (e.g. fatigue), that, whilst not predictive of a specific cancer, are nevertheless believed to be predictive of "cancer". These symptoms will typically be reported by a number of the studies included in the evidence, but will not have high enough positive predictive values for any individual cancer to meet the threshold for referral or investigation in primary care.

The GDG wanted to examine these symptoms to try to identify those that are predictive of cancer in general, rather than a specific cancer, and make recommendations accordingly.

A spreadsheet was constructed containing all the PPV evidence on the positive predictive values of signs and symptoms for the specific cancers. This spreadsheet was then used as follows:

- Symptoms for which referral recommendations were made for a specific cancer were filtered out of the spreadsheet. This was because these symptoms are predictive of a specific cancer.
- The individual symptoms and symptom combinations were then examined across all the cancer sites where there was evidence for patients across the whole 40-70 age range (this age range was specified in advance by the GDG due to being widely covered in the relevant literature). For each symptom/symptom combination, the highest positive predictive value for each cancer was identified and then added together to create a 'cumulative' positive predictive value. Positive predictive values can be added in this way with the only concern being multiple cancers in the same person. If these were common the 'cumulative' positive predictive values would be artificially high. However, multiple cancers in the same person at the same time are extremely rare so this issue was judged by the GDG to have negligible impact.

The GDG determined, in advance, that for those symptoms with a 'cumulative' positive predictive value of 2% or above, all the evidence for that symptom across all the cancer sites would be re-examined in detail. The GDG then debated whether recommendations should be made.

The GDG acknowledged that the 'cumulative' positive predictive values would probably be underestimates. This is due to the likelihood that some cancer site/symptom combinations might not have been reported in the searches, either because the research has not been done, or because the information related to the age range could not be extracted. The GDG therefore chose a threshold of 2% so that they could examine in more detail any instances where the true cumulative PPV might exceed 3% if cancer site/symptom combinations that had not been reported in the literature searches had been available.

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to the recognition of suspected cancer in primary care. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

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Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2012):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

A review of the economic literature was conducted at scoping. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter instead of the primary care filter.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

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Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies of 'cost of illness' studies are generally excluded from the reviews (NICE 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012; Appendix A). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 2).

Table 2: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 3).

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Table 3: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

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Agreeing the recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicitly in the accompanying LETR statement (see below).

Wording of the recommendations

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
- ‘Do not offer’ – the intervention will not be of benefit for most patients

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- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

LETR (Linking evidence to recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention
- the quality of the evidence
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus.

Consultation and validation of the guideline

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The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix E) had one opportunity to comment on the draft guideline which was posted on the NICE website between 20 November 2014 and 9 January 2015 in line with NICE methodology (NICE 2012).

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2012).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc)/

NICE also produces three other versions of the suspected cancer guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key research recommendations and all other recommendations

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- NICE pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP)', which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were repeated for all of the clinical questions at the end of the guideline development process, allowing any relevant papers published before August 2014 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

Update 2015

References

National Institute for Health and Clinical Excellence (2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, Group Q-2 (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine, 155: 529-536.

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1 Introduction

Cancer is an important condition, both in terms of the number of people affected and the impacts on those people and the people close to them. Around one third of a million new cancers are diagnosed annually in the UK, across over 200 different cancer types. Each of these cancer types has different presenting features, though there may be overlap. Approximately one third of the population will develop a cancer in their lifetime. Although there have been large advances in treatment and survival, with a half of cancer sufferers now living at least ten years after diagnosis, it remains the case that a quarter of people will die of cancer.

It is generally believed that early diagnosis of cancer is beneficial. However, this is quite difficult to prove scientifically, in part because the natural course of cancer, and of its symptoms, is imperfectly understood. The benefit from earlier diagnosis is usually thought of in terms of survival – with most people considering the chance of surviving their cancer to be higher the earlier it is diagnosed, as the cancer will have had less time to spread. There may be other benefits from expediting diagnosis, such as relief of symptoms. These factors have underpinned many initiatives in the UK and other countries aimed at improving cancer diagnosis. These include awareness campaigns, cancer screening, and better diagnosis of symptomatic cancer. There is also unwarranted variation in referral rates, investigation rates and clinical outcomes. This guideline, on the symptoms of possible cancer, seeks to improve cancer diagnosis.

This guideline is about people with symptoms, rather than about people in whom cancer is already suspected. It is increasingly recognised that selection of patients whose symptoms suggest cancer should be considered a primary care task, as the large majority of such patients present to a primary care clinician. As consideration of possible cancer typically occurs in primary care, evidence from primary care must inform the identification process. Previous approaches have relied mostly on evidence from secondary care, partly because evidence from primary care was lacking. More primary care evidence is now available.

Update 2015

The guiding principle of risk

Guidance on cancer diagnosis generally defines specific symptoms, or symptom combinations, which are thought to warrant consideration of the possibility of cancer. Whatever the exact arrangements for investigation of possible cancer are, the selection process ends up with some patients being investigated or referred, while others are not. To ensure internal consistency and equity within the guideline, the GDG unanimously supported the concept of a ‘risk threshold’, whereby if the risk of the patient’s symptoms representing a cancer was above a certain level then action was warranted. The chosen metric was a positive predictive value (PPV). Often, use of PPVs is accompanied by its corresponding metric, the negative predictive value (NPV). An NPV is the measure of the likelihood that a negative test, or absent symptom, rules out the condition. Because no symptom when absent accurately precludes cancer, NPVs are of little or no help in the field of cancer diagnosis.

At what value should the risk threshold be?

The GDG aspired to broaden recommendations to try and improve the timeliness and quality of cancer diagnosis. Patient viewpoints were central to the decision about where the risk threshold should be. The lower the threshold could reasonably be set, the more patients with cancer would have expedited diagnoses, with accompanying improvements in mortality and morbidity. The recommendations in previous NICE guidance equated to very different percentage risks of cancer. For instance in colorectal cancer, the estimated risk from diarrhoea in an adult is below 1%, and the risk from iron-deficiency anaemia in males in that guidance exceeded 10%. Across the whole guideline, few recommendations corresponded

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with a PPV below 5%. The GDG felt that, in order to improve diagnosis of cancer, a PPV threshold lower than 5% was preferable.

Also germane to the selection of a risk threshold are the resource implications of change. At the time of setting the threshold figure, there were no strong quality health-economic reports which could help with the decision. Many reports described the costs involved in expanding cancer diagnostics. The benefits from expedited diagnosis were much less clear. It was, however, clear that broadening of recommendations would bring economic and clinical costs. The clinical costs include potential harms to the patient through the side effects of investigations performed and also through increased anxiety. The lower a threshold is set, the more likely people are to be exposed to these potential harms.

Taking all of this into account, the GDG agreed to use a threshold value of 3% PPV to underpin their recommendations. This value represented a considerable liberalisation of the estimated PPVs of previous recommendations, but the GDG agreed that this change would not overwhelm clinical services, nor greatly increase the possible harms to patients from over-investigation. This 3% PPV governed recommendations for suspected cancer pathway referrals. The GDG also resolved to apply the same 3% PPV threshold to urgent direct access investigations in secondary care; such as brain scanning or endoscopy. The exception to this was where it was clear that appropriate investigation using tests previously unavailable to primary care could replace specialist referral. The implied economic advantages of this allowed the GDG to make recommendations below the 3% level. The GDG discussed these on a case by case basis. In instances where patients would not normally be referred on an urgent cancer pathway but would be referred routinely for specialist opinion, action at a PPV below 3% was considered to be appropriate. The same is true where a non-urgent direct-access test was considered to be more cost-effective use of resources.

Two exceptions to the 3% PPV threshold for urgent action were agreed. The first relates to children and young people. As children and young people have longer to live than adults, a successful cancer diagnosis leading to cure should yield more years of life gained. Thus it was agreed that the GDG should make recommendations for children and young people significantly below the 3% PPV threshold, although no explicit threshold value was set.

The second exception relates to tests routinely available in primary care, which can help to refine the underlying risk of cancer - this is the case whether the investigation is being carried out on an urgent basis or otherwise. These include blood tests such as PSA or imaging such as chest x-ray, which could be recommended at a lower PPV.

Symptoms present in multiple cancers but of low risk for each cancer site

There are a number of generic symptoms (e.g., fatigue), that, whilst not predictive of a specific cancer, are nevertheless believed to be predictive of “cancer”. These symptoms will typically be reported by a number of the studies included in the evidence, but will not have high enough positive predictive values for any individual cancer to meet the threshold for referral or investigation in primary care.

The GDG wanted to examine these symptoms to try to identify those that are predictive of cancer in general, rather than a specific cancer, and make recommendations accordingly.

A spreadsheet was constructed containing all the PPV evidence on the positive predictive values of signs and symptoms for the specific cancers. This spreadsheet was then used as follows:

- Symptoms for which referral recommendations were made for a specific cancer were filtered out of the spreadsheet. This was because these symptoms are predictive of a specific cancer.

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- The individual symptoms and symptom combinations were then examined across all the cancer sites where there was evidence for patients across the whole 40-70 age range (this age range was specified in advance by the GDG due to being widely covered in the relevant literature). For each symptom/symptom combination, the highest positive predictive value for each cancer was identified and then added together to create a 'cumulative' positive predictive value. Positive predictive values can be added in this way with the only concern being multiple cancers in the same person. If these were common the 'cumulative' positive predictive values would be artificially high. However, multiple cancers in the same person at the same time are extremely rare so this issue was judged by the GDG to have negligible impact.

The GDG determined, in advance, that for those symptoms with a 'cumulative' positive predictive value of 2% or above, all the evidence for that symptom across all the cancer sites would be re-examined in detail. The GDG then debated whether recommendations should be made.

The GDG acknowledged that the 'cumulative' positive predictive values would probably be underestimates. This is due to the likelihood that some cancer site/symptom combinations might not have been reported in the searches, either because the research has not been done, or because the information related to the age range could not be extracted. The GDG therefore chose a threshold of 2% so that they could examine in more detail any instances where the true cumulative PPV might exceed 3% if cancer site/symptom combinations that had not been reported in the literature searches had been available.

What is expected in primary care before these recommendations operate?

The assumption behind this guideline is that it should guide clinical decisions on a patient with symptoms, potentially of cancer, who is presenting to primary care. It is not a textbook of medicine. It was expected that the clinician will have taken an appropriate history, and to have performed an appropriate physical examination. This was expected to include urinalysis where required. It was also agreed within the GDG that in many patients without a clear diagnosis, simple blood tests would already have been taken, including a full blood count, biochemistry and inflammatory markers if relevant in the context of the patient's symptoms.

Update 2014

Actions in primary care

Some investigations may be performed in primary care, such as blood tests like prostate specific antigen or Ca125. Imaging investigations, such as chest X-rays, or ultrasound, are generally available directly to GPs. Conversely, some investigations are currently accessed through secondary care, and so require formal referral. Examples are colonoscopy, biopsy or more complex imaging. Specialist opinion also has value in making the diagnosis. There is variation across the country as to whether certain investigations can be directly accessed by primary care. Specific examples of these include upper gastrointestinal endoscopy and brain scanning where there is considerable variation.

The use of risk factors as well as symptoms

It is well recognised that some risk factors increase the chance of a person developing cancer in the future. Clear examples are increasing age or a family history of cancer. Asbestos exposure, for example, increases the risk of mesothelioma, but the mesothelioma generally occurs decades after the exposure. Risk factors make a person more likely to develop cancer, but do not affect the way the cancer presents.

Symptoms and findings are different from risk factors. These signify that a cancer may already be present. They include symptoms, abnormal physical signs, and abnormal investigation results. They work backwards in time over short periods. For example, haemoptysis suggests the possibility that lung cancer is already present.

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The interplay between these two different concepts is complex. The key decision for the GDG was whether their recommendations were to be the same for patients irrespective of whether a specific risk factor, such as family history, was also present. Thus, the searches sought to identify specific subgroups within research papers who may (or may not) have needed different recommendations. Of the possible risk factors that were reported in the literature identified in our searches, only age and smoking were found to significantly influence the chance of cancer in a patient with symptoms.

What these recommendations are, and what they are not

These recommendations are recommendations, not requirements. They do not override clinical judgement. It is well recognised that primary care clinicians have expertise in recognising patients who are 'ill' and in knowing that "something is wrong". Several research studies have supported the idea that clinical intuition has diagnostic value. This guidance seeks to assist primary care clinicians in selection of patients, and seeks to help patients in expediting their diagnosis when they may have cancer. It also helps secondary care in understanding what services to provide. Exceptions will occur, however, and clinicians should trust their clinical experience where there are particular reasons that this guidance does not pertain to the specific presentation of the patient.

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2 Definitions

The terms used in the guideline are as follows:

Immediate: an acute admission or referral occurring within a few hours, or even more quickly if necessary

Very urgent: to happen within 48 hours

Urgent: to happen within 2 weeks

Suspected cancer pathway referral: the patient is seen within the national target for cancer referrals (currently 2 weeks)

Raises the suspicion of: a mass or lesion that has an appearance or a feel that makes the clinician believe cancer is a significant possibility

Consistent with: the finding has characteristics that could be many things of which cancer is but one.

Children: from birth to 15 years

Young people: aged 16–24 years

Safety netting: a process where people at low risk, but not no risk, of having cancer are actively monitored in primary care to see if the risk of cancer changes.

Direct access: where a test is performed with primary care retaining clinical responsibility throughout, including acting upon the result.

Persistent: as used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional.

Unexplained: when used in a recommendation, unexplained refers to a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any).

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3 Research recommendations

3.1 Age thresholds in cancer

Longitudinal studies to identify and quantify factors in adults that are associated with development of specific cancers at a younger age than the norm. They should be designed to inform age thresholds in clinical guidance. The primary outcome should be likelihood ratios and positive predictive values for cancer occurring in younger age groups.

Why is this is important

It is recognised that several factors, such as deprivation and comorbidity, may lead to development of cancer at a younger age. People with these factors could be disadvantaged by the use of age thresholds for referral for suspected cancer.

3.2 Primary care testing

Diagnostic accuracy studies of tests accessible to primary care for a given cancer in symptomatic people. Priority areas for research should include tests for people with cough, non-visible haematuria, suspected prostate cancer, suspected pancreatic cancer, suspected cancer in childhood and young people and other suspected rare cancers. Outcomes of interest are the performance characteristics of the test, particularly sensitivity, specificity and positive and negative predictive values.

Why is this is important

There is very little information currently available on the diagnostic accuracy of tests available in primary care for people with suspected cancer. These studies will inform clinicians on the choice of investigation for symptomatic patients.

Update 2015

3.3 Cancers insufficiently researched in primary care

Observational studies of symptomatic primary care patients to estimate the positive predictive value of different symptoms for specific cancers. Priority areas for research are those where the evidence base is currently insufficient and should include prostate cancer, pancreatic cancer, cancer in childhood and young people and other rare cancers. Outcomes of interest are positive predictive values and likelihood ratios for cancer.

Why is this is important

For several cancer sites, the primary care evidence base on the predictive value of symptoms is thin or non-existent. Filling this gap should improve future clinical guidance.

3.4 Patient experience

Qualitative studies to assess the key issues in patient experience and patient information needs in the cancer diagnostic pathway, particularly in the interval between first presentation to primary care and first appointment in secondary care. Outcomes of interest are patient satisfaction, quality of life and patient perception of the quality of care and information.

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Why is this is important

There was very little information on both patient information needs and patient experience throughout the cancer diagnostic pathway. Filling this gap should improve future patient experience.

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4 Patient information and support

4.1 Patient information

Patient choice is central to healthcare. Although this is often taken to mean choice of treatments, it is just as important in choices around diagnosis. The ideal situation is a well-informed patient and a well-informed clinician coming to a joint decision. Therefore the GDG believed it was essential to consider the information needs of patients (and their carers or families) when cancer is suspected. This is relevant both for patients in whom investigation is being considered and in those who are being monitored for possible cancer in primary care.

Clinical question: What are the information needs of:

- **Patients who are referred for suspected cancer and their carers/families, and**
- **Patients who are being monitored (for suspected cancer) in primary care and their carers/families?**

Clinical evidence

No evidence was found pertaining to the information needs of patients in primary care who are referred for suspected cancer and their carers/families. No evidence was found pertaining to the information needs of patients who are being monitored for suspected cancer in primary care and their carers/families.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Discuss with people with suspected cancer (and their carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations including their potential risks and benefits. [2015]** **When cancer is suspected in a child, discuss the referral decision and information to be given to the child with the parents or carers (and the child if appropriate). 2015]** **Explain to people who are being referred with suspected cancer that they are being referred to a cancer service, but when appropriate reassure them that most people referred will not have a diagnosis of cancer, and discuss alternative diagnoses with them. [2015]** **Give the person information on the possible diagnosis (both benign and malignant) in accordance with their wishes for information (see also the NICE guideline on patient experience in adult NHS services). [2015]** **The information given to people with suspected cancer and**

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	their families and/or carers should cover, among other issues: • **where the person is being referred to** • **how long they will have to wait for the appointment** • **how to obtain further information about the type of cancer suspected or help before the specialist appointment** • **what to expect from the service the person will be attending** • **what type of tests may be carried out, and what will happen during diagnostic procedures** • **how long it will take to get a diagnosis or test results** • **whether they can take someone with them to the appointment** • **other sources of support. [2015]** **Provide information that is appropriate for the person in terms of language, ability and culture, recognising the potential for different cultural meanings associated with the possibility of cancer. [new 2015]** **Have information available in a variety of formats on both local and national sources of additional support for people who are being referred with suspected cancer. For more information on information sharing, see section 1.5 in the NICE guideline on patient experience in adult NHS services. [2015]** **Reassure people in the safety netting group (see recommendation in chapter 5) who are concerned that they may have cancer that with their current symptoms their risk of having cancer is low. [new 2015]** **Explain to people who are being offered safety netting (see recommendation in chapter 5) which symptoms to look out for and when they should return for re-evaluation. It may be appropriate to provide written information about this. [new 2015]**
Relative value placed on the outcomes considered	The GDG considered the information reported by patients/carers/families to be useful/not useful or wanted/not wanted when being referred for suspected cancer and when being monitoring for suspected cancer in primary care to be the most important outcome when considering these patients' information needs.
Quality of the evidence	No evidence was found pertaining to the information needs of patients or their carers/families when being referred for suspected cancer and when being monitoring for suspected cancer in primary care.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which information patients and their carers/families should receive would be to reduce anxiety and uncertainty and to encourage shared decision making. Equally the GDG recognised that provision of information can lead to increased anxiety and confusion. The GDG also recognised that the information needs are likely to differ between patients and between their carers/families both in type, amount and timing of the information. Overall, the GDG agreed that the benefits outweighed the harms.

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	However, the GDG noted that no evidence was found for this question, and therefore agreed to retain those of the recommendations in previous guidance that were specific to the information needs of patients or their carers/families when being referred for suspected cancer. The GDG noted that people being monitored for suspected cancer in primary care had a low risk of having cancer. They felt it was important that those people who suspected their symptoms were caused by cancer were reassured that they were at low risk. However the GDG also acknowledged that not everyone with symptoms would suspect their symptoms were caused by cancer. Telling such people that they had a low risk of cancer could actually cause anxiety rather than providing reassurance. The GDG therefore recommended, based on their clinical experience, that people who suspect they have cancer should be reassured that they were at low risk where appropriate. The GDG also agreed, based on their clinical experience that people being monitored for suspected cancer in primary care needed information on what symptoms should prompt re-evaluation. It was noted that providing this information in writing may be appropriate.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG estimated that the recommendations made on information provision were current practice so there will be no change in cost. For the information provision for patients being monitored in primary care, the GDG estimated that there is likely to be an increased demand on the time of primary care professionals in sharing information and thus an increase in costs.
Other considerations	The GDG noted that it was important for the information provided to be provided in a form accessible by people with learning disabilities. They therefore specified this in the recommendations.

Update 2014

4.2 Support

Suspicion of cancer may be very worrying for the person, who may need support and care to help them through this period.

Recommendations	**When referring a person with suspected cancer to a specialist service, assess their need for continuing support while waiting for their referral appointment. This should include inviting the person to contact their healthcare professional again if they have more concerns or questions before they see a specialist. [2005]** **If the person has additional support needs because of their personal circumstances, inform the specialist (with the person's agreement). [2005]**

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5 Safety netting

It is well recognised that atypical, generally low-risk, or non-specific symptoms may be early features of cancer. These may evolve to a clearer pattern suggesting disease over time – or they may resolve spontaneously. Persistence of a symptom increases the likelihood of serious disease. For these reasons, it may be appropriate to defer definitive investigation until the clinical situation, and the optimum route for investigation, become clearer. Early investigation may bring benefits from earlier diagnosis: however, it may also be associated with harms (such as increased anxiety, radiation exposure and rarer serious complications).

The process where investigation is deferred, or avoided, is variously called 'watchful waiting' or 'safety netting'. The GDG wished to seek evidence on the usefulness of this approach.

Clinical question: What safety-netting strategies are effective in primary care for patients being monitored for suspected cancer?

Clinical evidence

No evidence was found pertaining to the effectiveness of any safety-netting strategies in primary care for patients being monitored for suspected cancer.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a review for people with any symptom that is associated with an increased risk of cancer, but who do not meet the criteria for referral or other investigative action. The review may be:** • **planned within a time frame agreed with the person or** • **patient-initiated if their symptoms recur, persist or worsen, new symptoms develop or the person continues to be concerned. [new 2015]**
Relative value placed on the outcomes considered	The GDG considered the proportion of patients with cancer, the number of emergency presentations, stage at diagnosis, survival, delayed diagnosis, and psychological morbidity to be the most important outcomes when considering what safety-netting strategies are effective in primary care for patients being monitored for suspected cancer.
Quality of the evidence	No evidence was found pertaining to the effectiveness of safety-netting strategies in primary care for patients being monitored for suspected cancer.
Trade-off between clinical benefits and harms	The GDG noted that not all people with symptoms warrant a suspected cancer pathway referral or investigation in primary care for cancer. However it was still possible that some people with symptoms will have cancer. They therefore agreed that it was important to have a strategy to 'safety-net' such people, so that those who do actually have cancer will be identified – hopefully earlier than currently. This strategy could equally be applied to those people who were investigated in either primary or secondary care, whose tests result were negative for cancer,

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	but whose symptoms persist. The GDG noted that no evidence had been found for this question. Based on their clinical experience, the GDG recognised that almost any symptom could potentially indicate cancer, but it would not be possible to 'safety-net' all patients with symptoms. However it was also difficult to define a specific set of symptoms which should prompt 'safety-netting' because any list of symptoms would be incomplete. The GDG therefore decided to recommend that people with symptoms recognised to be associated with an increased risk of cancer, who did not meet the criteria for referral, should be 'safety-netted'. The GDG considered the benefit of this recommendation to be that it uses time - which can allow the predictive value of a patient's symptoms to increase or decrease, thus informing the most appropriate next step(s). The GDG noted that this prevents unnecessary intervention in people whose risk of cancer is low. The GDG considered the potential harms of the recommendation to be that it may lead to a potential delay in patients with cancer who could have been offered investigation earlier as well as potentially an increase in anxiety for the safety-netted patient. However, the GDG agreed that, on balance, the benefits outweigh the potential harms. The GDG agreed, based on their clinical experience, that 'safety-netting' would need to involve planned review of the person with symptoms. They noted that it was also important that patients were able to initiate a review - before the planned review if required - as a result of change to their symptoms, development of new symptoms or because they were concerned. The GDG acknowledged that there was no evidence to support a specific time-frame for the period of review and noted that this would vary dependant on the person and their circumstances. They therefore did not specify a time-frame for review in the recommendation.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG estimated that the recommendations are likely to result in an increase in the time used by primary care professionals (particularly GPs), with both greater number of consultations and length of consultations. However the recommendations may also lead to a reduction in emergency presentations of cancer. Overall, the GDG estimated that the net effect would be an increase in costs but it was difficult to determine the extent of this increase.

Update 2015

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6 The diagnostic process

Update 2015

The process of diagnosing cancer generally spans both primary and secondary care. It is important that the pathway from primary to secondary care is as smooth as possible and that those involved in this pathway have the knowledge and skills appropriate to the task.

Recommendations	**Take part in continuing education, peer review and other activities to improve and maintain clinical consulting, reasoning and diagnostic skills, in order to identify at an early stage people who may have cancer, and to communicate the possibility of cancer to the person. [2005]** **Discussion with a specialist (for example, by telephone or email) should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical. [2005]** **Put in place local arrangements to ensure that letters about non-urgent referrals are assessed by the specialist, so that the person can be seen more urgently if necessary. [2005]** **Put in place local arrangements to ensure that there is a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements. [2005]** **Ensure local arrangements are in place to identify people who miss their appointments so that they can be followed up. [2005]** **Include all appropriate information in referral correspondence, including whether the referral is urgent or non-urgent. [2005]** **Use local referral proformas if these are in use. [2005]** **Once the decision to refer has been made, make sure that the referral is made within 1 working day. [2005]**

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7 Lung and pleural cancers

7.1 Lung cancer

Over 43,000 new lung cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with lung cancer each year. It is seen in both sexes: historically, it was much more common in males, though 45% of new diagnoses are now in females. Five year survival is below 10%.

Lung cancer can present with a number of different symptoms, and there are often multiple symptoms simultaneously. Symptoms include cough, shortness of breath, haemoptysis, chest pain, loss of weight, loss of appetite and fatigue. The cancer may also present with persistent chest infection, or with metastases, particularly to bone or brain.

Most lung cancers can be identified on a plain chest X-ray, though false-negatives may occur. Other imaging techniques, especially CT, may be used, though these are generally performed following an indeterminate chest X-ray, or when the person has continuing symptoms and a normal chest X-ray. These imaging techniques are usually available in primary care, with CT often recommended by a radiologist reporting a chest X-ray.

Definitive diagnosis requires biopsy, usually by bronchoscopy or thoracoscopy. Sputum cytology is only used in those unable to have biopsy. These procedures are performed in secondary care.

Clinical questions:

- **What is the risk of lung cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected lung cancer should be done with clinical responsibility retained by primary care?**

Update 2015

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note are that patient sampling was not based on a consecutive or random series of patients in a number of the studies, some of which were also not conducted in a population directly relevant to the current question. Studies employing non-consecutive/random sampling are at high risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data, symptom coding and specification as well as suboptimal reference standard.

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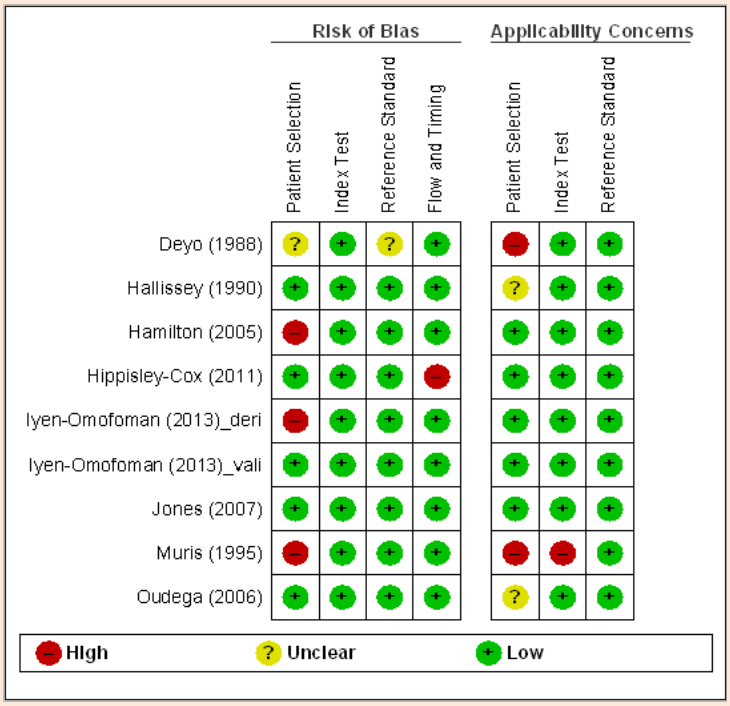

Evidence statements

Haemoptysis (4 studies, N = 15998) presenting in a primary care setting is associated with overall positive predictive values of 2.4-17% for lung cancer, which tended to increase with age in men and women (1 study, N = 4822). The studies were associated with 0-1 bias or applicability concern (see also Tables 4-6).

Single symptoms other than haemoptysis presenting in a primary care setting is associated with overall positive predictive values from 0.05% (for back pain) to 1.6% (for abnormal spirometry and thrombocytosis) for for lung cancer (6 studies, N = 1833698), and with positive predictive values from 0.9% (for cough) to 4.2% (for thrombocytosis) for smokers for lung cancer (1 study, N = 1482). The studies were associated with 1-3 bias or applicability concerns (see also Table 6).

Two symptoms presenting in combination in a primary care setting were associated with overall positive predictive values from 0.63% (for fatigue and cough) to > 10% (for haemoptysis with appetite loss, abnormal spirometry or thrombocytosis) for lung cancer (2 studies, N = 6030), and with positive predictive values from 0.9% (for chest pain and cough) to > 10% (for abnormal spirometry with fatigue, dyspnoea, chest pain or loss of weight, and for thrombocytosis with chest pain or loss of weight) for smokers for lung cancer (1 study, N = 1482). The studies were each associated with 1 bias concern (see also Table 7).

Table 4: Lung cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Jones (2007, at 6 months), Hippisley-Cox (2011), Iyen-Omofoman (2013)	Haemoptysis	All patients (N = 14516)	3.51 (1.61-7.5)
Jones (2007, at 3 years), Hippisley-Cox (2011), Iyen-Omofoman (2013)	Haemoptysis	All patients (N = 14516)	3.83 (1.66-8.62)

Please note that the data from Hamilton (2005) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the second table below.

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Table 5: Lung cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hippisley-Cox (2011)	Haemoptysis	All patients (N = 7861)	6.4 (5.9-7)
Iyen-Omofoman (2013)	Haemoptysis	All patients (N = 1843)	1.3 (0.9-2)
Jones (2007, at 6 months)	Haemoptysis	All patients (N =4822)	4.8 (4.2-5.5)
Jones (2007, at 3 years)	Haemoptysis	All patients (N = 4822)	6.3 (6-7)

Table 6: Lung cancer: Additional results reported by the individual papers: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Deyo (1988)	Back pain	All included patients	0.05 (0.003-0.3) 1/1975
Muris (1995)	Non-acute abdominal complaints	All included patients	0.2 (0.04-0.9) 2/933
Oudega (2006)	Deep vein thrombosis	All included patients	0.7 (0.2-2.2) 3/430
Hallissey (1990)	Dyspepsia	All patients	0.3 (0.1-0.6) 8/2585
Jones (2007)	Haemoptysis	Men (all ages) at 6 months	5.8 (5-6.7)
Jones (2007)	Haemoptysis	Men (all ages) at 3 years	7.5 (6.6-8.5)
Jones (2007)	Haemoptysis	Men < 45 years at 3 years	0.21 (0.03-7.55)
Jones (2007)	Haemoptysis	Men 45-54 years at 3 years	1.65 (0.67-3.37)
Jones (2007)	Haemoptysis	Men 55-64 years at 3 years	8.37 (6.12-11.1)
Jones (2007)	Haemoptysis	Men 65-74 years at 3 years	14.86 (12-18.1)
Jones (2007)	Haemoptysis	Men 75-84 years at 3 years	17.05 (13.5-21.1)
Jones (2007)	Haemoptysis	Men ≥ 85 years at 3 years	20.43 (12.8-30.1) 19/93
Jones (2007)	Haemoptysis	Women (all ages) at 6 months	3.3 (2.6-4.3)
Jones (2007)	Haemoptysis	Women (all ages) at 3 years	4.3 (3.4-5.3)
Jones (2007)	Haemoptysis	Women < 45 years at 3 years	0.36 (0.04-1.3)
Jones (2007)	Haemoptysis	Women 45-54 years at 3 years	1.84 (0.6-4.24)
Jones (2007)	Haemoptysis	Women 55-64 years at 3 years	4.12 (2.32-6.71)
Jones (2007)	Haemoptysis	Women 65-74 years at 3 years	8.38 (5.73-11.8)
Jones (2007)	Haemoptysis	Women 75-84 years at	10.47 (7.01-14.9)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		3 years	
Jones (2007)	Haemoptysis	Women ≥ 85 years at 3 years	2.6 (0.32-9.07) 2/77
Hamilton (2005)	Haemoptysis	All included patients	2.4 (1.4-4.1)
Hamilton (2005)	Haemoptysis	All smokers	4.5 (NR)
Hamilton (2005)	Haemoptysis (reported twice)	All included patients	17 (NR)
Hamilton (2005)	Haemoptysis (reported twice)	All smokers	12 (NR)
Hamilton (2005)	Haemoptysis	Patients ≥ 70 years	7.1 (NR)
Hamilton (2005)	Cough	All included patients	0.4 (0.3-0.5)
Hamilton (2005)	Cough	All smokers	0.9 (NR)
Hamilton (2005)	Cough (reported twice)	All included patients	0.58 (0.4-0.8)
Hamilton (2005)	Cough (reported twice)	All smokers	1.3 (NR)
Iyen-Omofoman (2013)	Haemoptysis 4-12 months prior to diagnosis	Derivation cohort	Cases: 247/12074 Controls: 125/120731
Iyen-Omofoman (2013)	Haemoptysis 13-24 months prior to diagnosis	Derivation cohort	Cases: 133/12074 Controls: 191/120731
Hamilton (2005)	Cough (reported 3 times)	All included patients	0.77 (0.54-1.1)
Iyen-Omofoman (2013)	Cough	Validation cohort	0.24 (0.2-0.3)
Iyen-Omofoman (2013)	Cough 4-12 months prior to diagnosis	Derivation cohort	Cases: 1938/12074 Controls: 7088/120731
Iyen-Omofoman (2013)	Cough 13-24 months prior to diagnosis	Derivation cohort	Cases: 1774/12074 Controls: 9087/120731
Iyen-Omofoman (2013)	Voice hoarseness	Validation cohort	0.17 (0.08-0.3)
Iyen-Omofoman (2013)	Voice hoarseness 4-12 months prior to diagnosis	Derivation cohort	Cases: 66/12074 Controls: 219/120731
Iyen-Omofoman (2013)	Voice hoarseness 13-24 months prior to diagnosis	Derivation cohort	Cases: 56/12074 Controls: 326/120731
Hamilton (2005)	Fatigue	All included patients	0.43 (0.3-0.6)
Hamilton (2005)	Fatigue	All smokers	0.8 (NR)
Hamilton (2005)	Fatigue (reported twice)	All included patients	0.57 (0.4-0.9)
Hamilton (2005)	Fatigue (reported twice)	All smokers	1.2 (NR)
Hamilton (2005)	Dyspnoea	All included patients	0.66 (0.5-0.8)
Hamilton (2005)	Dyspnoea	All smokers	1.2 (NR)
Hamilton (2005)	Dyspnoea (reported twice)	All included patients	0.88 (NR)
Hamilton (2005)	Dyspnoea (reported twice)	All smokers	1.5 (NR)
Iyen-Omofoman	Dyspnoea	Validation cohort	0.51 (0.5-0.6)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
(2013)			
Iyen-Omofoman (2013)	Dyspnoea 4-12 months prior to diagnosis	Derivation cohort	Cases: 1091/12074 Controls: 2479/120731
Iyen-Omofoman (2013)	Dyspnoea 13-24 months prior to diagnosis	Derivation cohort	Cases: 992/12074 Controls: 3047/120731
Hamilton (2005)	Chest pain	All included patients	0.82 (0.6-1.1)
Hamilton (2005)	Chest pain	All smokers	1.3 (NR)
Hamilton (2005)	Chest pain (reported twice)	All included patients	0.95 (0.7-1.4)
Hamilton (2005)	Chest pain (reported twice)	All smokers	1.4 (NR)
Iyen-Omofoman (2013)	Chest/shoulder pain	Validation cohort	0.18 (0.15-0.21)
Iyen-Omofoman (2013)	Chest/shoulder pain 4-12 months prior to diagnosis	Derivation cohort	Cases: 1002/12074 Controls: 4880/120731
Iyen-Omofoman (2013)	Chest/shoulder pain 13-24 months prior to diagnosis	Derivation cohort	Cases: 959/12074 Controls: 6540/120731
Hamilton (2005)	Weight loss	All included patients	1.1 (0.8-1.6)
Hamilton (2005)	Weight loss	All smokers	2.1 (NR)
Hamilton (2005)	Weight loss (reported twice)	All included patients	1.2 (0.7-2.3)
Hamilton (2005)	Weight loss (reported twice)	All smokers	1.7 (NR)
Iyen-Omofoman (2013)	Weight loss	Validation cohort	0.34 (0.23-0.5)
Iyen-Omofoman (2013)	Weight loss 4-12 months prior to diagnosis	Derivation cohort	Cases: 197/12074 Controls: 323/120731
Iyen-Omofoman (2013)	Weight loss 13-24 months prior to diagnosis	Derivation cohort	Cases: 139/12074 Controls: 416/120731
Hamilton (2005)	Appetite loss	All included patients	0.87 (0.6-1.3)
Hamilton (2005)	Appetite loss	All smokers	1.8 (NR)
Hamilton (2005)	Appetite loss	Patients 40-69 years	1.1 (NR)
Hamilton (2005)	Appetite loss (reported twice)	All included patients	1.7 (NR)
Hamilton (2005)	Appetite loss (reported twice)	All smokers	2.7 (NR)
Iyen-Omofoman (2013)	Constipation 4-12 months prior to diagnosis	Derivation cohort	Cases: 423/12074 Controls: 1469/120731
Iyen-Omofoman (2013)	Constipation 13-24 months prior to diagnosis	Derivation cohort	Cases: 421/12074 Controls: 1848/120731
Hamilton (2005)	Thrombocytosis	All included patients	1.6 (0.8-3.1)
Hamilton (2005)	Thrombocytosis	All smokers	4.2 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hamilton (2005)	Thrombocytosis	Patients 40-69 years	3 (NR)
Hamilton (2005)	Abnormal spirometry	All included patients	1.6 (0.9-2.9)
Hamilton (2005)	Abnormal spirometry	All smokers	4 (NR)
Hamilton (2005)	Abnormal spirometry	Patients ≥ 70 years	4.1 (NR)
Hamilton (2005) also reports that the PPVs for all the variables reported for this study apart from thrombocytosis were higher for patients aged ≥ 70 years than patients aged 40-69 years. In patients aged ≥ 70 years the PPVs ranged from 0.9-2.2% apart from for haemoptysis and abnormal spirometry (see separate entry)			
Iyen-Omofoman (2013)	Depressive disorders 4-12 months prior to diagnosis	Derivation cohort	Cases: 365/12074 Controls: 3365/120731
Iyen-Omofoman (2013)	Depressive disorders 13-24 months prior to diagnosis	Derivation cohort	Cases: 449/12074 Controls: 4705/120731
Iyen-Omofoman (2013)	Upper respiratory tract infections 4-12 months prior to diagnosis	Derivation cohort	Cases: 426/12074 Controls: 3082/120731
Iyen-Omofoman (2013)	Upper respiratory tract infections 13-24 months prior to diagnosis	Derivation cohort	Cases: 497/12074 Controls: 4274/120731
Iyen-Omofoman (2013)	Lower respiratory tract infections 4-12 months prior to diagnosis	Derivation cohort	Cases: 516/12074 Controls: 1585/120731
Iyen-Omofoman (2013)	Lower respiratory tract infections 13-24 months prior to diagnosis	Derivation cohort	Cases: 566/12074 Controls: 2218/120731
Iyen-Omofoman (2013)	Non-specific chest infections 4-12 months prior to diagnosis	Derivation cohort	Cases: 1398/12074 Controls: 4350/120731
Iyen-Omofoman (2013)	Non-specific chest infections 13-24 months prior to diagnosis	Derivation cohort	Cases: 1356/12074 Controls: 5856/120731
Iyen-Omofoman (2013)	Chronic obstructive pulmonary disease 4-12 months prior to diagnosis	Derivation cohort	Cases: 978/12074 Controls: 1349/120731
Iyen-Omofoman (2013)	Chronic obstructive pulmonary disease 13-24 months prior to diagnosis	Derivation cohort	Cases: 1024/12074 Controls: 1553/120731
Iyen-Omofoman (2013)	Outcome of blood tests 4-12 months prior to diagnosis	Derivation cohort	
	No blood test record		Cases: 6406/12074 Controls: 84997/120731
	Test without results		Cases: 5431/12074 Controls: 34295/120731
	Abnormal		Cases: 107/12074 Controls:

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
			528/120731
	Normal		Cases: 130/12074 Controls: 911/120731
Iyen-Omofoman (2013)	Outcome of blood tests 13-24 months prior to diagnosis	Derivation cohort	
	No blood test record		Cases: 6136/12074 Controls: 79446/120731
	Test without results		Cases: 5632/12074 Controls: 39255/120731
	Abnormal		Cases: 127/12074 Controls: 752/120731
	Normal		Cases: 179/12074 Controls: 1278/120731
Iyen-Omofoman (2013)	Number of GP consultations 4-12 months prior to diagnosis	Derivation cohort	
	0-10		Cases: 4316/12074 Controls: 77720/120731
	11-20		Cases: 4373/12074 Controls: 29327/120731
	≥21		Cases: 3385/12074 Controls: 13684/120731
Iyen-Omofoman (2013)	Number of GP consultations 13-24 months prior to diagnosis	Derivation cohort	
	0-10		Cases: 3491/12074 Controls: 64881/120731
	11-20		Cases: 3492/12074 Controls: 29296/120731
	≥21		Cases: 5091/12074 Controls: 26554/120731

NR = Not reported, TP = true positives, FP = false positives. Please note the calculations of the positive predictive values differ between the studies with Deyo (1988), Hippisley-Cox (2011), Jones (2007), Iyen-Omofoman (2013), Muris (1995) and Oudega (2003) using (TP)/(TP+FP) and Hamilton (2005) using Bayesian statistics due to the case-control design of this study.

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Table 7: Lung cancer: Additional results reported by the individual papers: Pairs of signs/symptoms

Hippisley-Cox (2011)	Haemoptysis + current/ex-smoking	Patients ≥ 40 years	9.7 (8.9-10.7)
Hamilton (2005)	Haemoptysis + cough	All included patients	2 (1.1-3.5)
Hamilton (2005)	Haemoptysis + cough	All smokers	3.9 (NR)
Hamilton (2005)	Haemoptysis + fatigue	All included patients	3.3 (NR)
Hamilton (2005)	Haemoptysis + fatigue	All smokers	6.1 (NR)
Hamilton (2005)	Haemoptysis + dyspnoea	All included patients	4.9 (NR)
Hamilton (2005)	Haemoptysis + dyspnoea	All smokers	6.9 (NR)
Hamilton (2005)	Haemoptysis + chest pain	All included patients	5 (NR)
Hamilton (2005)	Haemoptysis + chest pain	All smokers	4.1 (NR)
Hamilton (2005)	Haemoptysis + weight loss	All included patients	9.2 (NR)
Hamilton (2005)	Haemoptysis + weight loss	All smokers	*
Hamilton (2005)	Haemoptysis + appetite loss	All included patients	> 10 (NR)
Hamilton (2005)	Haemoptysis + appetite loss	All smokers	*
Hamilton (2005)	Haemoptysis + thrombocytosis	All included patients	> 10 (NR)
Hamilton (2005)	Haemoptysis + thrombocytosis	All smokers	NR
Hamilton (2005)	Haemoptysis + abnormal spirometry	All included patients	> 10 (NR)
Hamilton (2005)	Haemoptysis + abnormal spirometry	All smokers	*
Hamilton (2005)	Fatigue + cough	All included patients	0.63 (0.5-0.9)
Hamilton (2005)	Fatigue + cough	All smokers	1 (NR)
Hamilton (2005)	Fatigue + dyspnoea	All included patients	0.89 (0.6-?)
Hamilton (2005)	Fatigue + dyspnoea	All smokers	1.4 (NR)
Hamilton (2005)	Fatigue + chest pain	All included patients	0.84 (0.5-1.3)
Hamilton (2005)	Fatigue + chest pain	All smokers	1.3 (NR)
Hamilton (2005)	Fatigue + weight loss	All included patients	1 (0.6-1.7)
Hamilton (2005)	Fatigue + weight loss	All smokers	2 (NR)
Hamilton (2005)	Fatigue + appetite loss	All included patients	1.2 (0.7-2.1)
Hamilton (2005)	Fatigue + appetite loss	All smokers	2.3 (NR)
Hamilton (2005)	Fatigue + thrombocytosis	All included patients	1.8 (NR)
Hamilton (2005)	Fatigue + thrombocytosis	All smokers	2.4 (NR)
Hamilton (2005)	Fatigue + abnormal spirometry	All included patients	4 (NR)
Hamilton (2005)	Fatigue + abnormal spirometry	All smokers	>10 (NR)
Hamilton (2005)	Cough + dyspnoea	All included patients	0.79 (0.6-1)

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Hippisley-Cox (2011)	Haemoptysis + current/ex-smoking	Patients ≥ 40 years	9.7 (8.9-10.7)
Hamilton (2005)	Cough + dyspnoea	All smokers	1.4 (NR)
Hamilton (2005)	Cough + chest pain	All included patients	0.76 (0.6-1)
Hamilton (2005)	Cough + chest pain	All smokers	0.9 (NR)
Hamilton (2005)	Cough + weight loss	All included patients	1.8 (1.1-2.9)
Hamilton (2005)	Cough + weight loss	All smokers	2.3 (NR)
Hamilton (2005)	Cough + appetite loss	All included patients	1.6 (0.9-2.7)
Hamilton (2005)	Cough + appetite loss	All smokers	2.8 (NR)
Hamilton (2005)	Cough + thrombocytosis	All included patients	2 (1.1-3.5)
Hamilton (2005)	Cough + thrombocytosis	All smokers	6.5 (NR)
Hamilton (2005)	Cough + abnormal spirometry	All included patients	1.2 (0.6-2.6)
Hamilton (2005)	Cough + abnormal spirometry	All smokers	3.6 (NR)
Hamilton (2005)	Dyspnoea + chest pain	All included patients	1.2 (0.9-1.8)
Hamilton (2005)	Dyspnoea + chest pain	All smokers	2.2 (NR)
Hamilton (2005)	Dyspnoea + weight loss	All included patients	2 (1.2-3.8)
Hamilton (2005)	Dyspnoea + weight loss	All smokers	3.1 (NR)
Hamilton (2005)	Dyspnoea + appetite loss	All included patients	2 (1.2-3.8)
Hamilton (2005)	Dyspnoea + appetite loss	All smokers	5.5 (NR)
Hamilton (2005)	Dyspnoea + thrombocytosis	All included patients	2 (NR)
Hamilton (2005)	Dyspnoea + thrombocytosis	All smokers	2.4 (NR)
Hamilton (2005)	Dyspnoea + abnormal spirometry	All included patients	2.3 (NR)
Hamilton (2005)	Dyspnoea + abnormal spirometry	All smokers	>10 (NR)
Hamilton (2005)	Chest pain + weight loss	All included patients	1.8 (1-3.4)
Hamilton (2005)	Chest pain + weight loss	All smokers	4.4 (NR)
Hamilton (2005)	Chest pain + appetite loss	All included patients	1.8 (0.9-3.9)
Hamilton (2005)	Chest pain + appetite loss	All smokers	7.6 (NR)
Hamilton (2005)	Chest pain + thrombocytosis	All included patients	2 (NR)
Hamilton (2005)	Chest pain + thrombocytosis	All smokers	>10 (NR)
Hamilton (2005)	Chest pain + abnormal spirometry	All included patients	1.4 (NR)
Hamilton (2005)	Chest pain + abnormal spirometry	All smokers	>10 (NR)
Hamilton (2005)	Weight loss + appetite loss	All included patients	2.3 (1.2-4.4)
Hamilton (2005)	Weight loss + appetite loss	All smokers	5 (NR)
Hamilton (2005)	Weight loss + thrombocytosis	All included patients	6.1 (NR)

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Hippisley-Cox (2011)	**Haemoptysis + current/ex-smoking**	**Patients ≥ 40 years**	**9.7 (8.9-10.7)**
Hamilton (2005)	Weight loss + thrombocytosis	All smokers	>10 (NR)
Hamilton (2005)	Weight loss + abnormal spirometry	All included patients	1.5 (NR)
Hamilton (2005)	Weight loss + abnormal spirometry	All smokers	>10 (NR)
Hamilton (2005)	Appetite loss + thrombocytosis	All included patients	0.9 (NR)
Hamilton (2005)	Appetite loss + thrombocytosis	All smokers	*
Hamilton (2005)	Appetite loss + abnormal spirometry	All included patients	2.7 (NR)
Hamilton (2005)	Appetite loss + abnormal spirometry	All smokers	*
Hamilton (2005)	Thrombocytosis + abnormal spirometry	All included patients	3.6 (NR)
Hamilton (2005)	Thrombocytosis + abnormal spirometry	All smokers	NR

*TP = true positives, FP = false positives, NR = Not reported. * "The original study was not able to calculate figures for these boxes, but they are almost certainly worthy of a red shade [2 week wait referral]" (quoted in: http://webarchive.nationalarchives.gov.uk/20130513211237/http://www.ncat.nhs.uk/sites/default/files/work-docs/ncl%20lung%20guide.pdf), * effectively means >2%. Please note the calculations of the positive predictive values differ between the studies with Hippisley-Cox (2011) using (TP)/(TP+FP) and Hamilton (2005) using Bayesian statistics due to the case-control design of this study.*

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of chest X-ray, CT, sputum cytology, or bronchoscopy in patients with suspected lung cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:** • **have chest X-ray findings that suggest lung cancer or** • **are aged over 55 with haemoptysis or** • **are aged 40–55, smoke or have smoked in the past, and have haemoptysis or** • **are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms:** o **cough** o **fatigue** o **shortness of breath**

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	○ **chest pain** ○ **weight loss** ○ **appetite loss. [new 2015]** **Offer a full blood count and chest X-ray to assess for lung cancer in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Offer a full blood count and chest X-ray to assess for lung cancer in people aged 40 and over who have never smoked and have 2 or more of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Offer a full blood count to assess for lung cancer in people aged 40 and over who have never smoked and have any of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Consider an urgent full blood count and chest X-ray (within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:** • **finger clubbing or** • **supraclavicular lymphadenopathy or persistent cervical lymphadenopathy or** • **chest signs compatible with lung cancer. [new 2015]** **Offer an urgent chest X-ray (within 2 weeks) to assess for lung cancer in people with either:** • **thrombocytosis or** • **persistent or recurrent chest infection. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of lung cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms were predictive of lung cancer.

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	Investigations in primary care for lung cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	Signs and symptoms of lung cancer The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms although it could generally be considered of high quality. Investigations in primary care for lung cancer No evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT, sputum cytology, or bronchoscopy in primary care patients with suspected lung cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with lung cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without lung cancer who get inappropriately referred whilst maximising the number of people with lung cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with lung cancer outweighed the disadvantages to those without. The GDG noted, based on the evidence, that haemoptysis presenting in a primary care setting was associated with a positive predictive value of above 3% for lung cancer in people over 55 years of age. They therefore recommended this symptom should prompt a suspected cancer pathway referral. The GDG also noted that the positive predictive values of symptoms, were higher in people with a history of smoking. Consequently they agreed to recommend that people who smoke or had ever smoked with haemoptysis should be referred at a lower age range. The GDG acknowledged that haemoptysis was the only single symptom with a positive predictive value above 3% and therefore it would not be appropriate to recommend a suspected cancer pathway referral for any other symptoms. However, their clinical consensus was that there were a collection of other signs and symptoms that were sufficiently indicative of lung cancer that they could not be ignored. The GDG agreed that patients with these signs and symptoms should be investigated in primary care to determine if a suspected cancer pathway referral is needed. They also agreed that the triggers for such investigation should be different based on a person's smoking history.

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	It was recognised that some of the haemoptysis plus a second symptom combinations in a non-smoker had PPVs somewhat below 3%. The GDGs agreed for simplicity to retain all these symptom combinations in their recommendations. They considered that this would make the recommendation easier to implement, whilst maintaining the emphasis on investigation of haemoptysis, which they considered, based on their clinical experience, to be very important. The GDG noted the lack of evidence on the diagnostic accuracy of investigations in primary care patients with suspected lung cancer. However, it was noted, based on the evidence on the predictive value of signs and symptoms that a raised platelet count (indicated by the results of a full blood count) increased the likelihood of cancer. Based on clinical experience, the GDG also agreed that chest X-ray was a reasonably reliable test for lung cancer, although has a false negative rate. The GDG therefore considered that performing a full blood count and/or chest X-ray would help to focus the group of people presenting with symptoms to those who may actually have lung cancer. It was agreed that findings on chest X-ray that were indicative of lung cancer should prompt a suspected cancer pathway referral. The GDG also discussed whether or not spirometry would be a useful investigation in primary care. However, the evidence of the predictive value of signs and symptoms had shown abnormal spirometry had an inconsistent effect on the positive predictive values. Also it was know that there can be difficulties in access and use of this test. Therefore the GDG decided not to recommend this test as an investigation in primary care patients with suspected lung cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. They considered that the recommendation to refer people with haemoptysis may lead to a moderate increase in suspected cancer pathway referrals. There may also be a small reduction in referrals for patients with symptoms but normal chest X-rays. The GDG noted that the recommendations made could result in a small increase in the number of chest X-rays and full blood counts being performed. There would also be a resultant increase in the amount of time required in a consultation, both to order the tests and relay the results. This would also increase costs to primary care. The GDG also considered that the recommendations would hopefully result in an increased number of people being diagnosed earlier with lung cancer and a corresponding decrease in the number of emergency admissions. It was noted that earlier diagnosis may result in more radical treatment, and the costs associated with this. However the GDG agreed that this potential increase in costs was justified by the potential improvement in survival.

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7.21 Mesothelioma

Over 2,500 new mesotheliomas are diagnosed each year in the UK, though the incidence is increasing rapidly. Most are pleural, though peritoneal mesotheliomas also occur. A full time GP is likely to diagnose approximately 2-3 people with mesothelioma in their career. It is seen in both sexes, though currently 85% of new mesotheliomas occur in males. Five year survival is below 10%.

Pleural mesothelioma symptoms are thought to include cough, shortness of breath, chest pain, and loss of weight. However the rarity of this cancer means there are few studies of its clinical features.

Many of the symptoms overlap with those of lung cancer, and the initial primary care investigation (chest X-ray) is the same. Most mesotheliomas can be identified on a plain chest X-ray as a pleural abnormality. Other imaging techniques, especially CT, may be used though these are generally performed following an indeterminate chest X-ray. These imaging techniques are usually available in primary care, with CT often recommended by a radiologist reporting a chest X-ray.

Definitive diagnosis requires biopsy, usually by thoracoscopy. This is performed in secondary care.

Clinical questions:

- **What is the risk of mesothelioma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected mesothelioma should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of mesothelioma in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT, abdominal x-ray, or ultrasound in patients with suspected mesothelioma where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

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Recommendations	**Offer a full blood count and chest X-ray to assess for mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Offer a full blood count and chest X-ray to assess for mesothelioma in people aged 40 and over who have never smoked and have 2 or more of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Offer a full blood count to assess for mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms:** • **cough** • **fatigue** • **shortness of breath** • **chest pain** • **weight loss** • **appetite loss. [new 2015]** **Offer an urgent chest X-ray (within 2 weeks) to assess for mesothelioma in people aged 40 and over with either:** • **finger clubbing or** • **chest signs compatible with pleural disease. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of mesothelioma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms were predictive of mesothelioma. No evidence was found on this outcome. <u>Investigations in primary care for mesothelioma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of mesothelioma</u> No evidence was found pertaining to the positive predictive values of different symptoms of mesothelioma in primary care.

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	<u>Investigations in primary care for mesothelioma</u> No evidence was found pertaining to the diagnostic accuracy of chest x-ray, CT, abdominal x-ray, or ultrasound in primary care patients with suspected mesothelioma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with mesothelioma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without mesothelioma who get inappropriately referred whilst maximising the number of people with mesothelioma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with mesothelioma outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for mesothelioma. The GDG noted that the symptoms of mesothelioma are very difficult to differentiate from those of lung cancer, with the exception of haemoptysis which does not occur in mesothelioma. It was agreed that given the similarities in the symptoms, it would be appropriate to adopt the lung cancer recommendations for mesothelioma. The GDG discussed whether it was appropriate to make differential recommendations for ever smokers and never smokers for mesothelioma, since smoking history is not usually considered to be a risk factor for mesothelioma. It was noted that due to the lack of evidence it was not possible to determine if smoking history was a risk factor or not. However, it was also noted that if the recommendations for lung cancer were adopted for mesothelioma, but didn't differentiate according to smoking history, there would be two different instructions for the same symptom which would be confusing to implement. Therefore the GDG agreed to retain the different recommendations for ever and never smokers. The GDG discussed whether or not different recommendations should be made for those people with prior exposure to asbestos, as this is a risk factor for developing mesothelioma. The GDG noted it can be difficult to determine if prior exposure to asbestos has occurred. In addition, many people with mesothelioma have not been exposed to asbestos and the GDG considered that highlighting exposure in the recommendations could mean that mesothelioma is not considered in those who have not had prior asbestos exposure. Equally, although prior asbestos exposure is a risk factor for developing mesothelioma, the GDG

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	considered that once a person has symptoms, the referral pattern is not dependant on risk factors. The GDG therefore agreed not to make different recommendations based on prior exposure to asbestos.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendations made could result in a small increase in the number of chest X-rays and full blood counts being performed. There would also be a resultant increase in the amount of time required in a consultation, both to order the tests and relay the results. This would increase costs to primary care. The GDG also considered that the recommendations would hopefully result in an increased number of people being diagnosed earlier with mesothelioma and a corresponding decrease in the number of emergency admissions. It was noted that earlier diagnosis may result in more radical treatment, and the costs associated with this. However the GDG agreed that this potential increase in costs, balanced against the potential improvement in survival.

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Lung mesothelioma

None

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8 Upper gastro-intestinal tract cancers

8.1 Oesophageal cancer

Over 8,000 new oesophageal cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with oesophageal cancer every 3-5 years. It is seen in both sexes, though two-thirds of new diagnoses are in males. Five year survival is approximately 15%.

Oesophageal cancer can present with a number of different symptoms. The most classical is dysphagia, often accompanied by pain, acid reflux, loss of appetite and loss of weight. Anaemia may occur. A small percentage of oesophageal cancers are identified during endoscopic surveillance of a precursor lesion, Barrett's oesophagus.

The symptoms overlap with stomach cancer, but the usual investigative strategy, upper gastrointestinal endoscopy, is the same for both cancers.

Most oesophageal cancers can be identified on endoscopy, and a biopsy taken. This can be under the clinical responsibility of primary care, though the procedure is usually performed in secondary care. Older imaging techniques, such as barium swallow are rarely used.

Clinical questions:

- **What is the risk of oesophageal cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected oesophageal cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in setting that may not directly translate to UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity. The evidence base is also limited by the fact that some of the positive predictive value estimates are based on low numbers of patients and a number of the studies do not provide different estimates for stomach and oesophageal cancer, but only provide one estimate for these cancers combined.

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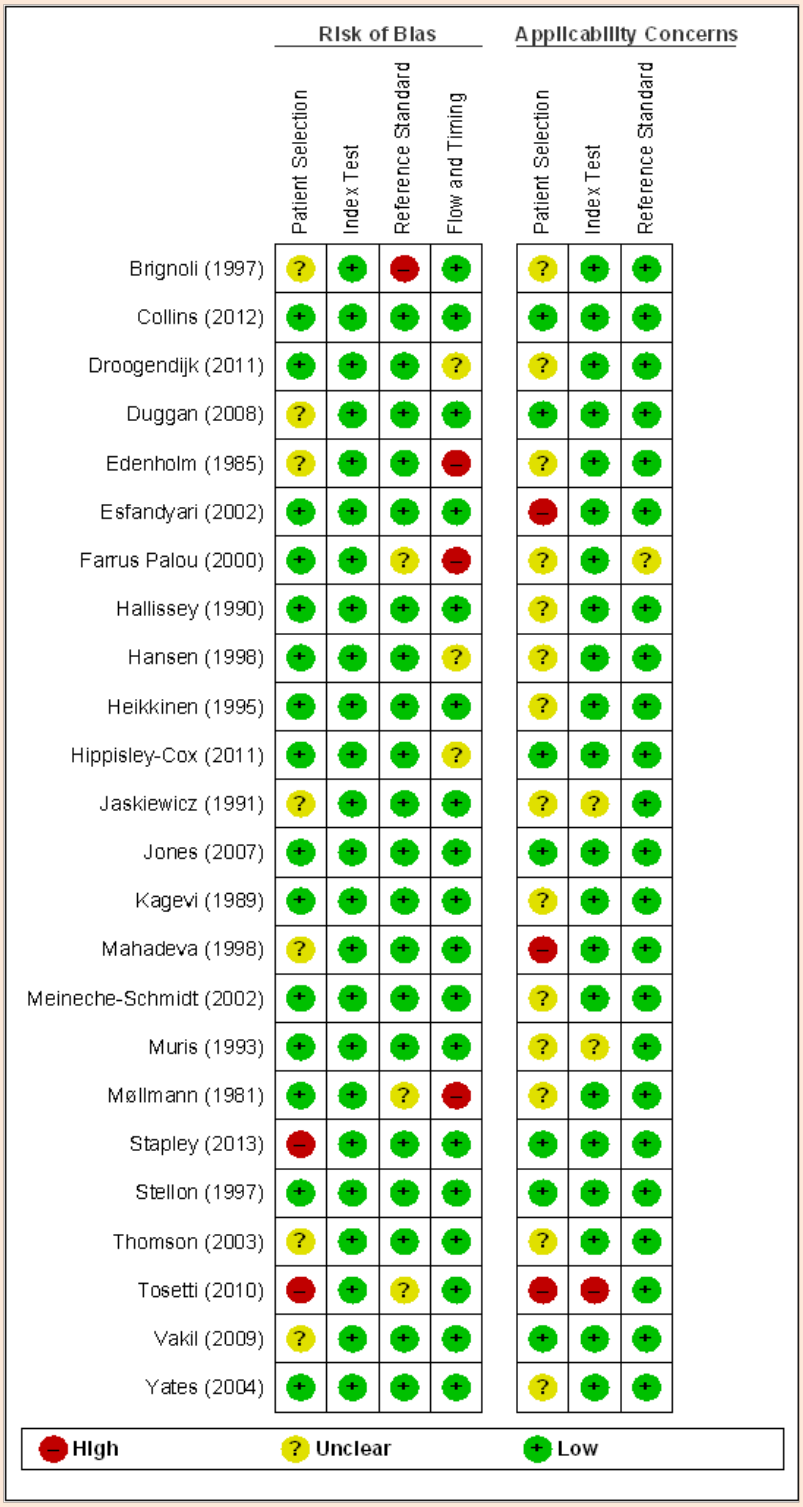

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Evidence statements

Abdominal pain (4 studies, N = 3,416,339) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.3% for oesophageal cancer. The studies were associated with 0-3 bias or applicability concerns (see also Tables 8-10).

Anaemia (8 studies, N = 3,417,170) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.94% for oesophageal cancer. The studies were associated with 0-4 bias or applicability concern (see also Tables 8-10).

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Dyspepsia (13 studies, N = 52,183) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.2% for oesophageal cancer. The studies were associated with 1-3 bias or applicability concerns (see also Tables 8-10).

Dysphagia (5 studies, N = 4,177,284) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.5% for oesophageal cancer. All the studies were associated with 0-1 bias or applicability concerns (see also Tables 8-10).

Other single symptoms (6 studies, N = 3,417,192) presenting in a primary care setting are associated with an overall positive predictive values for oesophageal cancer up to 2.3% (for haematemesis). The studies were associated with 0-4 bias or applicability concerns (see also Table 10).

Two or more symptom presenting in combination (3 studies, N = 43,319) in a primary care setting are associated with overall positive predictive values for oesophageal cancer up to 9.8% (for dysphagia and dyspepsia). The studies were associated with 1-3 bias or applicability concerns (see also Table 11).

Table 8: Oesophageal cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012) Hippisley-Cox (2011) Møllmann (1981)	Abdominal pain	All patients N = 3,389,979	0.23 (0.14-0.36)
Collins (2012) Droogendijk (2011) Farrus Palou (2000) Hippisley-Cox (2011) Stellon (1997) Yates (2004)	Anaemia	All patients N = 3,375,342	0.94 (0.54-1.64)
Brignoli (1997) Duggan (2008) Edenholm (1985) Hallissey (1990) Hansen (1998) Heikkinen (1995) Jaskiewicz (1991) Kagevi (1989) Meineche-Schmidt (2002) Thomson (2003) Vakil (2009)	Dyspepsia	All patients N = 11,403	0.25 (0.13-0.5)
Collins (2012) Esfandyari (2002) Hippisley-Cox (2011) Jones (2007) at 6 months	Dysphagia	All patients N = 4,136,936	4.96 (3.49-7.01)
Collins (2012) Esfandyari (2002) Hippisley-Cox (2011) Jones (2007) at 3 years	Dysphagia	All patients N = 4,136,936	5.11 (3.7-7.01)

Please note that the data from Stapley (2013) are not included in these meta-analyses due to the case-control design of the study, and the data from Mahadeva (1998) is not included due to the limited and different age range of the population. These data are instead reported in the table below entitled "Additional results reported by the

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individual papers: Single symptoms". When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead.

Table 9: Oesophageal cancer: Individual positive predictive values from the meta-analyses

Study	Symptom(s)	Patient group	PPVs % (95% CI); prevalence
Collins (2012)	Abdominal pain	All patients	0.2 (0.2-0.2) 437/246,998
Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/9,1627
Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	0 (0-0.8) 0/577
Collins (2012)	Anaemia	All patients	0.6 (0.5-0.8) 116/18,355
Droogendijk (2011)	Anaemia	All patients	0.35 (0.02-2.2) 1/287
Farrus Palou (2000)	Anaemia	All patients	0 (0-7.7) 0/58
Hippisley-Cox (2011)	Anaemia	All patients	1.1 (1-1.4) 119/10,349
Stellon (1997)	Anaemia	All patients (N = 26)	0 (0-16) 0/26
Yates (2004)	Anaemia	All patients	2.55 (1.35-4.66) 11/431 has UGI cancer: No distinction made between the different kinds
Brignoli (1997)	Dyspepsia	All patients	0 (0-0.58) 0/828
Duggan (2008)	Dyspepsia	All patients	0.27 (0.05-1.1) 2/753
Edenholm (1985)	Persisten epigastric pain/ulcer-like dyspepsia	All patients who received an UGI endoscopy	0.61 (0.03-3.8) 1/165
Hallissey (1990)	Dyspepsia	All patients	0.58 (0.33-0.98) 15/2,585
Hansen (1998)	Dyspepsia	All patients	1 (0.4-2.2) 6/612
Heikkinen (1995)	Dyspepsia	All patients	0.5 (0.09-2) 2/400
Jaskiewicz (1991)	Dyspepsia	All included patients	0 (0-0.8) 0/585
Kagevi (1989)	Dyspepsia	All included patients	0 (0-2.7) 0/172
Meineche-Schmidt (2002)	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1,491
Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040
Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741

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Study	Symptom(s)	Patient group	PPVs % (95% CI); prevalence
Collins (2012)	Dysphagia	All patients	4.2 (3.9-4.5) 810/19237
Esfandyari (2002)	Dysphagia	All patients	6 (2.5-13.1) 6/100
Hippisley-Cox (2011)	Dysphagia	All patients	7.8 (7.1-8.5) 434/5590
Jones (2007)	Dysphagia	All patients at 6 months	3.47 (3-4) 208/5999
Jones (2007)	Dysphagia	All patients at 3 years	3.85 (3.38-4.38) 231/5999

Table 10: Oesophageal cancer: Additional results reported by the individual papers: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Tosetti (2010)	Upper gastro-intestinal symptoms without alarming features	All patients	0.36 (0.02-2.3) 1/275
Muris (1993)	Non-acute abdominal complaints	All patients	0 (0-0.8) 0/578
Collins (2012)	Abdominal pain	Women	0.1 (0.1-0.1) 139/144266
		Men	0.3 (0.3-0.3) 298/102732
Stapley (2013)	Abdominal pain	Patients ≥ 55 years	0.3 (0.2-0.3)
Stapley (2013)	Epigastric pain	Patients ≥ 55 years	0.9 (0.8-1)
Collins (2012)	Anaemia	Women	0.4 (0.3-0.5) 49/13792
		Men	1.5 (1.1-1.9) 67/4563
Møllmann (1981)	Anaemia	Males	0 (0-44) 0/7
Stapley (2013)	Low haemoglobin	Patients ≥ 55 years	0.2 (0.2-109)
Stapley (2013)	Dyspepsia	Patients ≥ 55 years	0.7 (0.6-0.7)
Stapley (2013)	Dyspepsia (reported ≥ twice)	Patients ≥ 55 years	1.2 (1-1.5)
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.18 (0.03-0.71) 2/1127
		Patients ≥ 50 years old	0.24 (0.04-1) 2/829
		Patients ≥ 55 years old	0.18 (0.01-1.16) 1/554
		Patients ≥ 60 years old	0.3 (0.02-2) 1/323
Hansen (1998)	Ulcer-like dyspepsia	All patients	0.6 (0.03-3.9) 1/161
Hansen (1998)	Dysmotility-like dyspepsia	All patients	0 (0-2.9) 0/163

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hansen (1998)	Reflux-like dyspepsia	All patients	1.16 (0.2-4.6) 2/173
Hansen (1998)	Unclassifiable dyspepsia	All patients	0.9 (0.05-5.8) 1/107
Mahadeva (2008)	Dyspepsia	All patients (they were aged 18-45 years)	0 (0-1.1) 0/432
Collins (2012)	Dysphagia	Women	2.5 (2.2-2.8) 262/10391
		Men	6.2 (5.7-6.7) 548/8846
Jones	Dysphagia	Men (all ages) at 6 months	5.3 (4.4-6.2) 138/2628
		Men (all ages) at 3 years	5.7 (4.9-6.7) 150/2628
		Men < 45 years at 3 years	0.21 (0-1.15) 1/482
		Men 45-54 years at 3 years	4.03 (2.36-6.37) 17/422
		Men 55-64 years at 3 years	5.98 (4.1-8.39) 31/518
		Men 65-74 years at 3 years	9.03 (6.82-11.7) 52/576
		Men 75-84 years at 3 years	7.14 (5-9.84) 34/476
		Men ≥ 85 years at 3 years	9.74 (5.55-15.6) 15/154
Jones	Dysphagia	Women (all ages) at 6 months	2.1 (1.6-2.6) 70/3371
		Women (all ages) at 3 years	2.4 (1.9-3) 81/3371
		Women < 45 years at 3 years	0.16 (0-0.86) 1/642
		Women 45-54 years at 3 years	0.58 (0.12-1.68) 3/520
		Women 55-64 years at 3 years	1.92 (0.92-3.49) 10/522
		Women 65-74 years at 3 years	3.79 (2.47-5.55) 25/659
		Women 75-84 years at 3 years	4.03 (2.65-5.85) 26/645
		Women ≥ 85 years at 3 years	4.18 (2.41-6.7) 16/383
Stapley (2013)	Dysphagia	Patients ≥ 55 years	4.8 (4.3-5.9)
Stapley (2013)	Dysphagia (reported ≥ twice)	Patients ≥ 55 years	5.5 (4.2-7.9)
Collins (2012)	Appetite loss	All patients	0.6 (0.5-0.9) 37/5838

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Women	0.4 (0.2-0.7) 12/3317
		Men	1 (0.7-1.5) 25/2521
Hippisley-Cox (2011)	Appetite loss	All patients	1.1 (0.8-1.5) 35/3391
Møllmann (1981)	Weight loss and/or anorexia	All patients	0 (0-8.9) 0/50
Collins (2012)	Weight loss	All patients	0.8 (0.7-0.9) 218/28403
		Women	0.6 (0.4-0.7) 86/15465
		Men	1 (0.9-1.2) 132/12938
Hippisley-Cox (2011)	Weight loss	All patients	1.2 (1-1.4) 107/9170
Stapley (2013)	Weight loss	Patients ≥ 55 years	0.9 (0.7-1)
Collins (2012)	Haematemesis	All patients	1 (0.8-1.2) 110/10792
		Women	0.5 (0.3-0.7) 22/4630
		Men	1.4 (1.2-1.8) 88/6162
Hippisley-Cox (2011)	Haematemesis	All patients	2.3 (1.9-2.7) 101/4477
Stapley (2013)	Constipation	Patients ≥ 55 years	0.2 (0.2-0.2)
Stapley (2013)	Chest pain	Patients ≥ 55 years	0.2 (0.2-0.2)
Stapley (2013)	Reflux	Patients ≥ 55 years	0.6 (0.6-0.7)
Møllmann (1981)	Nausea and/or vomiting > 2 weeks	All patients	0 (0-12.3) 0/35
Stapley (2013)	Nausea/vomiting	Patients ≥ 55 years	0.6 (0.5-0.7)
Stapley (2013)	Nausea/vomiting reported ≥ twice	Patients ≥ 55 years	1 (0.8-1.2)
Stapley (2013)	Raised platelets	Patients ≥ 55 years	0.5 (0.4-0.5)
Stapley (2013) reported that all PPVs for symptom combinations in patients < 55 years were < 1%, and that the highest PPV in this age group was for dysphagia, 0.8 (0.4-1.5)%			
Møllmann (1981)	Gastrointestinal bleeding	All patients	0 (0-32) 0/11

Please note: The calculations of the positive predictive values differ between all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 11: Oesophageal cancer: Additional results reported by the individual papers: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Meineche-Schmidt (2002)	Dyspepsia and jaundice	All patients	0 (0-48.32) 0/6

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Meineche-Schmidt (2002)	Dyspepsia and black stools	All patients	0.91 (0.05-5.69) 1/110
Meineche-Schmidt (2002)	Dyspepsia and bloody stools	All patients	0.76 (0.04-4.81) 1/131
Stapley (2013)	Dysphagia and chest pain	Patients ≥ 55 years	5.8 (3.5-10.8)
Stapley (2013)	Dysphagia and loss of weight	Patients ≥ 55 years	9.2 (4.4-22.7)
Stapley (2013)	Dysphagia and abdominal pain	Patients ≥ 55 years	6.5 (3.5-13.5)
Stapley (2013)	Dysphagia and epigastric pain	Patients ≥ 55 years	9.3 (NR)
Stapley (2013)	Dysphagia and reflux	Patients ≥ 55 years	5 (3.3-8.4)
Stapley (2013)	Dysphagia and low haemoglobin	Patients ≥ 55 years	4.6 (3.4-6.6)
Stapley (2013)	Dysphagia and nausea/vomiting	Patients ≥ 55 years	7.3 (4.4-13.9)
Meineche-Schmidt (2002)	Dyspepsia and dysphagia	All patients	1.4 (0.04-4.36) 3/215
Stapley (2013)	Dysphagia and dyspepsia	Patients ≥ 55 years	9.8 (5.7-20.2)
Stapley (2013)	Dysphagia and raised platelets	Patients ≥ 55 years	6.1 (3.2-13.2)
Stapley (2013)	Dyspepsia and chest pain	Patients ≥ 55 years	0.7 (0.5-0.9)
Stapley (2013)	Dyspepsia and abdominal pain	Patients ≥ 55 years	1 (0.7-1.3)
Stapley (2013)	Dyspepsia and epigastric pain	Patients ≥ 55 years	1.4 (1-2)
Stapley (2013)	Dyspepsia and nausea/vomiting	Patients ≥ 55 years	1.3 (0.9-1.8)
Stapley (2013)	Dyspepsia and reflux	Patients ≥ 55 years	0.9 (0.7-1.2)
Meineche-Schmidt (2002)	Dyspepsia and weight loss	All patients	1.37 (0.35-4.28) 3/219
Stapley (2013)	Dyspepsia and loss of weight	Patients ≥ 55 years	2.1 (1.3-3.5)
Stapley (2013)	Dyspepsia and raised platelets	Patients ≥ 55 years	1.4 (0.9-2.2)
Meineche-Schmidt (2002)	Dyspepsia and anaemia	All patients	0 (0-11.71) 0/37
Stapley (2013)	Dyspepsia and low haemoglobin	Patients ≥ 55 years	1 (0.8-1.3)
Stapley (2013)	Constipation and chest pain	Patients ≥ 55 years	0.4 (0.3-0.5)
Stapley (2013)	Constipation and loss of weight	Patients ≥ 55 years	1.1 (0.8-1.7)
Stapley (2013)	Constipation and abdominal pain	Patients ≥ 55 years	0.4 (0.3-0.5)
Stapley (2013)	Constipation and epigastric pain	Patients ≥ 55 years	1.4 (0.8-2.3)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Stapley (2013)	Constipation and reflux	Patients ≥ 55 years	0.7 (0.5-1.1)
Stapley (2013)	Constipation and low haemoglobin	Patients ≥ 55 years	0.4 (0.4-0.5)
Stapley (2013)	Constipation and nausea/vomiting	Patients ≥ 55 years	0.6 (0.4-0.7)
Stapley (2013)	Constipation and dyspepsia	Patients ≥ 55 years	0.8 (0.6-1.1)
Stapley (2013)	Constipation and dysphagia	Patients ≥ 55 years	4.2 (2.7-7.2)
Stapley (2013)	Constipation and raised platelets	Patients ≥ 55 years	0.9 (0.6-1.4)
Stapley (2013)	Abdominal pain and chest pain	Patients ≥ 55 years	0.3 (0.3-0.4)
Stapley (2013)	Abdominal pain and epigastric pain	Patients ≥ 55 years	0.9 (0.7-1.2)
Stapley (2013)	Abdominal pain and reflux	Patients ≥ 55 years	0.6 (0.5-0.9)
Stapley (2013)	Abdominal pain and weight loss	Patients ≥ 55 years	1.4 (0.9-2.2)
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea and/or vomiting > 2 weeks	All patients	0 (0-1.6) 0/293
Stapley (2013)	Abdominal pain and nausea/vomiting	Patients ≥ 55 years	0.7 (0.5-0.9)
Stapley (2013)	Abdominal pain and low haemoglobin	Patients ≥ 55 years	0.5 (0.4-0.6)
Stapley (2013)	Abdominal pain and raised platelets	Patients ≥ 55 years	0.8 (0.6-1.1)
Møllmann (1981)	Upper abdominal pain > 2 weeks and gastrointestinal bleeding	All patients	0 (0-21) 0/19
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea/vomiting > 2 weeks and gastrointestinal bleeding	All patients	0 (0-44) 0/7
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea/vomiting > 2 weeks and weight loss/anorexia	All patients	0 (0-4) 0/116
Møllmann (1981)	Upper abdominal pain > 2 weeks and weight loss/anorexia and gastrointestinal bleeding	All patients	0 (0-20) 0/5
Møllmann (1981)	Upper abdominal pain > 2 weeks and weight loss/anorexia	All patients	0 (0-4.7) 0/98
Stapley (2013)	Chest pain and epigastric pain	Patients ≥ 55 years	0.9 (0.6-1.4)
Stapley (2013)	Chest pain and reflux	Patients ≥ 55 years	0.6 (0.5-0.9)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Stapley (2013)	Chest pain and weight loss	Patients ≥ 55 years	1.1 (0.7-1.8)
Stapley (2013)	Chest pain and nausea/vomiting	Patients ≥ 55 years	0.6 (0.4-0.8)
Stapley (2013)	Chest pain and low haemoglobin	Patients ≥ 55 years	0.3 (0.3-0.4)
Stapley (2013)	Chest pain and raised platelets	Patients ≥ 55 years	0.8 (0.6-1.2)
Stapley (2013)	Epigastric pain and reflux	Patients ≥ 55 years	1.5 (1-2.4)
Stapley (2013)	Epigastric pain and weight loss	Patients ≥ 55 years	4.2 (1.8-11)
Stapley (2013)	Epigastric pain and low haemoglobin	Patients ≥ 55 years	1.6 (1.1-2.2)
Stapley (2013)	Reflux and loss of weight	Patients ≥ 55 years	3.1 (1.5-6.7)
Stapley (2013)	Reflux and low haemoglobin	Patients ≥ 55 years	0.9 (0.7-1.2)
Stapley (2013)	Weight loss and low haemoglobin	Patients ≥ 55 years	1 (0.8-1.3)
Møllmann (1981)	Weight loss/anorexia and gastrointestinal bleeding	All patients	0 (0-80) 0/2
Møllmann (1981)	Weight loss/anorexia and gastrointestinal bleeding and nausea/vomiting > 2 week	All patients	0 (0-80) 0/2
Møllmann (1981)	Weight loss/anorexia and nausea/vomiting > 2 week	All patients	0 (0-16.6) 0/25
Stapley (2013)	Nausea/vomiting and weight loss	Patients ≥ 55 years	2.8 (1.7-4.8)
Stapley (2013)	Nausea/vomiting and epigastric pain	Patients ≥ 55 years	1.3 (0.9-2)
Stapley (2013)	Nausea/vomiting and reflux	Patients ≥ 55 years	2.3 (1.5-3.5)
Stapley (2013)	Nausea/vomiting and low haemoglobin	Patients ≥ 55 years	0.9 (0.7-1.1)
Stapley (2013)	Reflux and raised platelets	Patients ≥ 55 years	1.6 (0.9-2.9)
Stapley (2013)	Weight loss and raised platelets	Patients ≥ 55 years	1.8 (1.1-3)
Stapley (2013)	Nausea/vomiting and raised platelets	Patients ≥ 55 years	1.4 (1-2.1)
Stapley (2013)	Epigastric pain and raised platelets	Patients ≥ 55 years	1.9 (1-3.8)
Stapley (2013)	Low haemoglobin and raised platelets	Patients ≥ 55 years	0.6 (0.6-0.7)
Møllmann (1981)	Any of the inclusion symptoms + previous dyspepsia	All patients	0 (0-0.62) 0/773

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Møllmann (1981)	Any of the inclusion symptoms + no previous dyspepsia	All patients	0 (0-0.91) 0/524
Møllmann (1981)	Any of the inclusion symptoms + unchanged previous dyspepsia	All patients	0 (0-1.2) 0/407
Møllmann (1981)	Any of the inclusion symptoms + no previous or changed dyspepsia	All patients	0 (0-0.54) 0/890
Møllmann (1981)	Any of the inclusion symptoms + pain provoked by meals	All patients	0 (0-1.8) 0/257
Møllmann (1981)	Any of the inclusion symptoms + no pain provoked by meals	All patients	0 (0-0.52) 0/924
Møllmann (1981)	Any of the inclusion symptoms + relief of pain by meals	All patients	0 (0-0.7) 0/488
Møllmann (1981)	Any of the inclusion symptoms + no pain relief by meals	All patients	0 (0-2.8) 0/687
Møllmann (1981)	Any of the inclusion symptoms + irritable bowel syndrome	All patients	0 (0-2.8) 0/167
Møllmann (1981)	Any of the inclusion symptoms + no irritable bowel syndrome	All patients	0 (0-0.42) 0/1129

Please note: The calculations of the positive predictive values differ between the all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = not reported.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of upper gastrointestinal endoscopy, barium swallow or chest X-ray in patients with suspected oesophageal cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people:** • **with dysphagia or** • **aged 55 and over with weight loss and any of upper abdominal pain or reflux or dyspepsia. [new 2015]** **Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people with**

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	haematemesis. [new 2015] **Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people aged 55 or over with:** • **weight loss and nausea/vomiting or** • **reflux/dyspepsia and nausea/vomiting or** • **upper abdominal pain and raised platelet count. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of oesophageal cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict oesophageal cancer. Investigations in primary care for oesophageal cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	Signs and symptoms of oesophageal cancer The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of moderate-high quality. It was noted that a number of the included studies had merged stomach and oesophageal cancer making it difficult to tease out the specifics related to oesophageal cancer. The GDG also noted that for some of the symptoms the positive predictive values were based on very few patients and that this was likely to make these estimates unreliable. Investigations in primary care for oesophageal cancer No evidence was found pertaining to the diagnostic performance of chest x-ray, upper gastrointestinal endoscopy or barium swallow in primary care patients with suspected oesophageal cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with oesophageal cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without oesophageal cancer who get inappropriately referred whilst maximising the number of people with oesophageal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG had previously agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. However, the GDG noted that the availability of urgent direct access upper gastrointestinal endoscopy allows the GP to triage people presenting with symptoms of suspected oesophageal cancer prior to a suspected cancer pathway referral and thereby ensure that the right patients are referred based on the test results. The GDG noted that this would result in a slight delay for the people for whom a suspected cancer pathway referral is warranted, but the GDG judged that this slight delay would be

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	acceptable because it would prevent the suspected cancer pathway referral system from becoming overburdened with unnecessary referrals, thereby allowing it to operate more efficiently for those people on the suspected cancer pathway. The GDG also noted the absence of evidence for direct access upper gastrointestinal endoscopy in people presenting to primary care, but the GDG, based on clinical experience, judged that the accuracy of this test is acceptable. The GDG therefore decided not to recommend symptoms which should prompt a suspected cancer pathway referral but instead to recommend which symptoms should prompt an urgent direct access upper gastrointestinal endoscopy. By doing this the GDG hoped to refine the group of symptomatic people being referred to those with the greatest risk of having oesophageal cancer. The GDG chose the symptoms that prompted urgent direct access upper gastrointestinal endoscopy based on the positive predictive values presented in the evidence and based the specified age cut-offs on those used in the studies that comprised the evidence for the individual symptoms or symptom combinations. The GDG acknowledged that no other symptoms had a high enough positive predictive value for oesophageal cancer to warrant making recommendations on them. Although the PPV for oesophageal cancer in people with dysphagia only exceeds 3% in men over 45 and women over 65, when formulating their recommendation for urgent direct access upper gastrointestinal endoscopy to assess for oesophageal cancer the GDG also took account of their corresponding recommendation for stomach cancer, which has no age limit for dysphagia. Since dysphagia can indicate either oesophageal or stomach cancer, and the recommended action is the same, the GDG agreed to remove the age limit in the recommendation for urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people with dysphagia. The GDG noted that the distinction between epigastric pain, upper abdominal pain, dyspepsia and reflux to some extent is artificial and that there is significant overlap in the practical use of these terms. The GDG therefore decided to use upper abdominal pain rather than epigastric pain as the former term is more inclusive. Similarly, the GDG decided to make the same recommendation for dyspepsia as for reflux to take into account the overlap in the recording of these symptoms. The GDG hoped that this would ensure that variations in use of these terms would not stop any person from being investigated as recommended.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for urgent direct access upper gastrointestinal endoscopy is likely to result in a cost increase due to an increase number of endoscopies performed. However, this cost increase is likely to be counteracted to some extent by a cost saving from an optimised diagnostic process that will see an increase in the proportion of patients being referred on a suspected cancer pathway who

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	have oesophageal cancer and a decrease in the number of patients without oesophageal cancer being referred.
Other considerations	The GDG recognised that to implement these recommendations, there may initially be some capacity issues in some localities as urgent endoscopies are harder to accommodate than non-urgent endoscopies.

8.21 Pancreatic cancer

Nearly 9,000 new pancreatic cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with pancreatic cancer every 3-5 years. Most occur in the exocrine pancreas, though endocrine tumours also occur. Five year survival is below 5%.

Pancreatic cancer can present with a number of different symptoms, and there are often multiple symptoms simultaneously. Symptoms include pain, loss of appetite and weight. Lesions near the head of the pancreas may lead to obstructive jaundice. Endocrine cancers may produce symptoms from secretion of hormones such as insulin.

There is no standard pathway for all features of possible pancreatic cancer. CT provides more complete assessment for pancreatic cancer although ultrasound may also be of some use. Interpretation of pancreatic imaging is often performed by sub-specialist radiologists. Definitive diagnosis requires biopsy, often guided by imaging. This is performed in secondary care.

Clinical questions:

- **What is the risk of pancreatic cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected pancreatic cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and applicability concerns to note in terms of patient selection were that this was not clearly consecutive or random in four of the studies, with three of these studies conducted in a setting that is not clearly directly representative of UK-based primary care. The other bias and applicability concerns to note include missing data, population with restricted age range, short follow up and underspecified presenting symptoms. These issues should all be born in mind when evaluating the evidence.

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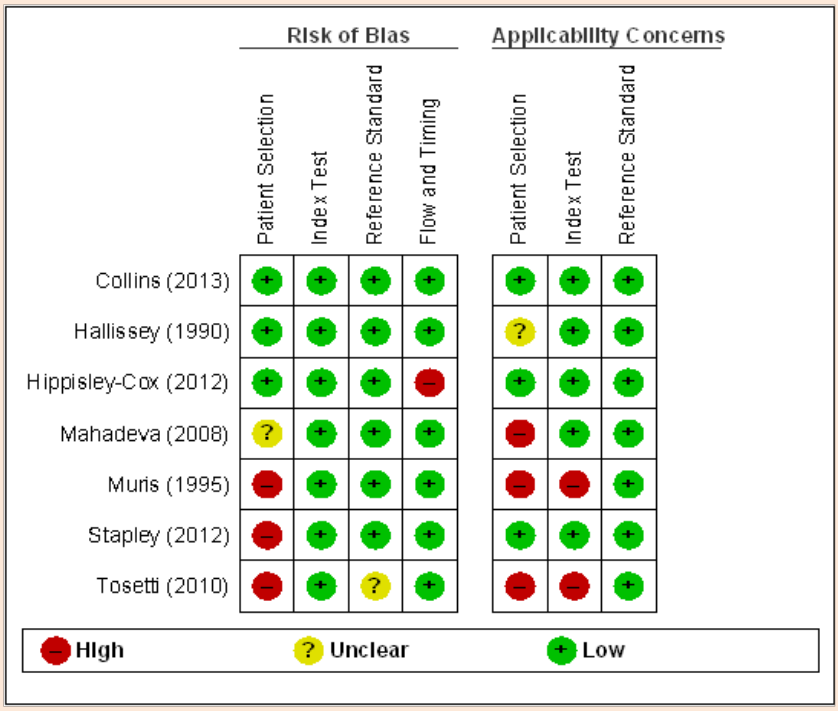

Evidence statements

For pancreatic cancer the positive predictive values of single symptoms (7 studies, N = 3,146,347) presenting in primary care ranged from 0.06% (for back pain) to 21.6% (for jaundice). The included studies were associated with 0-4 bias/applicability concerns (see also Table 12).

For pancreatic cancer the positive predictive values of symptom combinations (1 study, N = 20,094) presenting in primary care ranged from 0.2% (for diarrhoea in combination with either constipation, nausea/vomiting or back pain) to 22.3% (for new onset diabetes combined with jaundice). The included study was associated with 1 bias concern (see also Table 13).

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Table 12: Pancreatic cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Collins (2013)	Abdominal pain	All patients	0.14 (0.12-0.15)
		Women	0.1 (0.09-0.12)
		Men	0.19 (0.16-0.22)
Hippisley-Cox (2012)	Abdominal pain	All patients	0.3 (0.3-0.4)
Stapley (2012)	Abdominal pain	All patients	0.2 (0.19-0.22)
Stapley (2012)	Abdominal pain	Patients ≥ 60 years	0.3 (0.3-0.4)
Stapley (2012)	Abdominal pain (attended ≥ twice)	Patients ≥ 60 years	1 (0.8-1.2)
Hallissey (1990)	Dyspepsia	All patients	0.23 (0.09-0.53) 6/2585
Mahadeva (2008)	Dyspepsia	All patients (they were aged 18-45 years)	0.23 (0.01-1.49) 1/432
Hippisley-Cox (2012)	Abdominal distension	All patients	0.3 (0.1-0.5)
Collins (2013)	Abdominal distension	Women	0.16 (0.07-0.34)
Muris (1995)	Non-acute abdominal complaints	All patients	0.21 (0.04-0.86) 2/933

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Hippisley-Cox (2012)	Dysphagia	All patients	0.2 (0.1-0.4)
Collins (2013)	Dysphagia	Men	0.1 (0.05-0.19)
Collins (2013)	Appetite loss	All patients	0.39 (0.26-0.59)
		Women	0.32 (0.17-0.59)
		Men	0.49 (0.27-0.86)
Hippisley-Cox (2012)	Appetite loss	All patients	0.8 (0.5-1.2)
Collins (2013)	Weight loss	All patients	0.28 (0.22-0.35)
		Women	0.16 (0.11-0.24)
		Men	0.42 (0.32-0.54)
Hippisley-Cox (2012)	Weight loss	All patients	0.6 (0.5-0.8)
Stapley (2012)	Weight loss	All patients	0.44 (0.36-0.55)
Stapley (2012)	Weight loss	Patients ≥ 60 years	0.8 (0.7-1)
Stapley (2012)	Nausea/vomiting	All patients	0.19 (0.17-0.21)
Stapley (2012)	Nausea/vomiting	Patients ≥ 60 years	0.3 (0.3-0.4)
Stapley (2012)	Back pain	All patients	0.06 (0.05-0.07)
Stapley (2012)	Back pain	Patients ≥ 60 years	0.1 (0.1-0.1)
Stapley (2012)	Back pain (attended ≥ twice)	Patients ≥ 60 years	0.2 (0.1-0.2)
Stapley (2012)	Constipation	All patients	0.1 (0.09-0.11)
Stapley (2012)	Constipation	Patients ≥ 60 years	0.2 (0.2-0.2)
Collins (2013)	Constipation	Males	0.21 (0.11-0.38)
Stapley (2012)	Diarrhoea	All patients	0.09 (0.08-0.11)
Stapley (2012)	Diarrhoea	Patients ≥ 60 years	0.2 (0.2-0.2)
Stapley (2012)	Malaise	All patients	0.12 (0.1-0.15)
Stapley (2012)	Malaise	Patients ≥ 60 years	0.2 (0.2-0.3)
Stapley (2012)	Jaundice	All patients	12.9 (7.89-27.1)
Stapley (2012)	Jaundice	Patients ≥ 60 years	21.6 (14-52)
Stapley (2012)	Jaundice (attended ≥ twice)	Patients ≥ 60 years	31.6 (NR)
Stapley (2012)	New-onset diabetes	All patients	0.09 (0.08-0.1)
Stapley (2012)	New-onset diabetes	Patients ≥ 60 years	0.2 (0.2-0.2)
Tosetti (2010)	Upper gastro-intestinal symptoms without alarming features	All patients	0.36 (0.02-2.33) 1/275
Stapley (2012)	Abnormal liver function	All patients	0.16 (0.15-0.17)
Stapley (2012)	Low haemoglobin	All patients	0.1 (0.09-0.11)
Stapley (2012)	Raised inflammatory markers	All patients	0.16 (0.15-0.17)
Stapley (2012)	The authors report that in patients ≥ 70 years the PPVs for most symptoms were 1.5-4.5 times higher than in patients < 70 years.		

Stapley (2012) calculated the positive predictive values using Bayesian statistics. Meta-analyses are not undertaken as the Stapley data cannot be included due to the case-control design of the study. NR = not reported.

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Table 13: Pancreatic cancer: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Stapley (2012)	Abdominal pain and back pain	Patients ≥ 60 years	0.4 (0.3-0.5)
Stapley (2012)	Abdominal pain and constipation	Patients ≥ 60 years	0.5 (0.4-0.7)
Stapley (2012)	Abdominal pain and malaise	Patients ≥ 60 years	0.6 (0.4-0.8)
Stapley (2012)	Abdominal pain and diarrhoea	Patients ≥ 60 years	0.4 (0.3-0.5)
Stapley (2012)	Abdominal pain and nausea/vomiting	Patients ≥ 60 years	0.9 (0.7-1.2)
Stapley (2012)	Abdominal pain and loss of weight	Patients ≥ 60 years	2.5 (1.5-4.4)
Stapley (2012)	Abdominal pain and new onset diabetes	Patients ≥ 60 years	0.9 (0.7-1.1)
Stapley (2012)	Abdominal pain and jaundice	Patients ≥ 60 years	15 (NR)
Stapley (2012)	Back pain and constipation	Patients ≥ 60 years	0.3 (0.2-0.4)
Stapley (2012)	Back pain and malaise	Patients ≥ 60 years	0.3 (0.2-0.6)
Stapley (2012)	Back pain and diarrhoea	Patients ≥ 60 years	0.2 (0.1-0.3)
Stapley (2012)	Back pain and nausea/vomiting	Patients ≥ 60 years	0.3 (0.2-0.5)
Stapley (2012)	Back pain and loss of weight	Patients ≥ 60 years	2 (1-4.3)
Stapley (2012)	Back pain and new onset diabetes	Patients ≥ 60 years	0.3 (0.2-0.4)
Stapley (2012)	Back pain and jaundice	Patients ≥ 60 years	8.9 (NR)
Stapley (2012)	Diarrhoea and constipation	Patients ≥ 60 years	0.2 (0.1-0.3)
Stapley (2012)	Diarrhoea and malaise	Patients ≥ 60 years	0.3 (0.1-0.5)
Stapley (2012)	Diarrhoea and nausea/vomiting	Patients ≥ 60 years	0.2 (0.2-0.3)
Stapley (2012)	Diarrhoea and loss of weight	Patients ≥ 60 years	2.7 (NR)
Stapley (2012)	Diarrhoea and new onset diabetes	Patients ≥ 60 years	0.4 (0.3-0.5)
Stapley (2012)	Diarrhoea and jaundice	Patients ≥ 60 years	> 10*
Stapley (2012)	Constipation and malaise	Patients ≥ 60 years	0.3 (0.2-0.5)
Stapley (2012)	Nausea/vomiting and malaise	Patients ≥ 60 years	0.5 (0.3-0.8)
Stapley (2012)	Constipation and weight loss	Patients ≥ 60 years	1.5 (0.8-3)
Stapley (2012)	Constipation and nausea/vomiting	Patients ≥ 60 years	0.6 (0.4-0.8)
Stapley (2012)	Nausea/vomiting and weight loss	Patients ≥ 60 years	2.2 (1.1-4.6)
Stapley (2012)	Weight loss and new onset diabetes	Patients ≥ 60 years	1.6 (1-2.9)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Stapley (2012)	New onset diabetes and jaundice	Patients ≥ 60 years	22.3 (NR)
Stapley (2012)	Constipation and new onset diabetes	Patients ≥ 60 years	0.4 (0.3-0.6)
Stapley (2012)	Malaise and new onset diabetes	Patients ≥ 60 years	0.5 (0.3-0.9)
Stapley (2012)	Nausea/vomiting and new onset diabetes	Patients ≥ 60 years	0.7 (0.5-1)
Stapley (2012)	Weight loss and malaise	Patients ≥ 60 years	0.9 (0.4-2.1)
Stapley (2012)	Jaundice and nausea/vomiting	Patients ≥ 60 years	14.6 (NR)
Stapley (2012)	Jaundice and constipation	Patients ≥ 60 years	>10*
Stapley (2012)	Jaundice and malaise	Patients ≥ 60 years	>10*
Stapley (2012)	Jaundice and weight loss	Patients ≥ 60 years	>10*

*Stapley (2012) calculated the positive predictive values using Bayesian statistics. NR = not reported. * > 40 cases and 0 controls had these symptoms.*

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, MRI, CEA, Beta hCG or tumour markers CA19-9 and CA72-4 in patients with suspected pancreatic cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for pancreatic cancer if they are aged 40 and over and have jaundice. [new 2015]** **Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms:** • **diarrhoea** • **back pain** • **abdominal pain** • **nausea/vomiting** • **constipation** • **new-onset diabetes. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of pancreatic cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict pancreatic cancer. <u>Investigations in primary care for pancreatic cancer</u> The GDG identified sensitivity, specificity, positive predictive

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	values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of pancreatic cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but generally was of moderate to high quality. The GDG noted that the evidence did not distinguish between obstructive and non-obstructive jaundice, but instead grouped these two together as jaundice. <u>Investigations in primary care for pancreatic cancer</u> No evidence was found pertaining to the diagnostic accuracy of CT scan, ultrasound, MRI, CEA, Beta hCG or tumour markers CA19-9 and CA72-4 in primary care patients with suspected pancreatic cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with pancreatic cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without pancreatic cancer who get inappropriately referred whilst maximising the number of people with pancreatic cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with pancreatic cancer outweighed the disadvantages to those without. The GDG noted, based on the evidence, that jaundice presenting in a primary care setting was associated with a positive predictive value of above 3% for pancreatic cancer. They therefore recommended this symptom should prompt a suspected cancer pathway referral. The GDG also noted that the evidence for jaundice was established in a population aged 40 years and above; that the incidence of pancreatic cancer in people below 40 years is extremely low, and that jaundice in people aged below 40 years is much more likely to be caused by other conditions (such as alcoholism or hepatitis) than pancreatic cancer. The GDG therefore agreed to refer only people aged 40 and above who present with jaundice. The GDG noted that people under 40 with jaundice would usually be referred on non-cancer related pathways. The GDG noted the absence of evidence for investigations for pancreatic cancer in primary care. Based on their clinical experience they considered that whilst CT scan and ultrasound are investigations commonly used to diagnose pancreatic cancer in secondary care, they could have value as investigations in primary care to determine if a suspected cancer pathway referral was needed. The GDG acknowledged that ultrasound is only able to image the head of the pancreas, and is associated with both false

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	positives and negatives. In addition cancer in the head of the pancreas can be identified by the presence of jaundice. A CT scan can image the whole pancreas but is associated with the potential risk of radiation late effects. The GDG considered that the clinical benefits of investigation performed in primary care would be to expedite pancreatic cancer diagnosis in people whose symptoms may otherwise not be investigated. The GDG noted, based on the evidence, that weight loss presenting with diarrhoea, back pain, abdominal pain, nausea/vomiting, constipation or new diabetes are also associated with an appreciable risk of pancreatic cancer in people aged 60 and above. However, the GDG also noted that these symptoms are also associated with other types of cancer, some of which are more common than pancreatic cancer, such as colorectal, ovarian and prostate. Consequently it was possible that some people without pancreatic cancer may be investigated unnecessarily. The GDG agreed that the benefits of earlier diagnosis outweighed the potential harms. Whilst the GDG acknowledged that there was no evidence on which to base a timeframe for performing the investigation, they felt it was important not to introduce further delay to the diagnostic process since this was a cancer that tends to present late. A quicker scan would also enable symptom relief and treatment to start sooner. Therefore an urgent scan was recommended. The GDG therefore decided to recommend further investigation in primary care with urgent CT scan for people aged 60 and above for clinical scenarios where urgent referral is not warranted, based on symptoms at presentation, but pancreatic cancer is still a small possibility.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation made for jaundice could result in a small increase in the number of referrals because the recommendation is for jaundice as a whole and not just obstructive jaundice, as in the previous guidance. This increase is however likely to be counteracted by a small decrease in referrals because an age limit has now been included. The GDG acknowledged that CT scans are not as widely available in primary care as ultrasound and more expensive. However a CT scan can image the whole pancreas, whilst ultrasound can only image the head. The GDG therefore considered that a CT scan would be the most appropriate investigation in primary care. However, since it was not possible to do an analysis of the cost-effectiveness of these different investigations, due to a lack of directly relevant data, the GDG agreed to include ultrasound as an option where CT scans were not available. The GDG noted that the recommendation for an urgent CT scan is likely to result in a cost increase due to an increased number of CT scans performed. However, this cost increase is likely to

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	be counteracted by a cost saving from an optimised diagnostic process that will see an increase in the number of patients being referred to the right clinic after an abnormal CT scan. These patients could otherwise potentially be referred, consecutively, to three different suspected cancer clinics due to the generic nature of the presenting symptoms.
Other considerations	The GDG recognised that to implement these recommendations, there may initially be some capacity issues in some localities as urgent CT scans are harder to accommodate than non-urgent CT scans.

8.3 Stomach cancer

Over 7,000 new stomach cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with stomach cancer every 3-5 years. It is seen in both sexes, though two-thirds of new diagnoses are in males. Five year survival is approximately 20%.

Stomach cancer can present with a number of different symptoms, including dysphagia, pain, acid reflux, loss of appetite and loss of weight. Anaemia may also be a presenting feature.

The symptoms overlap with oesophageal cancer, but the usual investigative strategy, upper gastrointestinal endoscopy, is the same for both cancers. Most stomach cancers can be identified on endoscopy, and a biopsy taken. In some areas, this is currently available under the clinical responsibility of primary care. Older imaging techniques, such as barium meal, are rarely used.

Clinical questions:

- **What is the risk of stomach cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected stomach cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in a setting that may not directly translate to UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity. The evidence base is also limited by the fact that some of the positive predictive value estimates are based on low numbers of patients and a number of the studies do not provide different estimates for stomach and oesophageal cancer, but only provide one estimate for these cancers combined.

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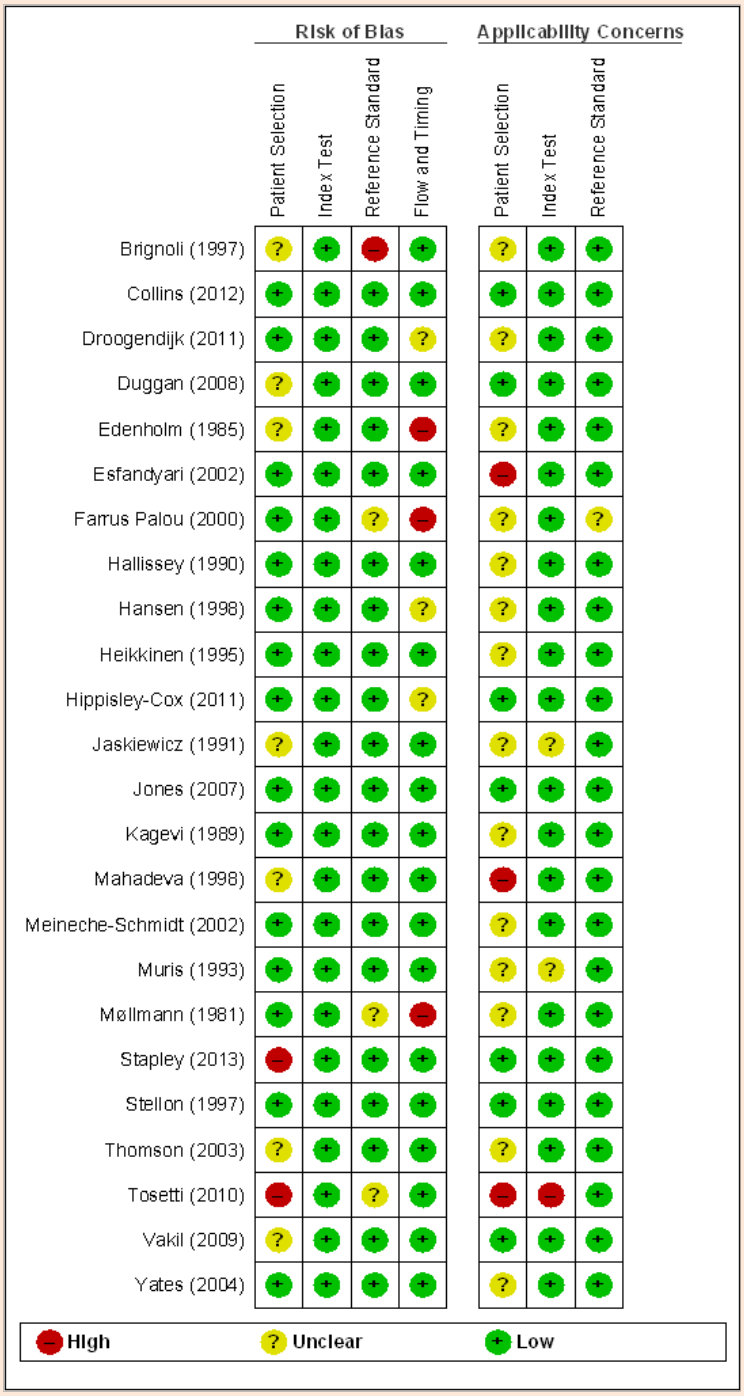

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Evidence statements

Abdominal pain (4 studies, N = 3416339) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.34% for stomach cancer. The studies were associated with 0-3 bias or applicability concerns (see also Tables 14-16).

Anaemia (8 studies, N = 3417170) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.09% for stomach cancer. The studies were associated with 0-4 bias or applicability concern (see also Tables 14-16).

Dyspepsia (13 studies, N = 52183) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.2% for stomach cancer. The studies were associated with 1-3 bias or applicability concerns (see also Tables 14-16).

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Dysphagia (5 studies, N = 4177284) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.5% for stomach cancer. All the studies were associated with 0-1 bias or applicability concerns (see also Tables 14-16).

Other single symptoms (6 studies, N = 3417192) presenting in a primary care setting are associated with an overall positive predictive values for stomach cancer up to 2.3% (for haematemesis). The studies were associated with 0-4 bias or applicability concerns (see also Table 16).

Two or more symptom presenting in combination (3 studies, N = 43319) in a primary care setting are associated with overall positive predictive values for stomach cancer ranging from 0% (dyspepsia with jaundice or anaemia, for 'gastrointestinal bleeding and nausea/vomiting and upper abdominal pain', and for 'gastrointestinal bleeding and anorexia/weightloss' with or without nausea/vomiting) to 20% (for 'upper abdominal pain and weight loss/anorexia and gastrointestinal bleeding'), but some of these positive predictive values were based on bvery low numbers of patients. The studies were associated with 1-3 bias or applicability concerns (see also Table 17).

Table 14: Stomach cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012) Hippisley-Cox (2011) Møllmann (1981)	Abdominal pain	All patients N = 3389979	0.34 (0.16-0.71)
Collins (2012) Droogendijk (2011) Farrus Palou (2000) Hippisley-Cox (2011) Stellon (1997) Yates (2004)	Anaemia	All patients N = 3375342	1.09 (0.67-1.77)
Brignoli (1997) Duggan (2008) Edenholm (1985) Hallissey (1990) Hansen (1998) Heikkinen (1995) Jaskiewicz (1991) Kagevi (1989) Meineche-Schmidt (2002) Thomson (2003) Vakil (2009)	Dyspepsia	All patients N = 11403	0.65 (0.33-1.3)
Collins (2012) Esfandyari (2002) Hippisley-Cox (2011) Jones (2007)	Dysphagia	All patients N = 4136936	3.6 (1.58-8.01)

Please note that the data from Stapley (2013) are not included in these meta-analyses due to the case-control design of the study, and the data from Mahadeva (1998) is not included due to the limited and different age range of the population. These data are instead reported in the table below entitled "Additional results reported by the individual papers: Single symptoms". When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead.

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Table 15: Stomach cancer: Individual positive predictive values from the meta-analyses

Study	Symptom(s)	Patient group	PPVs % (95% CI); prevalence
Collins (2012)	Abdominal pain	All patients	0.2 (0.2-0.2) 437/246998
Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/91627
Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	1 (0.4-2.4) 6/577
Collins (2012)	Anaemia	All patients	0.6 (0.5-0.8) 116/18355
Droogendijk (2011)	Anaemia	All patients	1.04 (0.27-3.28) 3/287
Farrus Palou (2000)	Anaemia	All patients	1.7 (0.09-10.5) 1/58
Hippisley-Cox (2011)	Anaemia	All patients	1.1 (1-1.4) 119/10349
Stellon (1997)	Anaemia	All patients (N = 26)	0 (0-16) 0/26
Yates (2004)	Anaemia	All patients	2.55 (1.35-4.66) 11/431 has UGI cancer: No distinction made between the different kinds
Brignoli (1997)	Dyspepsia	All patients	0.4 (0.09-1.14) 3/828
Duggan (2008)	Dyspepsia	All patients	0.27 (0.05-1.1) 2/753
Edenholm (1985)	Persisten epigastric pain/ulcer-like dyspepsia	All patients who received an UGI endoscopy	1.2 (0.21-4.77) 2/165
Hallissey (1990)	Dyspepsia	All patients	2.28 (1.76-3) 59/2585
Hansen (1998)	Dyspepsia	All patients	1 (0.4-2.2) 6/612
Heikkinen (1995)	Dyspepsia	All patients	1.75 (0.8-3.7) 7/400
Jaskiewicz (1991)	Dyspepsia	All included patients	2.7 (1.6-4.5) 16/585
Kagevi (1989)	Dyspepsia	All included patients	1.16 (0.2-4.6) 2/172
Meineche-Schmidt (2002)	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1491
Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040
Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741
Collins (2012)	Dysphagia	All patients	4.2 (3.9-4.5) 810/19237

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Study	Symptom(s)	Patient group	PPVs % (95% CI); prevalence
Esfandyari (2002)	Dysphagia	All patients	6 (2.5-13.1) 6/100
Hippisley-Cox (2011)	Dysphagia	All patients	7.8 (7.1-8.5) 434/5590
Jones (2007)	Dysphagia	All patients	0.78 (0.58-1.05) 47/5999

Table 16: Stomach cancer: Additional results reported by the individual papers: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Tosetti (2010)	Upper gastro-intestinal symptoms without alarming features	All patients	0 (0-1.7) 0/275
Muris (1993)	Non-acute abdominal complaints	All patients	0 (0-0.8) 0/578
Collins (2012)	Abdominal pain	Women	0.1 (0.1-0.1) 139/144266
		Men	0.3 (0.3-0.3) 298/102732
Stapley (2013)	Abdominal pain	Patients ≥ 55 years	0.3 (0.2-0.3)
Stapley (2013)	Epigastric pain	Patients ≥ 55 years	0.9 (0.8-1)
Collins (2012)	Anaemia	Women	0.4 (0.3-0.5) 49/13792
		Men	1.5 (1.1-1.9) 67/4563
Møllmann (1981)	Anaemia	Men	0 (0-44) 0/7
Stapley (2013)	Low haemoglobin	Patients ≥ 55 years	0.2 (0.2-109)
Jaskiewicz (1991)	Dyspepsia	Males	3.4 (1.8-6) 12/355
		Females	1.7 (0.6-4.7) 4/230
Stapley (2013)	Dyspepsia	Patients ≥ 55 years	0.7 (0.6-0.7)
Stapley (2013)	Dyspepsia (reported ≥ twice)	Patients ≥ 55 years	1.2 (1-1.5)
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.27 (0.07-0.84) 3/1127
		Patients ≥ 50 years old	0.36 (0.09-1.15) 3/829
		Patients ≥ 55 years old	0 (0-0.86) 0/554
		Patients ≥ 60 years old	0 (0-1.47) 0/323
Hansen (1998)	Ulcer-like dyspepsia	All patients	0.6 (0.03-3.9) 1/161
Hansen (1998)	Dysmotility-like dyspepsia	All patients	0 (0-2.9) 0/163

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hansen (1998)	Reflux-like dyspepsia	All patients	1.16 (0.2-4.6) 2/173
Hansen (1998)	Unclassifiable dyspepsia	All patients	0.9 (0.05-5.8) 1/107
Mahadeva (2008)	Dyspepsia	All patients (they were aged 18-45 years)	0 (0-1.1) 0/432
Collins (2012)	Dysphagia	Women	2.5 (2.2-2.8) 262/10391
		Men	6.2 (5.7-6.7) 548/8846
Jones (2007)	Dysphagia	Women	0.5 (0.3-0.8) 17/3371
		Men	1.14 (0.79-1.65) 30/2628
Stapley (2013)	Dysphagia	Patients ≥ 55 years	4.8 (4.3-5.9)
Stapley (2013)	Dysphagia (reported ≥ twice)	Patients ≥ 55 years	5.5 (4.2-7.9)
Collins (2012)	Appetite loss	All patients	0.6 (0.5-0.9) 37/5838
		Women	0.4 (0.2-0.7) 12/3317
		Men	1 (0.7-1.5) 25/2521
Hippisley-Cox (2011)	Appetite loss	All patients	1.1 (0.8-1.5) 35/3391
Møllmann (1981)	Weight loss and/or anorexia	All patients	2 (0.1-12) 1/50
Collins (2012)	Weight loss	All patients	0.8 (0.7-0.9) 218/28403
		Women	0.6 (0.4-0.7) 86/15465
		Men	1 (0.9-1.2) 132/12938
Hippisley-Cox (2011)	Weight loss	All patients	1.2 (1-1.4) 107/9170
Stapley (2013)	Weight loss	Patients ≥ 55 years	0.9 (0.7-1)
Collins (2012)	Haematemesis	All patients	1 (0.8-1.2) 110/10792
		Women	0.5 (0.3-0.7) 22/4630
		Men	1.4 (1.2-1.8) 88/6162
Hippisley-Cox (2011)	Haematemesis	All patients	2.3 (1.9-2.7) 101/4477
Stapley (2013)	Constipation	Patients ≥ 55 years	0.2 (0.2-0.2)
Stapley (2013)	Chest pain	Patients ≥ 55 years	0.2 (0.2-0.2)
Stapley (2013)	Reflux	Patients ≥ 55 years	0.6 (0.6-0.7)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Møllmann (1981)	Nausea and/or vomiting > 2 weeks	All patients	0 (0-12.3) 0/35
Stapley (2013)	Nausea/vomiting	Patients ≥ 55 years	0.6 (0.5-0.7)
Stapley (2013)	Nausea/vomiting reported ≥ twice	Patients ≥ 55 years	1 (0.8-1.2)
Stapley (2013)	Raised platelets	Patients ≥ 55 years	0.5 (0.4-0.5)
Stapley (2013) reported that all PPVs for symptom combinations in patients < 55 years were < 1%, and that the highest PPV in this age group was for dysphagia, 0.8 (0.4-1.5)%			
Møllmann (1981)	Gastrointestinal bleeding	All patients	0 (0-32) 0/11

Please note: The calculations of the positive predictive values differ between all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 17: Stomach cancer: Additional results reported by the individual papers: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Meineche-Schmidt (2002)	Dyspepsia and jaundice	All patients	0 (0-48.32) 0/6
Meineche-Schmidt (2002)	Dyspepsia and black stools	All patients	0.91 (0.05-5.69) 1/110
Meineche-Schmidt (2002)	Dyspepsia and bloody stools	All patients	0.76 (0.04-4.81) 1/131
Stapley (2013)	Dysphagia and chest pain	Patients ≥ 55 years	5.8 (3.5-10.8)
Stapley (2013)	Dysphagia and loss of weight	Patients ≥ 55 years	9.2 (4.4-22.7)
Stapley (2013)	Dysphagia and abdominal pain	Patients ≥ 55 years	6.5 (3.5-13.5)
Stapley (2013)	Dysphagia and epigastric pain	Patients ≥ 55 years	9.3 (NR)
Stapley (2013)	Dysphagia and reflux	Patients ≥ 55 years	5 (3.3-8.4)
Stapley (2013)	Dysphagia and low haemoglobin	Patients ≥ 55 years	4.6 (3.4-6.6)
Stapley (2013)	Dysphagia and nausea/vomiting	Patients ≥ 55 years	7.3 (4.4-13.9)
Meineche-Schmidt (2002)	Dyspepsia and dysphagia	All patients	1.4 (0.04-4.36) 3/215
Stapley (2013)	Dysphagia and dyspepsia	Patients ≥ 55 years	9.8 (5.7-20.2)
Stapley (2013)	Dysphagia and raised platelets	Patients ≥ 55 years	6.1 (3.2-13.2)
Stapley (2013)	Dyspepsia and chest pain	Patients ≥ 55 years	0.7 (0.5-0.9)
Stapley (2013)	Dyspepsia and abdominal pain	Patients ≥ 55 years	1 (0.7-1.3)
Stapley (2013)	Dyspepsia and epigastric pain	Patients ≥ 55 years	1.4 (1-2)
Stapley (2013)	Dyspepsia and	Patients ≥ 55 years	1.3 (0.9-1.8)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	nausea/vomiting		
Stapley (2013)	Dyspepsia and reflux	Patients ≥ 55 years	0.9 (0.7-1.2)
Meineche-Schmidt (2002)	Dyspepsia and weight loss	All patients	1.37 (0.35-4.28) 3/219
Stapley (2013)	Dyspepsia and loss of weight	Patients ≥ 55 years	2.1 (1.3-3.5)
Stapley (2013)	Dyspepsia and raised platelets	Patients ≥ 55 years	1.4 (0.9-2.2)
Meineche-Schmidt (2002)	Dyspepsia and anaemia	All patients	0 (0-11.71) 0/37
Stapley (2013)	Dyspepsia and low haemoglobin	Patients ≥ 55 years	1 (0.8-1.3)
Stapley (2013)	Constipation and chest pain	Patients ≥ 55 years	0.4 (0.3-0.5)
Stapley (2013)	Constipation and loss of weight	Patients ≥ 55 years	1.1 (0.8-1.7)
Stapley (2013)	Constipation and abdominal pain	Patients ≥ 55 years	0.4 (0.3-0.5)
Stapley (2013)	Constipation and epigastric pain	Patients ≥ 55 years	1.4 (0.8-2.3)
Stapley (2013)	Constipation and reflux	Patients ≥ 55 years	0.7 (0.5-1.1)
Stapley (2013)	Constipation and low haemoglobin	Patients ≥ 55 years	0.4 (0.4-0.5)
Stapley (2013)	Constipation and nausea/vomiting	Patients ≥ 55 years	0.6 (0.4-0.7)
Stapley (2013)	Constipation and dyspepsia	Patients ≥ 55 years	0.8 (0.6-1.1)
Stapley (2013)	Constipation and dysphagia	Patients ≥ 55 years	4.2 (2.7-7.2)
Stapley (2013)	Constipation and raised platelets	Patients ≥ 55 years	0.9 (0.6-1.4)
Stapley (2013)	Abdominal pain and chest pain	Patients ≥ 55 years	0.3 (0.3-0.4)
Stapley (2013)	Abdominal pain and epigastric pain	Patients ≥ 55 years	0.9 (0.7-1.2)
Stapley (2013)	Abdominal pain and reflux	Patients ≥ 55 years	0.6 (0.5-0.9)
Stapley (2013)	Abdominal pain and weight loss	Patients ≥ 55 years	1.4 (0.9-2.2)
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea and/or vomiting > 2 weeks	All patients	0.7 (0.12-2.7) 2/293
Stapley (2013)	Abdominal pain and nausea/vomiting	Patients ≥ 55 years	0.7 (0.5-0.9)
Stapley (2013)	Abdominal pain and low haemoglobin	Patients ≥ 55 years	0.5 (0.4-0.6)
Stapley (2013)	Abdominal pain and raised platelets	Patients ≥ 55 years	0.8 (0.6-1.1)
Møllmann (1981)	Upper abdominal pain > 2 weeks and	All patients	0 (0-21)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	gastrointestinal bleeding		0/19
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea/vomiting > 2 weeks and gastrointestinal bleeding	All patients	0 (0-44) 0/7
Møllmann (1981)	Upper abdominal pain > 2 weeks and nausea/vomiting > 2 weeks and weight loss/anorexia	All patients	5.2 (2.1-11.4) 6/116
Møllmann (1981)	Upper abdominal pain > 2 weeks and weight loss/anorexia and gastrointestinal bleeding	All patients	20 (1.1-70) 1/5
Møllmann (1981)	Upper abdominal pain > 2 weeks and weight loss/anorexia	All patients	2 (0.4-7.9) 2/98
Stapley (2013)	Chest pain and epigastric pain	Patients ≥ 55 years	0.9 (0.6-1.4)
Stapley (2013)	Chest pain and reflux	Patients ≥ 55 years	0.6 (0.5-0.9)
Stapley (2013)	Chest pain and weight loss	Patients ≥ 55 years	1.1 (0.7-1.8)
Stapley (2013)	Chest pain and nausea/vomiting	Patients ≥ 55 years	0.6 (0.4-0.8)
Stapley (2013)	Chest pain and low haemoglobin	Patients ≥ 55 years	0.3 (0.3-0.4)
Stapley (2013)	Chest pain and raised platelets	Patients ≥ 55 years	0.8 (0.6-1.2)
Stapley (2013)	Epigastric pain and reflux	Patients ≥ 55 years	1.5 (1-2.4)
Stapley (2013)	Epigastric pain and weight loss	Patients ≥ 55 years	4.2 (1.8-11)
Stapley (2013)	Epigastric pain and low haemoglobin	Patients ≥ 55 years	1.6 (1.1-2.2)
Stapley (2013)	Reflux and loss of weight	Patients ≥ 55 years	3.1 (1.5-6.7)
Stapley (2013)	Reflux and low haemoglobin	Patients ≥ 55 years	0.9 (0.7-1.2)
Stapley (2013)	Weight loss and low haemoglobin	Patients ≥ 55 years	1 (0.8-1.3)
Møllmann (1981)	Weight loss/anorexia and gastrointestinal bleeding	All patients	0 (0-80) 0/2
Møllmann (1981)	Weight loss/anorexia and gastrointestinal bleeding and nausea/vomiting > 2 week	All patients	0 (0-80) 0/2
Møllmann (1981)	Weight loss/anorexia and nausea/vomiting > 2 week	All patients	0 (0-16.6) 0/25
Stapley (2013)	Nausea/vomiting and	Patients ≥ 55 years	2.8 (1.7-4.8)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	weight loss		
Stapley (2013)	Nausea/vomiting and epigastric pain	Patients ≥ 55 years	1.3 (0.9-2)
Stapley (2013)	Nausea/vomiting and reflux	Patients ≥ 55 years	2.3 (1.5-3.5)
Stapley (2013)	Nausea/vomiting and low haemoglobin	Patients ≥ 55 years	0.9 (0.7-1.1)
Stapley (2013)	Reflux and raised platelets	Patients ≥ 55 years	1.6 (0.9-2.9)
Stapley (2013)	Weight loss and raised platelets	Patients ≥ 55 years	1.8 (1.1-3)
Stapley (2013)	Nausea/vomiting and raised platelets	Patients ≥ 55 years	1.4 (1-2.1)
Stapley (2013)	Epigastric pain and raised platelets	Patients ≥ 55 years	1.9 (1-3.8)
Stapley (2013)	Low haemoglobin and raised platelets	Patients ≥ 55 years	0.6 (0.6-0.7)
Møllmann (1981)	Any of the inclusion symptoms + previous dyspepsia	All patients	0.9 (0.4-1.9) 7/773
Møllmann (1981)	Any of the inclusion symptoms + no previous dyspepsia	All patients	2.1 (1.1-3.8) 11/524
Møllmann (1981)	Any of the inclusion symptoms + unchanged previous dyspepsia	All patients	1.2 (0.5-3) 5/407
Møllmann (1981)	Any of the inclusion symptoms + no previous or changed dyspepsia	All patients	1.5 (0.8-2.6) 13/890
Møllmann (1981)	Any of the inclusion symptoms + pain provoked by meals	All patients	2.3 (1-5.3) 6/257
Møllmann (1981)	Any of the inclusion symptoms + no pain provoked by meals	All patients	1.1 (0.6-2.1) 10/924
Møllmann (1981)	Any of the inclusion symptoms + relief of pain by meals	All patients	1.2 (0.5-2.8) 6/488
Møllmann (1981)	Any of the inclusion symptoms + no pain relief by meals	All patients	1.5 (0.7-2.8) 10/687
Møllmann (1981)	Any of the inclusion symptoms + irritable bowel syndrome	All patients	1.2 (0.2-4.7) 2/167
Møllmann (1981)	Any of the inclusion symptoms + no irritable bowel syndrome	All patients	1.4 (0.8-2.3) 16/1129

Please note: The calculations of the positive predictive values differ between the all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = not reported.

Investigations in primary care

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No primary care evidence was identified pertaining to the diagnostic accuracy of upper gastrointestinal endoscopy, barium meal or abdominal ultrasound in patients with suspected stomach cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with an upper abdominal mass consistent with stomach cancer. [new 2015]** **Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with dysphagia. [new 2015]** **Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who:** • **are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting or** • **are aged 55 and over with upper abdominal pain, reflux or dyspepsia. [new 2015]** **Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with weight loss who:** • **also have appetite loss or** • **are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more or** • **are aged 55 and over with nausea/vomiting. [new 2015]** **Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 and over with reflux and nausea/vomiting. [new 2015]** **Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 and over with upper abdominal pain and raised platelet counts. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of stomach cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict stomach cancer. <u>Investigations in primary care for stomach cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of stomach cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of moderate-high quality. It was noted that a number of the included studies had merged stomach and

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	oesophageal cancer making it difficult to tease out the specifics related to stomach cancer. The GDG also noted that for some of the symptoms the positive predictive values were based on very few patients and that this was likely to make these estimates unreliable. <u>Investigations in primary care for stomach cancer</u> No evidence was found pertaining to the diagnostic performance of abdominal ultrasound, upper gastrointestinal endoscopy or barium meal in primary care patients with suspected stomach cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with stomach cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without stomach cancer who get inappropriately referred whilst maximising the number of people with stomach cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG had previously agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with stomach cancer outweighed the disadvantages to those without. However, the GDG noted that the availability of urgent direct access upper gastrointestinal endoscopy allows the GP to triage people presenting with symptoms of suspected stomach cancer prior to a suspected cancer pathway referral and thereby ensure that the right patients are referred based on the test results. The GDG noted that this would result in a slight delay for the people for whom a suspected cancer pathway referral is warranted, but the GDG judged that this slight delay would be acceptable because it would prevent the suspected cancer pathway referral system from becoming overburdened with unnecessary referrals, thereby allowing it to operate more efficiently for those people on the suspected cancer pathway. The GDG also noted the absence of evidence for direct access upper gastrointestinal endoscopy in people presenting to primary care, but the GDG, based on clinical experience, judged that the accuracy of this test is acceptable. The GDG therefore decided not to recommend symptoms which should prompt a suspected cancer pathway referral but instead to recommend which symptoms should prompt an urgent direct access upper gastrointestinal endoscopy. By doing this the GDG hoped to refine the group of symptomatic people being referred to those with the greatest risk of having stomach cancer. The GDG chose the symptoms that prompted urgent direct access upper gastrointestinal endoscopy based on the positive predictive values presented in the evidence and based the specified age cut-offs on those used in the studies that comprised the evidence for the individual symptoms or symptom combinations. The GDG discussed whether an age threshold should be included on the recommendation for dysphagia, but

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	decided against it as most causes of dysphagia are serious and the incidence of this symptom is very low in younger people. In addition, the absence of any subgroup analyses based on age made it difficult for the GDG to determine what the appropriate age threshold would be. The GDG noted that Møllman (1981) reported a 3 symptom combination (upper abdominal pain lasting 2 weeks or more, weight loss/anorexia and gastrointestinal bleeding) with a PPV of 20. However, the GDG also noted the wide confidence interval, which indicated uncertainty about this point estimate. The GDG agreed that people with the symptoms reported by Møllman (1981) would be encompassed by the existing recommendation to offer urgent direct access gastrointestinal endoscopy to people with weight loss plus upper abdominal pain (lasting two weeks or more) and nausea/vomiting. Therefore no recommendation was made specifically for this 3 symptom combination. Several symptom combinations in stomach cancer had positive predictive values below the 3% threshold, so urgent investigation for these symptoms was not recommended. However the GDG agreed that routine direct access upper gastrointestinal endoscopy would be of benefit in trying to refine the patient group. The GDG decided to use the term “loss of appetite” instead of “anorexia”, which was the term used in the evidence because the former is the symptom patients would report and the latter is the term the GP would use. The GDG agreed, based on their clinical experience, that an upper abdominal mass consistent with stomach cancer was likely to be associated with a positive predictive value of 3% or above and should prompt a suspected cancer pathway referral. The GDG acknowledged that no other symptoms had a high enough positive predictive value for stomach cancer to warrant making recommendations on them. The GDG noted that the distinction between epigastric pain, upper abdominal pain, dyspepsia and reflux to some extent is artificial and that there is significant overlap in the practical use of these terms. The GDG therefore decided to use upper abdominal pain rather than epigastric pain as the former term is more inclusive. Similarly, the GDG decided to use dyspepsia instead of reflux to take into account the overlap in the recording of these symptoms. The GDG hoped that this would ensure that variations in use of these terms would not stop any person from being investigated as recommended.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for urgent direct access upper gastrointestinal endoscopy is likely to result in a cost increase due to an increase number of endoscopies performed. However, this cost increase is likely to be counteracted by a cost saving from an optimised diagnostic process that will see an increase in the proportion of patients

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	being referred on a suspected cancer pathway who have stomach cancer and a decrease in the number of patients without stomach cancer being referred.
Other considerations	The GDG recognised that to implement these recommendations, there may initially be some capacity issues in some localities as urgent endoscopies are harder to accommodate than non-urgent endoscopies.

8.4 Small intestinal cancer

This is a rare cancer of the duodenum, jejunum or ileum, with different histological subtypes. Most GPs will not diagnose a case during their career.

The rarity of this cancer means there are no relevant studies of its clinical features. It may have symptoms similar to those of stomach or colorectal cancers.

The main method of diagnosis is by biopsy, which is performed in secondary care.

Clinical questions:

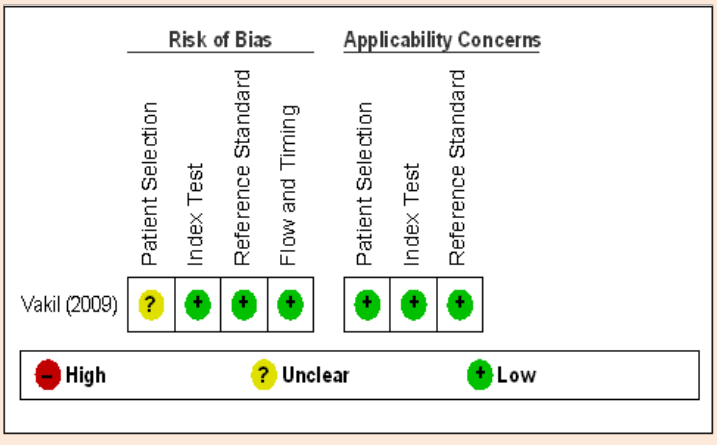
- **What is the risk of small intestine cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected small intestine cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the patient recruitment method is unclear and that the study patients may therefore not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP.



Evidence statements

Dyspepsia without accompanying alarm features (1 study, N = 2741) presenting in a primary care setting do not appear to confer an increased risk of small intestine cancer, although the study population is probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 18).

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Table 18: Small intestinal cancer: Study results

Study	Symptom(s)	Patient group	PPVs % (95% CI); prevalence
Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.2 (0.09-0.5) 6/2741 Cancer: Oesophagus: N = 3 Stomach: N = 3
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.4 (0.2-1.1) 5/1127 Cancer: Oesophagus: N = 2 Stomach: N = 3
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 50 years old	0.6 (0.2-1.5) 5/829 Cancer: Oesophagus: N = 2 Stomach: N = 3
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 55 years old	0.2 (0.009-1.2) 1/554 Cancer: Oesophagus: N = 1 Stomach: N = 0
Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 60 years old	0.3 (0.02-2) 1/323 Cancer: Oesophagus: N = 1 Stomach: N = 0

TP = True positives, FP = False positives.

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Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of CT scan, barium follow through or capsule endoscopy in patients with suspected small intestine cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	No recommendations made
Relative value placed on the outcomes considered	<u>Signs and symptoms of cancer of the small intestinal</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict cancer of the small intestine. <u>Investigations in primary care for cancer of the small intestinal</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of cancer of the small intestinal</u>

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	The quality of the available evidence, as assessed by QUADAS-II, was low. The GDG noted that there was limited evidence, only comprising one study. This study had been included because it covered the symptom of dyspepsia although it was acknowledged that this was in patients with stomach and oesophaegeal cancer, not cancer of the small intestine. In addition, the study population was thought not to be directly representative of the typical unselected symptomatic UK primary care population. <u>Investigations in primary care for cancer of the small intestinal</u> No evidence was found pertaining to the diagnostic accuracy of capsule endoscopy, barium follow-through or CT scans in primary care patients with suspected cancer of the small intestine.
Trade-off between clinical benefits and harms	Within the evidence presented, none related to cancer of the small intestine so the evidence was discounted. Based on their clinical experience, the GDG were able to agree the signs and symptoms of cancer of the small intestine. However they noted that these symptoms were common to several other gastrointestinal cancers. The GDG were not able to identify any symptoms which were sufficiently predictive of cancer of the small intestine to warrant making recommendations. The GDG also noted the lack of evidence on investigations in primary care. Given these, the GDG agreed not to make any recommendations on the primary care referral or investigation of suspected cancer of the small intestine.

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8.5 Gall bladder cancer

Around 700 new gallbladder cancers are diagnosed each year in the UK, almost twice as many in women as in men. A full time GP is unlikely to diagnose more than one person with gallbladder cancer in their career.

Pain and jaundice are thought to be the main presenting symptoms of gallbladder cancer. However the rarity of this cancer means there are few studies of its clinical features.

These features of gallbladder cancer can also be present in other cancers, especially pancreas or liver.

Because of the rarity of gallbladder cancer there is no standard diagnostic pathway. Ultrasound in primary care may show abnormalities suggestive of the cancer, but definitive diagnosis requires biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of gall bladder cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected gall bladder cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

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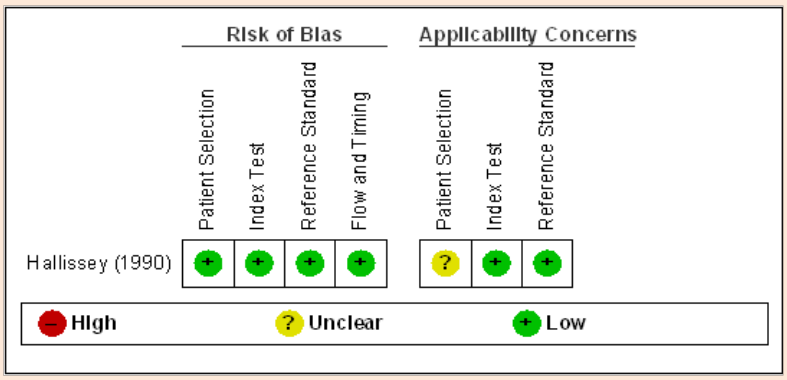
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the patient sample may not be directly applicable to the current question.



Evidence statements

The positive predictive value of having gall bladder cancer was 0.04% (for dyspepsia) for patients aged > 40 years (1 study, N = 2585). The included study was associated with 1 applicability concern (see also Table 19).

Table 19: Gall bladder cancer: Positive predictive values for gall bladder cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, liver function tests or tumour marker CA19-9 in patients with suspected gall bladder cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for gall bladder cancer in people with an upper abdominal mass consistent with an enlarged gall bladder. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of gall bladder cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict gall bladder cancer. No evidence was found on this outcome. Investigations in primary care for gall bladder cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes

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Quality of the evidence	<u>Signs and symptoms of gall bladder cancer</u> No evidence was found pertaining to the positive predictive values of different symptoms of gall bladder cancer in primary care. <u>Investigations in primary care for gall bladder cancer</u> No evidence was found pertaining to the diagnostic accuracy of CT scan, ultrasound, liver function tests or tumour marker CA19-9 in primary care patients with suspected gall bladder cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with gall bladder cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without gall bladder cancer who get inappropriately referred whilst maximising the number of people with gall bladder cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of suspected cancer pathway referral in those with gall bladder cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for gall bladder cancer. The clinical opinion of the GDG was that there is a sign of gall bladder cancer that is sufficiently predictive to justify further investigation. Therefore it was important to provide guidance on this. The GDG noted the lack of evidence on the diagnostic accuracy of ultrasound. However, based on their clinical experience, they noted that ultrasound was an accessible, non-invasive test that could be used to discriminate between malignant and non-malignant disorders of the gall bladder. They therefore agreed to recommend that ultrasound be considered for those patients where an upper abdominal mass consistent with an enlarged gall bladder is found in order to help determine the appropriate clinic for subsequent referral. The GDG considered that the clinical benefits of ultrasound performed in primary care would be to expedite gall bladder cancer diagnosis in people whose symptoms may otherwise not be investigated. The GDG also recognised that it was difficult to define exactly which symptoms should prompt an ultrasound and consequently some people without gall bladder cancer may also be investigated unnecessarily. The GDG agreed that the benefits of earlier diagnosis outweighed the potential harms.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for ultrasound is likely to be cost-neutral as it is already standard practice.

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8.6 Liver cancer

Over 4,000 new primary liver cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 2-3 people with liver cancer in their whole career.

Primary liver cancer often presents as a complication of cirrhosis, usually following chronic viral hepatitis or alcoholic liver disease. Pain and worsening of liver function and enlargement of the liver are thought to be the main presenting symptoms of liver cancer. However the rarity of this cancer means there are few studies of its clinical features.

The cancer may be identified on ultrasound or other imaging techniques, though definitive diagnosis requires biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of liver cancer in patients presenting in primary care with symptom X?**
- **Which investigations of symptoms of suspected liver cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included studies in the figure below. In one of the included studies, the main issue to note is that the population in the study comprises a mix of 'old' and 'new' investigated or uninvestigated symptoms, and it is unclear how directly applicable this sample is to the current question. In the other included study, it is unclear whether the patient selection was consecutive. This study also used a sub-optimal reference standard and was also subject to varying degrees of missing data; all of which challenges the validity of the reported results.

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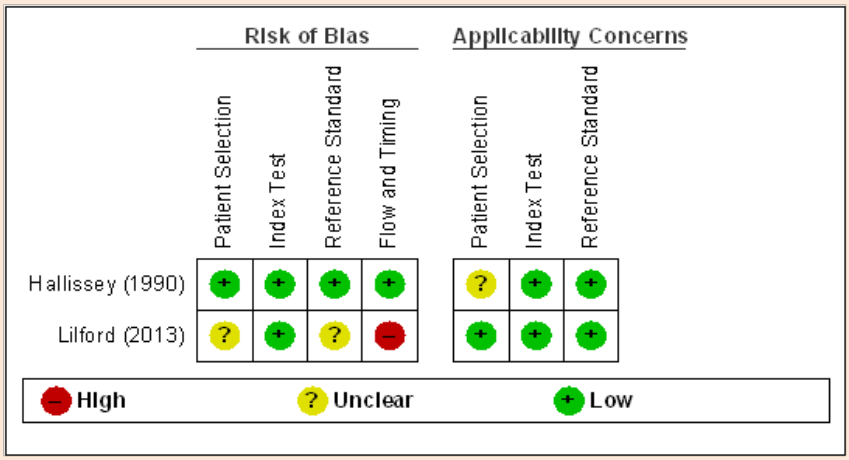

Evidence statement

The positive predictive value for liver cancer ranged from 0% (for abnormal bilirubin/ albumin/ globulin/ total [hepatic] protein) to 1.59% (for abnormal alkaline phosphatise; 2 studies, N = 3875) presenting in primary care was 0.04%. The included studies were associated with 1-3 bias/applicability concerns (see also Table 20).

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Table 20: Liver cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585
Lilford (2013)	LFT: Abnormal alanine aminotransferase	All patients	0.46 (0.08-1.8) 2/438
Lilford (2013)	LFT: Abnormal aspartate aminotransferase	All patients	0.39 (0.02-2.5) 1/255
Lilford (2013)	LFT: Abnormal γ-glutamyltransferase	All patients	0.92 (0.43-1.9) 8/867
Lilford (2013)	LFT: Abnormal bilirubin	All patients	0 (0-3.2) 0/148
Lilford (2013)	LFT: Abnormal alkaline phosphatase	All patients	1.59 (0.41-4.9) 3/189
Lilford (2013)	LFT: Abnormal albumin	All patients	0 (0-14) 0/30
Lilford (2013)	LFT: Abnormal globulin	All patients	0 (0-8.1) 0/55
Lilford (2013)	LFT: Abnormal total protein	All patients	0 (0-4.7) 0/97

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of ultrasound, CT, MRI or alpha feta protein in patients with suspected liver cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for liver cancer in people with an upper abdominal mass consistent with an enlarged liver. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of liver cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict liver cancer. <u>Investigations in primary care for liver cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of liver cancer</u> The quality of the evidence as assessed by QUADAS-II was not high. The evidence was also very limited, consisting of two

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	papers, one of which reported on one symptom in a population of questionable applicability to an unselected UK-based primary care population. The other reported on abnormal liver function tests in an under-defined UK-based primary care population. <u>Investigations in primary care for liver cancer</u> No evidence was found pertaining to the diagnostic accuracy of CT scan, ultrasound, MRI or alpha feta protein in primary care patients with suspected liver cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with liver cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without liver cancer who get inappropriately referred whilst maximising the number of people with liver cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with liver cancer outweighed the disadvantages to those without. Based on the limited evidence and the uncertainty over which symptoms were likely to have a high PPV for primary liver cancer, compared with other GI cancers, the GDG agreed not to make a recommendation for a suspected cancer pathway referral. The GDG did not make a recommendation for people presenting with jaundice or upper abdominal pain as they considered that these symptoms were most likely to be caused by other upper GI cancers and not liver cancer. Based on their clinical experience the GDG agreed that an upper abdominal mass was the symptom likely to have the highest PPV for liver cancer, although this was unlikely to be above the 3% threshold set for a suspected cancer pathway referral. They therefore recommended that this symptom should prompt investigation in primary care with ultrasound. The GDG noted the lack of evidence on the diagnostic accuracy of ultrasound. However, based on their clinical experience, they noted that ultrasound was an accessible, non-invasive test that could be used to discriminate between malignant and non-malignant disorders of the liver. They therefore agreed to recommend that ultrasound be considered for those patients where an upper abdominal mass consistent with an enlarged liver is found, in order to help determine the appropriate clinic for subsequent referral. The GDG considered that the clinical benefits of ultrasound performed in primary care would be to expedite liver cancer diagnosis in people whose symptoms may otherwise not be investigated. The GDG also recognised that it was difficult to define exactly which symptoms should prompt an ultrasound and consequently some people without liver cancer may also be

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	investigated unnecessarily. The GDG agreed that the benefits of earlier diagnosis outweighed the potential harms.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for ultrasound is cost-neutral as it is standard practice.

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Small intestinal cancer

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Liver cancer

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9 Lower gastrointestinal tract cancers

9.1 Colorectal cancer

Around 40,000 new colorectal cancers are diagnosed each year in the UK, up to a quarter of these following screening. A full time GP is likely to diagnose approximately 1 person with colorectal cancer every year. Five year survival is approximately 60%, though this figure includes cancers detected by screening as well as those identified after symptoms have occurred.

Several symptoms have been reported, with rectal bleeding, diarrhoea, constipation (sometimes referred to as 'change of bowel habit') loss of weight, and abdominal pain the most common. Colorectal cancer may present with anaemia, particularly iron deficiency anaemia.

These features of colorectal cancer can also be present in other cancers, especially intra-abdominal ones. The symptoms of colorectal cancer may also be misdiagnosed as non-malignant conditions, such as irritable bowel disease.

A number of methods of diagnosing colorectal cancer are available. Colonoscopy is considered to be the gold standard, though some clinicians offer flexible sigmoidoscopy to selected patients with rectal bleeding. Both these methods allow biopsy. CT colonography is increasingly used for those unfit for colonoscopy, but does not include biopsy. These diagnostic tests can be performed with the GP retaining clinical responsibility.

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Clinical questions:

- **What is the risk of colorectal cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected colorectal cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in setting or with patients that may not directly translate to the current question and UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity.

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Evidence statement

Rectal bleeding (16 studies, N = 134794) presenting in a primary care setting is associated with an overall positive predictive value of up to 4.88% for colorectal cancer, which tended to increase with age (10 studies, N = 33874) both in men (3 studies, N = 103846) and in women (3 studies, N = 103846). All the studies were associated with ≤ 2 bias or applicability concerns (see also Tables 21-23, 26-28).

Abdominal pain (5 studies, N = 373796) presenting in a primary care setting is associated with an overall positive predictive value of up to 2.04% for colorectal cancer, which tended to increase with age (1 study, N = 2093) both in men (1 study, N = 43791) and in women (1 study, N = 43791). All the studies were associated with ≤ 2 bias or applicability concerns (see also Tables 21-23, 26-28).

Anaemia (10 studies, N = 89550) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.87% for colorectal cancer, which tended to increase with age (1 study, N = 2093) both in men (2 studies, N = 118672) and in women (2 studies, N = 118672). Seven of the studies were associated with ≤ 2 bias or applicability concern, while the remaining two studies were associated with 3 and 4 bias or applicability concerns, respectively (see also Tables 21-23, 27-28).

Constipation (2 studies, N = 2373) presenting in a primary care setting is associated with an overall positive predictive value of up to 15.7% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 0.42-0.81% reported by another study (N = 2093) that also showed that the positive predictive values increase with age, which seems to be the case for both men (1 study, N = 43791) and for women (1 study, N = 43791). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 23, 26-28).

Diarrhoea (2 studies, N = 2373) presenting in a primary care setting is associated with an overall positive predictive value of up to 11.8% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 0.94-1.5% reported by another study (N = 2093) that also showed that the positive predictive values increase with age, which seems to be the case for both men (1 study, N = 43791) and for women (1 study, N = 43791). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 23, 26-28).

Change in bowel habit (3 studies, N = 621601) presenting in a primary care setting is associated with an overall positive predictive value of up to 14% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 2.8% and 2.9% reported by two other studies in men only (N = 621321). The positive predictive values of change in bowel habit for colorectal cancer also appears to increase with age in men (2 studies, N = 71315) and in women (2 studies, N = 71315). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 23, 27-28).

Weight loss (4 studies, N = 44431) presenting in a primary care setting is associated with an overall positive predictive value of up to 3% for colorectal cancer which tended to increase with age (1 study, N = 2093) both in men (1 study, N = 43791) and in women (1 study, N = 43791). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 21-23, 26-28).

Dyspepsia (3 studies, N = 4476) presenting in a primary care setting is associated with an overall positive predictive value of 0.6% for colorectal cancer. All the studies were associated with 1 applicability concerns (see also Table 23).

Other single symptoms (8 studies, N = 1245637) presenting in a primary care setting are associated with overall positive predictive values of up to 13.2% for colorectal cancer, but

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this estimate comes from a small study (N = 280) of selected patients and may therefore be inflated. All the studies were associated with ≤ 3 bias or applicability concerns (see also Table 23).

Rectal bleeding presenting with other symptoms (9 studies, N = 5770) in a primary care setting are associated with overall positive predictive values ranging from 0-100%, but many of these estimates are artificially inflated due to small numbers of patients in the calculations. All the studies were associated with ≤ 2 bias or applicability concerns (see also Table 24).

Other symptom combinations (2 studies, N = 3494) presenting in a primary care setting are associated with overall positive predictive values for colorectal cancer ranging from 0% for dyspepsia with dysphagia or jaundice to 13.51% for dyspepsia and anaemia. Both studies were associated with 1 bias/applicability concern (see also Table 25).

Table 21: Colorectal cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012) Du Toit (2006) Ellis (2005) Fijten (1995) Heintze (2005) Helfand (1997) Hippisley-Cox (2012) Jones (2007, at 6 months) Mant (1989) Metcalf (1996) Nørrelund (1996) Panzuto (2003) Parker (2007) Robertson (2006) Wauters (2000)	Rectal bleeding	All patients N = 132701	4.79 (3.37-6.77)
		Without Heintze (2005) and Panzuto (2003) N = 132187	4.41 (3.1-6.28)
Collins (2012) Du Toit (2006) Ellis (2005) Fijten (1995) Heintze (2005) Helfand (1997) Hippisley-Cox (2012) Jones (2007, at 3 years) Mant (1989) Metcalf (1996) Nørrelund (1996) Panzuto (2003) Parker (2007) Robertson (2006) Wauters (2000)	Rectal bleeding	All patients N = 132701	4.88 (3.48-6.79)
		Without Heintze (2005) and Panzuto (2003) N = 132187	4.5 (3.2-6.3)
Collins (2012) Bellentani (1990) Hippisley-Cox (2012) Panzuto (2003)	Abdominal pain	All patients N = 371703	2.04 (0.53-7.55)
		Without Panzuto (2003)	1.02 (0.38-2.69)

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Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		N = 371480	
Collins (2012) Droogendijk (2011) Farrus Palou (2000) Hippisley-Cox (2012) Lucas (1996) Panzuto (2003) Stellon (1997) Yates (2004)	Anaemia	All patients N = 35949	5.87 (2.64-12.)
		Without Panzuto (2003) N = 35880	4.09 (2.24-7.34)
Collins (2012) Hippisley-Cox (2012) Panzuto (2003)	Weight loss	All patients N = 42338	3 (0.32-22.89)
		Collins (2012) N = 28289	0.8 (0.7-0.9)
		Hippisley-Cox (2012) N = 14007	0.8 (0.7-0.9)
Hallissey (1990) Heikkinen (1995) Meineche-Schmidt (2002)	Dyspepsia	All patients N = 4476	0.6 (0.27-1.35)

Please note that the data from Hamilton (2005, 2008, 2009) are not included in these meta-analyses due to the case-control design of the studies. These data are instead reported in the table below. In addition, sensitivity analyses were conducted where the studies with a high risk of patient selection bias were excluded. When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead. Secondary analyses were performed excluding Panzuto (2003) due to the concern that the population appeared to be higher risk than the unselected patients specified in the clinical question,

Table 22: Colorectal cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012)	Rectal bleeding	All patients (N = 56234)	2.4 (2.3-2.6)
Du Toit (2006)	Rectal bleeding	All patients (N = 265)	5.7 (3.3-9.4)
Ellis (2005),	Rectal bleeding	All patients (N = 319)	3.4 (1.8-6.3)
Fijten (1995),	Rectal bleeding	All patients (N = 269)	3.3 (1.6-6.5)
Heintze (2005)	Rectal bleeding	All patients (N = 400)	4.3 (2.6-6.9)
Helfand (1997)	Rectal bleeding	All patients (N = 201)	6.5 (3.6-11.1)
Hippisley-Cox (2012)	Rectal bleeding	All patients (N = 28952)	2.9 (2.7-3.1)
Jones (2007, at 6 months)	Rectal bleeding	All patients (N = 15289)	1.7 (1.5-1.9)
Jones (2007, at 3 years)	Rectal bleeding	All patients (N = 15289)	2.2 (2-2.5)
Mant (1989)	Rectal bleeding	All patients (N = 145)	11.7 (7.2-18.4)
Metcalf (1996)	Rectal bleeding	All patients (N = 99)	8.1 (3.8-15.8)
Nørrelund (1996)	Rectal bleeding	All patients (N = 417)	13.7 (10.6-17.4)
Panzuto (2003)	Rectal bleeding	All patients (N = 114)	15.8 (9.9-24.1)
Parker (2007)	Rectal bleeding	All patients (N = 29007)	2.2 (2.1-2.4)
Robertson (2006)	Rectal bleeding	All patients (N = 604)	3.6 (2.4-5.6)

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Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Wauters (2000)	Rectal bleeding	All patients (N = 386)	7 (4.7-10.1)
Bellentani (1990)	Abdominal pain	All patients (N = 254)	3.9 (2-7.3)
Collins (2012)	Abdominal pain	All patients (N = 245989)	0.5 (0.5-0.5)
Hippisley-Cox (2012)	Abdominal pain	All patients (N = 125237)	0.7 (0.6-0.7)
Panzuto (2003)	Abdominal pain	All patients (N = 223)	13.5 (9.4-18.8)
Collins (2012)	Anaemia	All patients (N = 18125)	1.7 (1.5-1.9)
Droogendijk (2011)	Anaemia	All patients (N = 287)	8.4 (5.5-12.3)
Farrus Palou (2000)	Anaemia	All patients (N = 58)	3.4 (0.6-13)
Hippisley-Cox (2012)	Anaemia	All patients (N = 16823)	1.5 (1.3-1.7)
Lucas (1996)	Anaemia	All patients (N = 130)	6.9 (3.4-13.1)
Panzuto (2003)	Anaemia	All patients (N = 69)	40.6 (29.1-53.1)
Stellon (1997)	Anaemia	All patients (N = 26)	7.7 (1.3-26.6)
Yates (2004)	Anaemia	All patients (N = 431)	8.6 (6.2-11.7)
Collins (2012)	Weight loss	All patients (N = 28289)	0.8 (0.7-0.9)
Hippisley-Cox (2012)	Weight loss	All patients (N = 14007)	0.8 (0.7-0.9)
Panzuto (2003)	Weight loss	All patients (N = 42)	35.7 (22-52)
Hallissey (1990)	Dyspepsia	All patients	0.5 (0.3-0.9) 14/2585
Heikkinen (1995)	Dyspepsia	All patients	0/400
Meineche-Schmidt (2002)	Dyspepsia	All patients	1.14 (0.7-1.9)

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Table 23: Colorectal cancer: Additional results reported by the individual papers: Individual symptoms

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hamilton (2005)	Rectal bleeding (reported once)	All patients	2.4 (1.9-3.2) Cases: 148/349 Controls: 73/1744
Hamilton (2005)	Rectal bleeding (reported twice)	All patients	6.8 (NR)
Hamilton (2005)	Constipation (reported once)	All patients	0.42 (0.3-0.5) Cases: 91/349 Controls: 258/1744
Hamilton (2005)	Constipation (reported twice)	All patients	0.81 (0.5-1.3)
Panzuto (2003)	Constipation	All patients	15.7 (10.2-23.2) 21/134
Hamilton (2005)	Diarrhoea (reported once)	All patients	0.94 (0.7-1.1) Cases: 132/349 Controls: 171/1744

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Panzuto (2003)	Diarrhoea	All patients	11.8 (6.1-21)
Hamilton (2005)	Diarrhoea (reported twice)	All patients	1.5 (1-2.2)
Panzuto (2003)	Bloating	All patients	13.2 (8.6-19.5) 22/167
Panzuto (2003)	Change in bowel habit	All patients	14 (6.7-26.3) 8/57
Hamilton (2005)	Loss of weight (reported once)	All patients	1.2 (0.9-1.6) Cases: 94/349 Controls: 92/1744
Hamilton (2005)	Loss of weight (reported twice)	All patients	1.4 (0.8-2.6)
Collins (2012)	Loss of appetite	All patients	0.8 (0.6-1.1)
Hippisley-Cox (2012)	Loss of appetite	All patients	0.9 (0.6-1.2)
Hamilton (2005)	Abdominal pain (reported once)	All patients	1.1 (0.9-1.3) Cases: 148/349 Controls: 163/1744
Hamilton (2005)	Abdominal pain (reported twice)	All patients	3 (1.8-5.2)
Hamilton (2005)	Abdominal tenderness (reported once)	All patients	(0.8-1.5) Cases: 62/349 Controls: 67/1744
Muris (1993)	Non-acute abdominal complaints	All patients	0.52 (0.1-1.6)
Muris (1995)	Non-acute abdominal complaints	All patients	0.43 (0.1-1.2)
Hamilton (2005)	Abnormal rectal exam (reported once)	All patients	1.5 (1-2.2) Cases: 51/349 Controls: 14/1744
Hamilton (2005)	Haemoglobin 10-13 g dl-1 (reported once)	All patients	0.97 (0.8-1.3)
Hamilton (2008)	Haemoglobin 10-12.9 g dl-1	All patients	0.3 (0.2-0.3)
Hamilton (2005)	Haemoglobin < 10 g dl-1 (reported once)	All patients	2.3 (1.6-3.1)
Hamilton (2008)	Haemoglobin < 9.9 g dl-1	All patients	2 (1.7-2.3)
Hamilton (2005)	Haemoglobin 12-12.9 g dl-1	All patients	Cases: 17/349 Controls: 20/1744
Hamilton (2005)	Haemoglobin 10-11.9 g dl-1	All patients	Cases: 38/349 Controls: 49/1744
Hamilton (2005)	Haemoglobin < 10 g dl-1	All patients	Cases: 40/349 Controls: 21/1744
Hamilton (2005)	Positive faecal occult blood	All patients	Cases: 31/79 Controls: 5/47
Hamilton (2005)	Blood sugar > 10 mmol l-1	All patients	Cases: 25/349 Controls: 39/1744
Oudega (2006)	Deep vein thrombosis	All patients	0.7 (0.2-2.2)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
			3/430
Hamilton (2005)	History of diabetes	All patients	Cases: 37/349 Controls: 119/1744

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 24: Colorectal cancer: Additional results reported by the individual papers: Rectal bleeding with other symptoms/signs

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hamilton (2005)	Rectal bleeding and constipation	All patients	2.4 (1.4-4.4)
Metcalf (1996)	Rectal bleeding and constipation	All patients	2.6 (0.1-15.1) 1/39
Hamilton (2005)	Rectal bleeding and diarrhoea	All patients	3.4 (2.1-6)
Metcalf (1996)	Rectal bleeding and diarrhoea	All patients	7.4 (1.3-25.8) 2/27
Hamilton (2005)	Rectal bleeding and abdominal tenderness	All patients	4.5 (NR)
Hamilton (2005)	Rectal bleeding and abnormal rectal exam	All patients	8.5 (NR)
Wauters (2000)	Rectal bleeding and fatigue	All patients	7.1 (??)
Hamilton (2005)	Rectal bleeding and haemoglobin 10-13 g dl-1	All patients	3.6 (NR)
Hamilton (2005)	Rectal bleeding and haemoglobin < 10 g dl-1	All patients	3.2 (NR)
Ellis (2005)	Rectal bleeding and change in bowel habit	Patients with flexible sigmoidoscopy/ questionnaire data	9.2 (4.9-16.3) 11/119
Mant (1989)	Rectal bleeding and change in bowel habit	All patients	11 (NR)
Metcalf (1996)	Rectal bleeding and change in bowel habit	All patients	10.3 (3.3-25.2) 4/39
Nørrelund (1996)	New onset or changed pattern rectal bleeding and change in bowel habit	All patients	26.85 (19-36.4) 29/108
Nørrelund (1996)	New onset or changed pattern rectal bleeding and uncertain change in bowel habit	All patients	25 (8.3-52.6) 4/16
Nørrelund (1996)	New onset or changed pattern rectal bleeding and no change in bowel habit	All patients	8.75 (5.6-13.2)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Ellis (2005)	Rectal bleeding and no change in bowel habit	Patients with flexible sigmoidoscopy/ questionnaire data	0 0/147
Mant (1989)	Rectal bleeding and no change in bowel habit	All patients	11 (NR)
Ellis (2005)	Rectal bleeding and change in bowel habit (loose ± frequent)	Patients with flexible sigmoidoscopy/ questionnaire data	12 (6.2-21.5) 10/83
Robertson (2006)	Rectal bleeding and increased frequency/loose motions	All patients	4.8 (2.7-8.3)
Robertson (2006)	Rectal bleeding and no 'increased frequency/loose motions'	All patients	2.8 (1.4-5.5)
Ellis (2005)	Rectal bleeding and change in bowel habit (hard ± infrequent)	Patients with flexible sigmoidoscopy/ questionnaire data	2.8 (0.1-16.2) 1/36
Ellis (2005)	Rectal bleeding and no perianal symptoms	Patients with flexible sigmoidoscopy/ questionnaire data	11.1 (5-22.2) 7/63
Ellis (2005)	Rectal bleeding and perianal symptoms	Patients with flexible sigmoidoscopy/ questionnaire data	1.97 (0.6-5.3) 4/203
Mant (1989)	Rectal bleeding and feeling of incomplete evacuation of rectum	All patients	12 (NR)
Mant (1989)	Rectal bleeding and no feeling of incomplete evacuation of rectum	All patients	11 (NR)
Mant (1989)	Rectal bleeding and pain on defecation	All patients	7 (NR)
Mant (1989)	Rectal bleeding and no pain on defecation	All patients	12 (NR)
Wauters (2000)	Rectal bleeding and spasm	All patients	5.4 (2-11.4)
Nørrelund (1996)	New onset or changed pattern rectal bleeding and discomfort	All patients	16.67 (10.1-26) 16/96
Nørrelund (1996)	New onset or changed pattern rectal bleeding and uncertain discomfort	All patients	23.08 (9.8-44.1) 6/26
Nørrelund (1996)	New onset or changed pattern rectal bleeding and no discomfort	All patients	13.22 (9.3-18.3)
Ellis (2005)	Rectal bleeding and change in bowel habit and abdominal pain	Patients with flexible sigmoidoscopy/ questionnaire data	9 (3.7-19.1) 6/67
Ellis (2005)	Rectal bleeding and change in bowel habit and no abdominal pain	Patients with flexible sigmoidoscopy/ questionnaire data	9.6 (3.6-21.8) 5/52
Ellis (2005)	Rectal bleeding:	Patients with flexible	9.7 (2.5-26.9)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	Dark blood	sigmoidoscopy/ questionnaire data	3/31
Mant (1989)	Rectal bleeding: Dark blood	All patients	19 (NR)
Robertson (2006)	Rectal bleeding: Dark blood	All patients	7.4 (3.7-14)
Metcalf (1996)	Rectal bleeding: Dark red blood loss	All patients	9.7 (2.5-26.9) 3/31
Robertson (2006)	Rectal bleeding: No/not dark blood	All patients	2.7 (1.5-4.7)
Ellis (2005)	Rectal bleeding: Bright blood	Patients with flexible sigmoidoscopy/ questionnaire data	4 (1.9-8.1) 8/199
Mant (1989)	Rectal bleeding: Bright blood	All patients	10 (NR)
Metcalf (1996)	Rectal bleeding: Bright red blood loss	All patients	8.6 (3.5-18.4) 6/70
Ellis (2005)	Rectal bleeding: Blood on paper only	Patients with flexible sigmoidoscopy/ questionnaire data	2.4 (0.4-9.4) 2/82
Mant (1989)	Rectal bleeding: Blood seen on paper	All patients	9 (NR)
Metcalf (1996)	Rectal bleeding: Blood only on paper	All patients	8.3 (1.5-28.5) 2/24
Mant (1989)	Rectal bleeding: Blood seen in toilet bowl	All patients	14 (NR)
Ellis (2005)	Rectal bleeding: Blood in pan and on paper	Patients with flexible sigmoidoscopy/ questionnaire data	4.9 (2.4-9.4) 9/184
Mant (1989)	Rectal bleeding: Blood seen on paper and in toilet bowl	All patients	11 (NR)
Ellis (2005)	Rectal bleeding: Large volume of blood	Patients with flexible sigmoidoscopy/ questionnaire data	1.3 (0.07-7.8) 1/79
Ellis (2005)	Rectal bleeding: Small volume of blood	Patients with flexible sigmoidoscopy/ questionnaire data	5.3 (2.7-9.9) 10/187
Ellis (2005)	Rectal bleeding: First time	Patients with flexible sigmoidoscopy/ questionnaire data	4.7 (1.7-11.2) 5/106
Nørrelund (1996)	Rectal bleeding: New onset	All patients	14.24 (10.7-18.7) 45/316
Ellis (2005)	Rectal bleeding: Not first time	Patients with flexible sigmoidoscopy/ questionnaire data	3.8 (1.5-8.3) 6/160
Nørrelund (1996)	Rectal bleeding: Not first time, unchanged bleeding pattern	All patients	4.4 (0.8-16.4) 2/45
Nørrelund (1996)	Rectal bleeding:	All patients	18.75 (9.4-33.1)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	Not first time, changed bleeding pattern		9/48
Fijten (1995)	Rectal bleeding: Blood on stool or mixed with only	All patients	7 (NR) Total positives N = 54
Fijten (1995)	Rectal bleeding: Blood mixed with stool only	All patients	14 (NR) Total positives N = 14
Mant (1989)	Rectal bleeding: Blood seen mixed with faeces	All patients	21 (NR)
Metcalf (1996)	Rectal bleeding: Blood mixed with stool	All patients	10.9 (4.1-24.4) 5/46
Ellis (2005)	Rectal bleeding: Blood mixed with the stool	Patients with flexible sigmoidoscopy/ questionnaire data	3 (0.2-17.5) 1/33
Robertson (2006)	Rectal bleeding: Blood mixed with stool	All patients	5.4 (3.3-8.7)
Fijten (1995)	Rectal bleeding: Others or combinations apart from “blood on stool or mixed with stool only”	All patients	1 (NR) Total positives N = 122
Robertson (2006)	Rectal bleeding: Dark blood and blood mixed with stool	All patients	10.2 (5.1-19) 9/88
Robertson (2006)	Rectal bleeding: Not ‘dark blood and blood mixed with stool’	All patients	2.5 (1.4-4.4)
Robertson (2006)	Rectal bleeding: Blood neither dark nor mixed with stool	All patients	1.9 (0.7-4.7)
Robertson (2006)	Rectal bleeding: Not ‘blood neither dark nor mixed with stool’	All patients	4.9 (3-7.9)
Fijten (1995)	Rectal bleeding: Unknown how blood was seen	All patients	7 (NR) Total positives N = 54
Ellis (2005)	Rectal bleeding: Blood not mixed with the stool	Patients with flexible sigmoidoscopy/ questionnaire data	4.3 (2.2-8) 10/233
Robertson (2006)	Rectal bleeding: Blood not mixed with stool	All patients	1.7 (0.6-4.2)
Mant (1989)	Rectal bleeding: Blood seen separate from faeces	All patients	7 (NR)
Metcalf (1996)	Rectal bleeding and associated slime	All patients	10.7 (2.8-29.4) 3/28
Fijten (1995)	Rectal bleeding and nausea	All patients	2 (NR) Total positives N = 68
Fijten (1995)	Rectal bleeding and abdominal pain	All patients	2 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
			Total positives N = 135
Hamilton (2005)	Rectal bleeding and abdominal pain	All patients	3.1 (1.9-5.3)
Mant (1989)	Rectal bleeding and abdominal pain	All patients	9 (NR)
Metcalf (1996)	Rectal bleeding and abdominal pain	All patients	7.1 (1.9-20.6) 3/42
Robertson (2006)	Rectal bleeding and abdominal pain	All patients	1.7 (0.6-4.6)
Nørrelund (1996)	New onset or changed pattern rectal bleeding and abdominal pain	All patients	23.33 (15.3-33.7) 21/90
Meineche-Schmidt (2002)	Rectal bleeding and dyspepsia	All patients	2.6 (1.1-5.9) 6/227
Meineche-Schmidt (2002)	Rectal bleeding (visible blood in stools only) and dyspepsia	All patients	4 (1.5-9.6) 5/124
Nørrelund (1996)	New onset or changed pattern rectal bleeding and uncertain abdominal pain	All patients	22.22 (3.9-59.8) 2/9
Mant (1989)	Rectal bleeding and no abdominal pain	All patients	12 (NR)
Robertson (2006)	Rectal bleeding and no abdominal pain	All patients	4.5 (2.7-7.3)
Nørrelund (1996)	New onset or changed pattern rectal bleeding and no abdominal pain	All patients	11.7 (8.2-16.3)
Fijten (1995)	Rectal bleeding and decreased appetite	All patients	2 (NR) Total positives N = 42
Fijten (1995)	Rectal bleeding and pain at night	All patients	0 (0-8.9) Total positives N = 50
Wauters (2000)	Rectal bleeding and pain	All patients	0 (0-10.2)
Fijten (1995)	Rectal bleeding and weight loss	All patients	10 (NR) Total positives N = 42
Hamilton (2005)	Rectal bleeding and weight loss	All patients	4.7 (NR)
Robertson (2006)	Rectal bleeding and weight loss	All patients	4.8 (1.3-14.4) 3/62
Mant (1989)	Rectal bleeding and weight loss	All patients	13 (NR)
Metcalf (1996)	Rectal bleeding and weight loss	All patients	13.3 (2.3-41.6) 2/15
Nørrelund (1996)	New onset or changed pattern rectal bleeding and weight loss	All patients	22.73 (12-38.2) 10/44

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Wauters (2000)	Rectal bleeding and weight loss	All patients	16 (4.5-36.1)
Nørrelund (1996)	New onset or changed pattern rectal bleeding and uncertain weight loss	All patients	28.57 (9.6-58) 4/14
Mant (1989)	Rectal bleeding and no weight loss	All patients	11 (NR)
Robertson (2006)	Rectal bleeding and no weight loss	All patients	3.6 (2.2-5.6)
Nørrelund (1996)	New onset or changed pattern rectal bleeding and no weight loss	All patients	13.07 (9.6-17.5)
Fijten (1995)	Rectal bleeding and pale conjunctivae	All patients	17 (NR) Total positives N = 6
Mant (1989)	Rectal bleeding and nongastrointestinal symptoms	All patients	5 (NR)
Mant (1989)	Rectal bleeding and no nongastrointestinal symptoms	All patients	12 (NR)
Fijten (1995)	Rectal bleeding and perianal eczema	All patients	18 (NR) Total positives N = 17
Mant (1989)	Rectal bleeding and anal itch	All patients	3 (NR)
Mant (1989)	Rectal bleeding and no anal itch	All patients	14 (NR)
Fijten (1995)	Rectal bleeding and haemorrhoid on rectal palpation	All patients	10 (NR) Total positives N = 20 (but out of 208, not 269)
Mant (1989)	Rectal bleeding and haemorrhoids identified by GP	All patients	5 (NR)
Robertson (2006)	Rectal bleeding and haemorrhoids	All patients	3.1 (1.6-5.9)
Robertson (2006)	Rectal bleeding and haemorrhoids and bright red blood not mixed with stools	All patients	1.9 (0.5-5.8)
Robertson (2006)	Rectal bleeding and haemorrhoids and no other symptoms except bright non-mixed bleeding	All patients	3.3 (0.9-10.1) 3/90
Mant (1989)	Rectal bleeding and no haemorrhoids identified by GP	All patients	17 (NR)
Robertson (2006)	Rectal bleeding and no haemorrhoids	All patients	4.6 (2.4-8.3)
Robertson (2006)	Rectal bleeding and no	All patients	4.5 (2.8-7.2)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	'haemorrhoids and bright red blood not mixed with stools'		
Robertson (2006)	Rectal bleeding and no 'haemorrhoids and no other symptoms except bright non-mixed bleeding'	All patients	3.8 (2.4-6.1)
Fijten (1995)	Rectal bleeding and tumour on rectal palpation	All patients	100 (NR) Total positives N = 1 (but out of 208, not 269)
Wauters (2000)	Rectal bleeding and palpable tumour	All patients	31.5 (12.5-56.5)
Mant (1989)	Rectal bleeding and anal protrusion noticed by patient	All patients	3 (NR)
Mant (1989)	Rectal bleeding and no anal protrusion noticed by patient	All patients	13 (NR)
Fijten (1995)	Rectal bleeding and abnormal prostate on rectal palpation	All patients	50 (NR) Total positive N = 2 (but out of 208, not 269)
Fijten (1995)	Rectal bleeding and previous history of rectal bleeding	All patients	0 (0-4.8) Total positives N = 96
Mant (1989)	Rectal bleeding and first degree relative with colorectal cancer	All patients	10 (NR)
Mant (1989)	Rectal bleeding and no first degree relative with colorectal cancer	All patients	11 (NR)
Metcalf (1996)	Rectal bleeding and family history of bowel cancer	All patients	0 (0-40.2) 0/8
Fijten (1995)	Rectal bleeding and family history of abdominal disease	All patients	0 (0-5.5) Total positives N = 83
Robertson (2006)	Rectal bleeding and history of irritable bowel syndrome	All patients	0 (0-4.8) 0/96
Robertson (2006)	Rectal bleeding and no history of irritable bowel syndrome	All patients	4.4 (2.8-6.7)
Robertson (2006)	Rectal bleeding and history of diverticular disease	All patients	0 (0-12.6) 0/34
Robertson (2006)	Rectal bleeding and no history of diverticular disease	All patients	3.9 (2.5-6)
Fijten (1995)	Rectal bleeding and abnormal proctoscopy	All patients	0 (0-14.1) Total positives N =

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
			30 (but out of 45, not 269)
Robertson (2006)	Rectal bleeding and deprivation category (deprivation category 1 = least deprived, deprivation category 7 = most deprived)	Deprivation category 1	4.1 (1.1-12.2) 3/74
		Deprivation category 2	3.4 (1.1-8.9) 4/119
		Deprivation category 3	2.6 (0.8-6.9) 4/155
		Deprivation category 4	5.8 (2.7-11.6) 8/137
		Deprivation category 5	0/53 (0-8.4)
		Deprivation category 6	0/25 (0-16.6)
		Deprivation category 7	5.3 (0.3-28.1) 1/19

Please note:
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 25: Colorectal cancer: Additional results reported by the individual papers: Other symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hamilton (2005)	Constipation and diarrhoea	All patients	1.1 (0.6-1.8)
Hamilton (2005)	Constipation and loss of weight	All patients	3 (1.7-5.4)
Hamilton (2005)	Constipation and abdominal pain	All patients	1.5 (1-2.2)
Hamilton (2005)	Constipation and abdominal tenderness	All patients	1.7 (0.9-3.4)
Hamilton (2005)	Constipation and abnormal rectal exam	All patients	2.6 (NR)
Hamilton (2005)	Constipation and haemoglobin 10-13 g dl-1	All patients	1.2 (0.6-2.7)
Hamilton (2005)	Constipation and haemoglobin < 10 g dl-1	All patients	2.6 (NR)
Hamilton (2005)	Diarrhoea and loss of weight	All patients	3.1 (1.8-5.5)
Hamilton (2005)	Diarrhoea and abdominal pain	All patients	1.9 (1.4-2.7)
Hamilton (2005)	Diarrhoea and abdominal tenderness	All patients	2.4 (1.3-4.8)
Hamilton (2005)	Diarrhoea and abnormal rectal exam	All patients	11 (NR)
Hamilton (2005)	Diarrhoea and haemoglobin 10-13 g dl-1	All patients	2.2 (1.2-4.3)
Hamilton (2005)	Diarrhoea and haemoglobin < 10 g dl-1	All patients	2.9 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hamilton (2005)	Abdominal pain and loss of weight	All patients	3.4 (2.1-6)
Hamilton (2005)	Abdominal pain and abdominal tenderness	All patients	1.4 (0.3-2.2)
Hamilton (2005)	Abdominal pain and abnormal rectal exam	All patients	3.3 (NR)
Hamilton (2005)	Abdominal pain and haemoglobin 10-13 g dl-1	All patients	2.2 (1.1-4.5)
Hamilton (2005)	Abdominal pain and haemoglobin < 10 g dl-1	All patients	6.9 (NR)
Hamilton (2005)	Abdominal tenderness and loss of weight	All patients	6.4 (NR)
Hamilton (2005)	Abdominal tenderness and abnormal rectal exam	All patients	5.8 (NR)
Hamilton (2005)	Abdominal tenderness and haemoglobin 10-13 g dl-1	All patients	2.7 (NR)
Hamilton (2005)	Abdominal tenderness and haemoglobin < 10 g dl-1	All patients	>10 (NR) (no controls had this pair of symptoms)
Hamilton (2005)	Loss of weight and abnormal rectal exam	All patients	7.4 (NR)
Hamilton (2005)	Loss of weight and haemoglobin 10-13 g dl-1	All patients	1.3 (0.7-2.6)
Hamilton (2005)	Loss of weight and haemoglobin < 10 g dl-1	All patients	4.7 (NR)
Meineche-Schmidt (2002)	Dyspepsia and anaemia	All patients	13.51 (5-29.57) 5/37
Meineche-Schmidt (2002)	Dyspepsia and dysphagia	All patients	0 (0-2.2) 0/215
Meineche-Schmidt (2002)	Dyspepsia and jaundice	All patients	0 (0-48.32) 0/6
Meineche-Schmidt (2002)	Dyspepsia and weight loss	All patients	1.37 (0.35-4.28) 3/219

Please note:
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = not reported.

Table 26: Colorectal cancer: Additional results reported by the individual papers: Age

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Du Toit (2006)	Rectal bleeding	Patients 45-54 years	3.9 (NR)
		Patients 55-64 years	1.3 (NR)
		Patients 65-74 years	9.5 (NR)
		Patients ≥ 75 years	7.9 (NR)
Ellis (2005)	Rectal bleeding and aged ≥ 60 years	Patients with flexible sigmoidoscopy/	5.2 (2.4-10.3) 8/155

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	Rectal bleeding and aged ≤ 59 years	questionnaire data	1.8 (0.5-5.7) 3/164
Fijten (1995)	Rectal bleeding	Patients 18-59 years	0.4 (0.03-2.8) 1/229
		Patients 60-75 years	20 (9.6-36.1) 8/40
Nørrelund (1996)	New onset or changed pattern rectal bleeding	Patients 40-69 years	7.87 (5-12.1)
		Patients 70-79 years	34.12 (24.4-45.3)
		Patients 80+ years	20 (7.6-41.3)
Hamilton (2005)	Rectal bleeding	Patients 40-69 years	1.4 (NR)
		Patients ≥ 70 years	4.8 (NR)
Heintze (2005)	Rectal bleeding	Patients < 50 years	2/≤153*
		Patients ≥ 50 years	15/≤268*
Mant (1989)	Rectal bleeding	Patients 40-60 years	8 (NR)
		Patients > 60 years	16 (NR)
Parker (2007)	Rectal bleeding	Patients 25-34 years	0.1 3/4717
		Patients 35-44 years	0.3 17/5301
		Patients 45-54 years	1.5 (1.2-1.8)
		Patients 55-64 years	2.8 (2.3-3.3)
		Patients 65-74 years	4.3 (3.7-5)
		Patients 75-84 years	5.5 (4.7-6.3)
		Patients ≥ 85 years	3.7 (2.8-4.8)
Robertson (2006)	Rectal bleeding	Patients < 50 years	1.1 (0.3-3.5)
		Patients 50-69 years	4.8 (2.6-8.7)
		Patients ≥ 70 years	7.5 (3.5-14.6)
Wauters (2000)	Rectal bleeding	Patients < 50 years	0.7 (0-4.9)
		Patients 50-59 years	1.7 (0-9.4) 1/57
		Patients 60-69 years	11.2 (5-21) 8/71
		Patients 70-79 50 years	21.2 (12-33) 14/66
		Patients ≥ 80 years	5.8 (1.2-16.2) 3/51
Nørrelund (1996)	New onset or changed pattern rectal bleeding and change in bowel habit	Patients 40-69 years	16.13 (8.4-28.1) 10/62
		Patients 70-79 years	42.5 (27.4-59) 17/40
		Patients 80+ years	33.3 (6-75.9) 2/6
Nørrelund (1996)	New onset or changed pattern rectal bleeding and uncertain change in bowel habit	Patients 40-69 years	18.18 (3.2-52.2) 2/11
		Patients 70-79 years	66.7 (12.5-98.2) 2/3

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Patients 80+ years	0 (0-80.2) 0/2
Nørrelund (1996)	New onset or changed pattern rectal bleeding and no change in bowel habit	Patients 40-69 years	4.42 (2.1-8.8) 8/181
		Patients 70-79 years	23.81 (12.6-39.8) 10/42
		Patients 80+ years	17.65 (4.7-44.2) 3/17
Hamilton (2005)	Abdominal pain	Patients 40-69 years	0.65 (NR)
		Patients ≥ 70 years	2 (NR)
Hamilton (2005)	Diarrhoea	Patients 40-69 years	0.63 (NR)
		Patients ≥ 70 years	1.7 (NR)
Hamilton (2005)	Constipation	Patients 40-69 years	0.2 (NR)
		Patients ≥ 70 years	1.3 (NR)
Hamilton (2005)	Weight loss	Patients 40-69 years	0.74 (NR)
		Patients ≥ 70 years	2.5 (NR)

**Data missing from 22/422 patients, but it is unclear which of the age subgroups the missing data belongs to.*
Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies.

Table 27: Colorectal cancer: Additional results reported by the individual papers: Men

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012)	Rectal bleeding	Men 30-84 years	2.8 (2.6-3)
Jones (2007)	Rectal bleeding at 6 months	Men (all ages)	1.8 (15-2.2)
Fijten (1995)	Rectal bleeding	Men (all ages)	5.9 (2.6-12.3) 7/118
Jones (2007)	Rectal bleeding at 3 years	Men (all ages)	2.4 (2.1-2.8)
Mant (1989)	Rectal bleeding	Men ≥ 40 years	9 (NR)
Nørrelund (1996)	New onset or changed pattern rectal bleeding	Men ≥ 40 years	17.26 (12-24)
Robertson (2006)	Rectal bleeding	Men (all ages)	4.8 (2.7-8.2)
Jones (2007)	Rectal bleeding at 3 years	Men < 45 years	0.07 (0.01-0.27)
		Men 45-54 years	1.56 (1-2.31)
		Men 55-64 years	3.38 (2.47-4.51)
		Men 65-74 years	4.8 (3.65-6.17)
		Men 75-84 years	7.74 (5.78-10.1)
		Men ≥ 85 years	5.1 (2.23-9.79)
Hamilton (2009)	Rectal bleeding at 2 years (read off graph)	Men < 60 years	0.5 (0.3-0.7)
		Men 60-69 years	2.4 (1.8-3.2)
		Men 70-79 years	3.5 (2.8-4.6)
		Men ≥ 80 years	4.5 (3.3-5.9)
Lawrenson (2006)	Rectal bleeding	Men 40-49 years	0.92 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Men 50-59 years	2.75 (NR)
		Men 60-69 years	5.99 (NR)
		Men 70-79 years	7.69 (NR)
		Men 80-89 years	9.13 (NR)
Helfand (1007)	Rectal bleeding	Men < 50 years	0 (0-7.7) 0/58
Collins (2012)	Change in bowel habit	Men 30-84 years	2.9 (2.2-3.9)
Hippisley-Cox (2012)	Change in bowel habit	Men 30-84 years	2.8 (1.8-4.2)
Hamilton (2009)	Change in bowel habit (read off graph)	Men < 60 years	1.1 (0.6-2.4)
		Men 60-69 years	3 (2.1-4.2)
		Men 70-79 years	4.2 (3.2-5.4)
		Men ≥ 80 years	3.9 (2.8-5.6)
Lawrenson (2006)	Change in bowel habit	Men 40-49 years	0.89 (NR)
		Men 50-59 years	4.07 (NR)
		Men 60-69 years	6.89 (NR)
		Men 70-79 years	8.48 (NR)
		Men 80-89 years	7.73 (NR)
Collins (2012)	Abdominal pain	Men 30-84 years	0.6 (0.6-0.7)
Hamilton (2009)	Abdominal pain (read off graph)	Men < 60 years	0.15 (0.1-0.15)
		Men 60-69 years	0.9 (0.7-1)
		Men 70-79 years	1.1 (0.9-1.3)
		Men ≥ 80 years	1.2 (1-1.5)
Hamilton (2009)	Diarrhoea (read off graph)	Men < 60 years	0.1 (0.1-0.1)
		Men 60-69 years	0.9 (0.7-1.1)
		Men 70-79 years	1.3 (1.1-1.5)
		Men ≥ 80 years	1.2 (1-1.5)
Hamilton (2009)	Constipation (read off graph)	Men < 60 years	0.2 (0.2-0.2)
		Men 60-69 years	0.8 (0.6-0.9)
		Men 70-79 years	0.8 (0.7-0.9)
		Men ≥ 80 years	0.7 (0.6-0.8)
Collins (2012)	Appetite loss	Men 30-84 years	1 (0.6-1.5)
Collins (2012)	Weight loss	Men 30-84 years	1 (0.8-1.1)
Hamilton (2009)	Weight loss 5-10% (read off graph)	Men aged < 60 years	0.1 (0.05-0.2)
		Men aged 60-69 years	0.3 (0.2-0.4)
		Men aged 70-79 years	0.7 (0.5-0.8)
		Men aged ≥ 80 years	0.5 (0.3-0.8)
Hamilton (2009)	Weight loss ≥ 10% (read off graph)	Men < 60 years	0.2 (0.1-0.3)
		Men 60-69 years	0.7 (0.4-0.9)
		Men 70-79 years	1.5 (1.2-1.8)
		Men ≥ 80 years	0.8 (0.6-1.4)
Hamilton (2008)	Haemoglobin ≥ 13 g dl-1	Men 30-59 years	0.1 (0.1-0.1)
		Men 60-69 years	0.3 (0.3-0.3)
		Men 70-79 years	0.4 (0.3-0.4)
		Men ≥ 80 years	0.4 (0.3-0.5)
Hamilton (2008)	Haemoglobin 12-12.9 g	Men 30-59 years	0.2 (0.1-0.3)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	dl-1	Men 60-69 years	0.7 (0.5-1)
		Men 70-79 years	1 (0.7-1.2)
		Men ≥ 80 years	0.6 (0.5-0.8)
Hamilton (2008)	Haemoglobin 11-11.9 g dl-1	Men 30-59 years	0.8 (0.2-2.9)
		Men 60-69 years	1.4 (0.9-2.3)
		Men 70-79 years	1.5 (1.2-2)
		Men ≥ 80 years	1 (0.8-1.4)
Hamilton (2008)	Haemoglobin 10-10.9 g dl-1	Men 30-59 years	0.8 (0.3-2.2)
		Men 60-69 years	2.3 (1.1-4.8)
		Men 70-79 years	3.2 (2.2-4.8)
		Men ≥ 80 years	1.6 (1.1-2.2)
Hamilton (2008)	Haemoglobin 9-9.9 g dl-1	Men 30-59 years	1.4 (0.2-10)
		Men 60-69 years	7.2 (2.9-17)
		Men 70-79 years	4 (2.5-6.3)
		Men ≥ 80 years	6 (3.4-10)
Hamilton (2008)	Haemoglobin < 9 g dl-1	Men 30-59 years	1.3 (0.4-4.3)
		Men 60-69 years	7.6 (3.4-16)
		Men 70-79 years	8.8 (5.4-14)
		Men ≥ 80 years	6.8 (4.2-11)
Hamilton (2008)	Haemoglobin ≥ 13 g dl-1 + indicators of iron deficiency**	Men 60-69 years	1.4 (0.6-3.6)
		Men 70-79 years	1.7 (0.9-3.1)
		Men ≥ 80 years	1.4 (0.6-3.1)
Hamilton (2008)	Haemoglobin 12-12.9 g dl-1 + indicators of iron deficiency**	Men 60-69 years	1.8 (0.7-4.2)
		Men 70-79 years	3.9 (1.8-8.5)
		Men ≥ 80 years	1.5 (0.5-4.2)
Hamilton (2008)	Haemoglobin 11-11.9 g dl-1 + indicators of iron deficiency**	Men 60-69 years	6.5 (2-19)
		Men 70-79 years	4.1 (2.1-8)
		Men ≥ 80 years	4 (1.6-9.3)
Hamilton (2008)	Haemoglobin 10-10.9 g dl-1 + indicators of iron deficiency**	Men 60-69 years	5.5 (1.2-21)
		Men 70-79 years	14 (5.9-29)
		Men ≥ 80 years	8.2 (3.7-17)
Hamilton (2008)	Haemoglobin 9-9.9 g dl-1 + indicators of iron deficiency**	Men 60-69 years	12 (3.1-37)
		Men 70-79 years	16 (6.3-35)
		Men ≥ 80 years	31 (5.6-77)
Hamilton (2008)	Haemoglobin < 9 g dl-1 + indicators of iron deficiency**	Men 60-69 years	>5 (30 cases, 0 controls)
		Men 70-79 years	18 (8.7-34)
		Men ≥ 80 years	15 (7.3-28)
Hamilton (2008)	Haemoglobin < 11 g dl-1 + indicators of iron deficiency	Men > 60 years	13.3 (9.7-18)
Collins (2012)	Anaemia	Men 30-84 years	3 (2.5-3.6)
Yates (2004)	Anaemia	Men > 20 years	18.2 (12.6-25.4)
Lawrenson (2006)	Anaemia	Men 40-49 years	1.07 (NR)
		Men 50-59 years	1.86 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Men 60-69 years	3.02 (NR)
		Men 70-79 years	3.38 (NR)
		Men 80-89 years	2.98 (NR)

***For the 30-59 years group 64 cases, but only 11 controls had markers of iron deficiency making meaningful analysis impossible.*
Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NP = Not reported.

Table 28: Colorectal cancer: Additional results reported by the individual papers: Women

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2012)	Rectal bleeding	Women 30-84 years	2.1 (1.9-2.2)
Jones (2007)	Rectal bleeding at 6 months	Women (all ages)	1.5 (1.3-1.8)
Fijten (1995)	Rectal bleeding	Women (all ages)	1.3 (0.2-5.2) 2/151
Jones (2007)	Rectal bleeding at 3 years	Women (all ages)	2 (1.7-2.3)
Mant (1989)	Rectal bleeding	Women ≥ 40 years	13 (NR)
Nørrelund (1996)	New onset or changed pattern rectal bleeding	Women ≥ 40 years	12.76 (8.6-18.4)
Robertson (2006)	Rectal bleeding	Women (all ages)	2.7 (1.3-5.3)
Jones (2007)	Rectal bleeding at 3 years	Women < 45 years	0.22 (0.08-0.47)
		Women 45-54 years	0.63 (0.27-1.24)
		Women 55-64 years	2.75 (1.9-3.84)
		Women 65-74 years	2.42 (1.62-3.48)
		Women 75-84 years	7.2 (5.63-9.06)
		Women > 85 years	2.79 (1.45-4.82)
Hamilton (2009)	Rectal bleeding at 2 years (read off graph)	Women < 60 years	0.4 (0.3-0.5)
		Women 60-69 years	2.1 (1.4-3.1)
		Women 70-79 years	2.2 (1.7-2.9)
		Women ≥ 80 years	2.9 (2.1-3.8)
Lawrenson (2006)	Rectal bleeding	Women 40-49 years	0.87 (NR)
		Women 50-59 years	2.16 (NR)
		Women 60-69 years	3.5 (NR)
		Women 70-79 years	4.61 (NR)
		Women 80-89 years	4.89 (NR)
Hamilton (2009)	Change in bowel habit (read off graph)	Women < 60 years	0.4 (0.3-0.5)
		Women 60-69 years	1.3 (0.8-1.9)
		Women 70-79 years	1.5 (1.1-1.9)
		Women ≥ 80 years	1.9 (1.3-2.7)
Lawrenson (2006)	Change in bowel habit	Women 40-49 years	0.64 (NR)
		Women 50-59 years	1.64 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Women 60-69 years	2.42 (NR)
		Women 70-79 years	3.25 (NR)
		Women 80-89 years	4.09 (NR)
Collins (2012)	Abdominal pain	Women 30-84 years	0.4 (0.4-0.5)
Hamilton (2009)	Abdominal pain (read off graph)	Women < 60 years	0.01 (0.1-0.1)
		Women 60-69 years	0.4 (0.35-0.5)
		Women 70-79 years	0.7 (0.6-0.75)
		Women ≥ 80 years	0.9 (0.8-1)
Hamilton (2009)	Diarrhoea (read off graph)	Women < 60 years	0.01 (0.1-0.1)
		Women 60-69 years	0.35 (0.25-0.4)
		Women 70-79 years	0.5 (0.4-0.6)
		Women ≥ 80 years	0.7 (0.6-0.8)
Hamilton (2009)	Constipation (read off graph)	Women < 60 years	0.1 (0.1-0.1)
		Women 60-69 years	0.5 (0.4-0.6)
		Women 70-79 years	0.5 (0.4-0.6)
		Women aged ≥ 80 years	0.5 (0.4-0.6)
Collins (2012)	Appetite loss	Women 30-84 years	0.6 (0.4-1)
Collins (2012)	Weight loss	Women 30-84 years	0.6 (0.5-0.7)
Hamilton (2009)	Weight loss 5-10% (read off graph)	Women < 60 years	0.05 (0.05-0.05)
		Women 60-69 years	0.2 (0.1-0.3)
		Women 70-79 years	0.4 (0.3-0.6)
		Women ≥ 80 years	0.4 (0.3-0.6)
Hamilton (2009)	Weight loss ≥ 10% (read off graph)	Women < 60 years	0.06 (0.06-0.08)
		Women 60-69 years	0.5 (0.3-0.7)
		Women 70-79 years	0.8 (0.6-1.1)
		Women ≥ 80 years	0.8 (0.6-1.1)
Hamilton (2008)	Haemoglobin ≥ 13 g dl-1	Women 30-59 years	0 (0-0)
		Women 60-69 years	0.1 (0.1-0.2)
		Women 70-79 years	0.2 (0.2-0.2)
		Women ≥ 80 years	0.2 (0.2-0.3)
Hamilton (2008)	Haemoglobin 12-12.9 g dl-1	Women 30-59 years	0.0 (0.0-0.1)
		Women 60-69 years	0.2 (0.1-0.2)
		Women 70-79 years	0.3 (0.3-0.4)
		Women ≥ 80 years	0.3 (0.2-0.4)
Hamilton (2008)	Haemoglobin 11-11.9 g dl-1	Women 30-59 years	0.1 (0.1-0.2)
		Women 60-69 years	0.4 (0.3-0.6)
		Women 70-79 years	0.5 (0.4-0.6)
		Women ≥ 80 years	0.6 (0.5-0.8)
Hamilton (2008)	Haemoglobin 10-10.9 g dl-1	Women 30-59 years	0.4 (0.2-0.8)
		Women 60-69 years	1.2 (0.7-2)
		Women 70-79 years	1.9 (1.4-2.6)
		Women ≥ 80 years	1.2 (0.9-1.5)
Hamilton (2008)	Haemoglobin 9-9.9 g dl-1	Women 30-59 years	0.3 (0.1-0.6)
		Women 60-69 years	2.7 (1.2-5.9)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		Women 70-79 years	3.6 (2.1-6)
		Women ≥ 80 years	2.2 (1.5-3.1)
Hamilton (2008)	Haemoglobin < 9 g dl-1	Women 30-59 years	0.9 (0.3-2.9)
		Women 60-69 years	>5 (41 cases, 0 controls)
		Women 70-79 years	8.6 (5.4-14)
		Women ≥ 80 years	7.1 (4.5-11)
Hamilton (2008)	Haemoglobin ≥ 13 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.1 (0-0.3)
		Women 60-69 years	2.9 (0.6-12)
		Women 70-79 years	0.4 (0.2-1.1)
		Women ≥ 80 years	0.8 (0.3-1.8)
Hamilton (2008)	Haemoglobin 12-12.9 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.1 (0.0-0.3)
		Women 60-69 years	0.1 (0.0-0.8)
		Women 70-79 years	0.8 (0.4-1.7)
		Women ≥ 80 years	1.5 (0.5-4.2)
Hamilton (2008)	Haemoglobin 11-11.9 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.2 (0.1-0.4)
		Women 60-69 years	1.5 (0.7-3.3)
		Women 70-79 years	2.1 (1.1-4)
		Women ≥ 80 years	3.6 (2-6.5)
Hamilton (2008)	Haemoglobin 10-10.9 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.6 (0.2-2.1)
		Women 60-69 years	2.4 (1-5.7)
		Women 70-79 years	5.9 (3-11)
		Women ≥ 80 years	2.5 (1.5-4.1)
Hamilton (2008)	Haemoglobin 9-9.9 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.3 (0.1-0.8)
		Women 60-69 years	3.5 (1.1-11)
		Women 70-79 years	8.6 (3.8-18)
		Women ≥ 80 years	5.7 (3-11)
Hamilton (2008)	Haemoglobin < 9 g dl-1 + indicators of iron deficiency	Women 30-59 years	0.6 (0.2-2.2)
		Women 60-69 years	>5 (36 cases, 0 controls)
		Women 70-79 years	10 (5.2-19)
		Women ≥ 80 years	10 (5.6-17)
Hamilton (2008)	Haemoglobin < 10 g dl-1	Women > 60 years	7.7 (5.7-11)
Collins (2012)	Anaemia	Women 30-84 years	1.3 (1.1-1.5)
Yates (2004)	Anaemia	Women > 50 years	3.2 (1.6-6.3)
Lawrenson (2006)	Anaemia	Women 40-49 years	0.08 (NR)
		Women 50-59 years	0.56 (NR)
		Women 60-69 years	1.38 (NR)
		Women 70-79 years	1.99 (NR)
		Women 80-89 years	2.01 (NR)

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported

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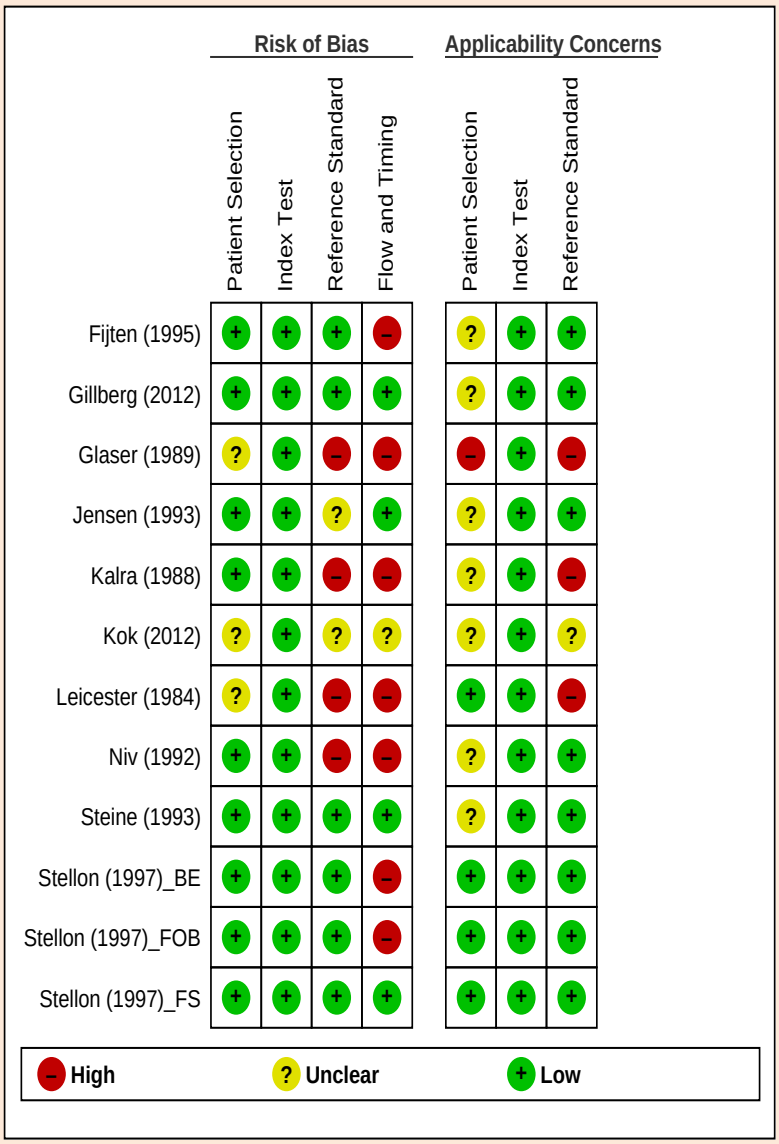
Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The studies were associated with a number of bias and validity issues. Two of the main issues to note relate to the patient selection methods employed and study settings, some of which were not clearly consecutive or random (and may therefore bias the results) or clearly transferable to UK-based primary care. Other issues of concern relate to missing data (and the concern that this may not be missing at random) and sub-optimal reference standards, which may both influence the results to an unknown extent.



Evidence statement

Faecal occult blood (6 studies, N = 9871) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 0-84%, specificities that ranged from 76-87%, positive predictive values that ranged from 0-16%, and false negativity rates that ranged from 16-100% for colorectal cancer. All the studies were associated with 1-5 bias or applicability concerns (see also Table 29).

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Sigmoidoscopy (5 studies, N = 1322) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 0-40%, specificities of up to 100%, positive predictive values that ranged from 0-100%, and false negativity rates that ranged from 60-100% for colorectal cancer. All the studies were associated with 0-5 bias or applicability concerns (see also Table 30).

Double-contrast barium enema (3 studies, N = 360) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 50-100%, specificities that ranged from 98-100%, positive predictive values that ranged from 66.7-100%, and false negativity rates that ranged from 0-50% for colorectal cancer. All the studies were associated with ≤ 2 bias or applicability concerns (see also Table 31).

Table 29: Colorectal cancer: Faecal occult blood

Study	Test	Prevalence	Sensi-tivity	Speci-ficity	Other results (95% CI)
Fijten (1995)	Faecal occult blood (Haemoccult)	5/225	50%	82%	Positive predictive value = 5% Negative predictive value = 99% False negativity rate = 50% 95% CI cannot be calculated as 2-by2 table could not be extracted
Gillberg (2012)	Faecal occult blood (Haemoccult II)	161/8928	75%	87%	TP = 120 FN = 41 TN = 7585 FP = 1182 Positive predictive value = 9.2% (7.7-11) False negativity rate = 25%
Jensen (1993)	Faecal occult blood (Hemoccult II)	5/149	60%	79%	TP = 3 FN = 2 TN = 114 FP = 30 Positive predictive value = 9.1% (2.4-25.5) False negativity rate = 40%
Kok (2012)	Faecal occult blood (Clearview One Step immune-chemical)	19/386	84%	76%	Data only available for N = 376 TP = 16 FN = 3 TN = 270 FP = 87 Positive predictive value = 15.5% (9.4-24.3) False negativity rate = 16%
Leicester (1984)	Faecal occult blood (Haemoccult)	4 cancers in 25 positive results out of 161 tests	56%	Not reported	Positive predictive value = 16% False negativity rate = 44% 95% CI cannot be calculated as 2-by2 table could not be extracted
Stellon (1997)	Faecal occult blood (Haemoccult)	1/22	0%	76%	TP = 0 FN = 1 TN = 16 FP = 5 Positive predictive value = 0% (0-54) False negativity rate = 100%

The data were not meta-analysed due to concerns about excessive heterogeneity (see forest plots below), differences in the tests employed and missing data. TP = true positives, FP = false positives, TN = true negatives, FN = false negatives. See forest plots below for the 95% CI for sensitivity and specificity.

Table 30: Colorectal cancer: Sigmoidoscopy

Study	Test	Prevalence	Sensi-tivity (95% CI)	Speci-ficity (95% CI)	Other results (95% CI)

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Study	Test	Prevalence	Sensi-tivity (95% CI)	Speci-ficity (95% CI)	Other results (95% CI)
Glaser (1989)	Rigid sigmoidoscopy	7/351	37.5% (10.2-74.1)	100% (98.6-100)	TP = 3 FN = 5 TN = 343 FP = 0 Positive predictive value = 100% (31-100) False negativity rate = 62.5%
Jensen (1993)	Rectosigmoidoscopy	5/149	40% (7.3-83)	100% (96.8-100)	TP = 2 FN = 3 TN = 144 FP = 0 Positive predictive value = 100% (19.8-100) False negativity rate = 60%
Kalra (1988)	Fibre-sigmoidoscopy	64 cancers in 216 abnormnal findings in 541 patients	Not reported	Not reported	- Fibresigmoidoscopy unsuccessful in 31/541 patients - 4 cancers missed by fibresigmoidoscopy Positive predictive value = 29.6% 95% CI cannot be calculated as 2-by2 table could not be extracted
Niv (1992)	Flexible sigmoidoscopy	5/255	Not reported	Not reported	TP = 4 FN = ≥ 1 TN = ? FP = 0 Positive predictive value = 100% (39.6-100) False negativity rate = cannot be ascertained as negative cases did not appear to be followed up
Stellon (1997)	Flexible sigmoidoscopy	2/26	0% (0-80.2)	100% (82.8-100)	TP = 0 FN = 2 TN = 24 FP = 0 Positive predictive value = 0% False negativity rate = 100%

The data were not meta-analysed due to concerns about differences in the tests employed and missing data. TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Table 31: Colorectal cancer: Double-contrast barium enema

Study	Test	Prevalence	Sensi-tivity	Speci-ficity	Other results
Jensen (1993)	Double-contrast barium enema	5/149	60%	100%	TP = 3 FN = 2 TN = 144 FP = 0 Positive predictive value = 100% (31-100) False negativity rate = 40%
Steine (1993)	Double-contrast barium enema	8/189	100%	98%	TP = 8 FN = 0 TN = 177 FP = 4 False negativity rate = 0% Positive predictive value = 66.7% (35.4-88.7) 1 patient with anal cancer was not examined
Stellon (1997)	Double-contrast barium enema	2/22	50%	100%	TP = 1 FN = 1 TN = 20 FP = 0 Positive predictive value = 100% (54.6-100)

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Study	Test	Prevalence	Sensi -tivity	Speci -ficity	Other results
					False negativity rate = 50%

The data were not meta-analysed due to concerns about excessive heterogeneity (see forest plot below). TP = true positives, FP = false positives, TN = true negatives, FN = false negatives. See forest plots below for the 95% CI for sensitivity and specificity.

Cost-effectiveness evidence (see also Appendix A)

Background

Colonoscopy is considered the gold standard investigation for the diagnosis of colorectal cancer due to its ability to visualise the entire colon and perform biopsies. Other investigations used in the diagnosis of colorectal cancer include flexible sigmoidoscopy and barium enema. Both investigations are associated with a lower risk of adverse events compared to colonoscopy however sensitivity is considerably lower. Recently, computerised tomography colonography (CTC) has begun to replace barium enema as the investigation of choice, for patients with co-morbidities due to the minimally invasive procedure. The technology uses CT imaging of the colon to visualise tumours.

Currently, the national bowel cancer screening programme uses faecal occult blood tests (FOBT) or faecal immunochemical tests (FIT) to detect occult blood in the faeces which is indicative of colorectal cancer. These tests are given to asymptomatic people aged 60 years or older. They are easy to use and can be performed by the person at home. Currently these tests are not routinely available to GPs to order if they suspect their patient has colorectal cancer and falls outside the bowel cancer screening age parameters.

Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 634 possibly relevant economic papers relating to colorectal cancer. Of these, ten full papers were obtained for appraisal. No study directly assessed the decision problem. The majority of literature in this area focuses on screening for asymptomatic patients. One study was identified, Allen et al 2004, which addressed a similar question to this decision problem; diagnostic tests to investigate rectal bleeding in patients aged 40 years and over.

This study could not be included within the economic evidence for this topic because it did not include a change in bowel habit as the main symptom and included other benign diseases of the bowel as an outcome. However it did provide a useful structure for the de novo analysis. The study used a decision tree combined with a Markov state transition model. The disease natural history section of the model was consistent with existing UK based screening economic models and divided the disease states by Dukes grading[a].

The study perspective was a USA modified societal perspective. The investigations included in the study were; air contrast barium enema (ACBE) alone, ACBE and flexible Sigmoidoscopy, flexible sigmoidoscopy, colonoscopy and watchful waiting. Faecal occult blood tests were not included in the analysis because the study was investigating people with visible rectal bleeding therefore occult blood tests are not relevant to this population. The authors concluded that colonoscopy was cost-effective compared to flexible sigmoidoscopy alone (ICER $5,480). Watchful waiting, defined as bleeding for one year followed by colonoscopy, was the most expensive option and was dominated by flexible sigmoidoscopy.

Aim

To estimate the cost-effectiveness of diagnostic tests for suspected colorectal cancer ordered in primary care for patients aged 40 years and over with a change in bowel habit.

a Method of assessing the level of invasion and the spread of a colorectal tumour within the bowel.

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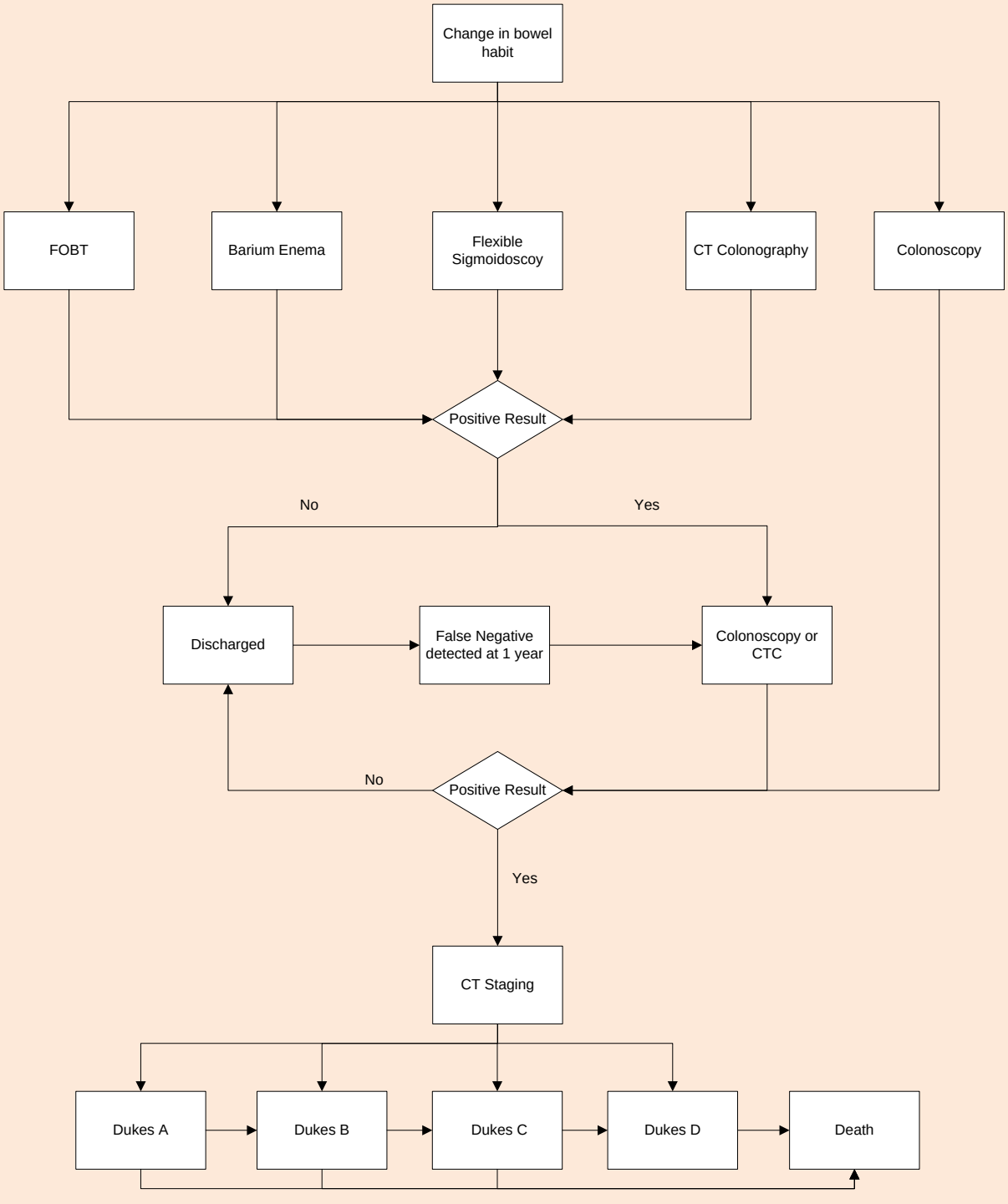
De Novo Economic Model

Model Structure

A decision tree analysis with combined Markov states was used to capture the diagnosis and staging of colorectal cancer. The full model structure is shown in the Figure below.



The cohort begins with people aged 40 years and over with a change in bowel habit who have presented to their GP for the first time. The cohort can have one of five initial investigations outlined in the decision problem. If the initial test result is positive they are referred to a clinic for either a colonoscopy or CTC depending on the probability of them being unsuitable for colonoscopy (for those receiving a colonoscopy as a first line

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investigation, no further test is required). If after colonoscopy or CTC the person tests positive for colorectal cancer, a CT scan is ordered to establish the stage of the cancer.

The initial cancer stage for those people with colorectal cancer is determined with defined probability of entering one of the four colorectal cancer markov states. These states are based on the Dukes grading system for colorectal cancer. Patients with diagnosed cancer can either remain in their current health state or die from colorectal cancer or another cause.

A lifetime horizon with a one year cycle length captures the probability of progression for treated and untreated colorectal cancer. For those patients with a negative result who have the underlying disease (false negatives), it is assumed that their symptoms would persist and they would be diagnosed within at one year with a colonoscopy. During this time the patient has a probability of progressing to a worse cancer state. All true negative patients are discharged after either their first investigation or if false positive at initial stage they are discharged after their second investigation.

Estimated total costs and quality adjusted life years (QALYs) are collected over the modelled forty year time horizon for each diagnostic strategy. The total costs will include all costs associated with initial and follow up investigations, staging, and treatment. These are described in more detail in the cost section of this report. QALYs are calculated by multiplying the life years that patients spend in each health state by the associated quality of life (QoL) weighting, which represent the valuation of the patient's health state. QALYs and QoL values are discussed in more detail in later sections of the report. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

Probability of progression

The GDG noted that obtaining observed probabilities of progression in colorectal cancer patients is unlikely. Therefore, in the absence of such evidence, estimated transition probabilities between cancer stages from a study by Tappenden et al 2004 were utilised. Using such calibrated probabilities will lead to uncertainty within the model results; however this was fully explored in the one way sensitivity analysis and probabilistic sensitivity analysis.

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The probabilities of progression with undiagnosed colorectal cancer that were applied in the model are shown in table 32 below.

Table 32: Probability of progression for undiagnosed colorectal cancer

Colorectal Stage	Annual probability of progression for undiagnosed CRC (95% CI)	PSA Distribution	Reference
Dukes A – Dukes B	0.58 (0.57-0.59)	Uniform	Tappenden et al 2004
Dukes B – Dukes C	0.66 (0.64-0.67)	Uniform	Tappenden et al 2004
Dukes C – Dukes D	0.87 (0.85-0.88)	Uniform	Tappenden et al 2004

Diagnostic accuracy

Diagnostic accuracy was captured in the model using data on sensitivity and specificity. Sensitivity is defined as; the probability that the index test result will be positive in a diseased case. The specificity is defined as; the probability that the index test result will be negative in a non diseased case.

All included evidence for the guideline is required to come from primary care studies. Patient selection, overall clinical responsibility and setting should all have been conducted in primary care to be eligible for inclusion. Upon review of the evidence six papers were identified as relevant for faecal occult blood tests and three were relevant for barium enema.

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Table 33: Key Diagnostic Accuracy Data

Investigation	Sensitivity (95% CI)	Specificity (95% CI)	Reference
FOBT	50.0% (15.0%,85.0%)	88.0% (85.0%,89.0%)	Gillberg et al 2012
FITb	74.7% (64.5%,83.3%)	86.4% (84.1%,88.4%)	Oono et al 2010
Barium Enema	60.0% (15.0%,95.0%)	100.0% (97.0%,100.0%)	Jensen et al 1993.
Flexible Sigmoidoscopy	68.6% (65.5%,71.6%)	100.0%	Thompson et al 2008
CT Colonography	96.1% (93.8%,97.7%)	79.2% (76.8%,81.5%)	Pickhardt et al 2011 (only reported sensitivity) & Halligan et al 2013
Colonoscopy	94.7% (90.4%,97.2%)	100.0%	Pickhardt et al 2011

Costs and Quality of Life

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2012-13 prices.

The majority of costs were sourced from NHS reference costs 2012/13 by applying tariffs associated with the appropriate HRG code. Data on lifetime costs associated with colorectal cancer (based on the stage of cancer at diagnosis) were sourced from Tappenden et al 2004 and inflated to 2014 prices. All the costs applied in the model are shown in the table below.

Table 34: List of all costs included in the analysis

Type of Cost	Mean Cost (Standard error)	Gamma PSA Distribution (alpha, beta)	Reference
Investigations			
FOBT	£4.86 (4.45)	(1.19, 4.07)	Estimated[c]
FIT	£9.42 (7.41)	(1.61,5.83)	Estimated[d]
Colonoscopy	£368.00 (145.88)	(6.36, 57.83)	NHS Reference Costs 2012/13
CT colonography	£275.00 (29.65)	(86.01,3.19)	NHS Reference Costs 2012/13
Barium Enema	£101.00 (32.55)	(9.63,10.49)	NHS Reference Costs 2012/13
Flexible Sigmoidoscopy	£351.00 (130.10)	(7.28,48.21)	NHS Reference Costs 2012/13
CT Scan	£146.53 (68.94)	(4.52,32.43)	NHS Reference Costs 2012/13
Adverse Event			
Gastro intestinal bleeding	£265 (148.26)	(3.19, 82.95)	NHS Reference Costs 2012/13
Bowel Perforation	£2,240 (593.03)	(14.27, 157.00)	NHS Reference Costs 2012/13
Referral			

[b] Examined in supplementary analysis
c Estimated from UK bowel screening Southern hub contract prices 2011.
d Estimated from UK bowel screening Southern hub contract prices 2011.

Type of Cost	Mean Cost (Standard error)	Gamma PSA Distribution (alpha, beta)	Reference
GP visit	£45.00 (not reported)	n/a	PSSRU 2013.
Lower Gastrointestinal appointment	£171.00 (60.79)	(7.91,21.61)	NHS Reference Costs 2012/13.
Cancer Stage			
Dukes A	£8,221 (3047.24)	(7.28,1129.44)	Tappenden et al 2004
Dukes B	£13,863 (5138.60)	(7.28,1904.60)	Tappenden et al 2004
Dukes C	£22,428 (8313.13)	(7.28,3081.22)	Tappenden et al 2004
Dukes D	£14,925 (5531.89)	(7.28,2050.37)	Tappenden et al 2004

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs were estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature. The utilities used in the model were sourced from a U.S. study by Ness et al. 1999, in which quality of life values associated with various stages of cancer and treatment were assessed using the standard gamble technique. The utilities applied in the model are shown in Table 35 below.

Table 35: List of all costs included in the analysis

Model State	QoL	Beta distribution (alpha, beta)	Reference
Healthy	0.79	(267.00,71.00)	Kind et al 1999
Dukes A	0.74	(145.00,51.69)	Ness et al 1999
Dukes B	0.70	(56.60,24.53)	Ness et al 1999
Dukes C	0.50	(33.78,32.28)	Ness et al 1999
Dukes D	0.25	(1.03,2.35)	Ness et al 1999

Update 2015

Base case results

The results of the economic model are presented as expected costs and QALYs for intervention along with an incremental cost-effectiveness ratio (ICER) for each comparison. The ICER is used to measure the cost-effectiveness of one intervention over another; it is calculated as shown in the figure below.

ICER = (Δ Cost) / (Δ QALYs)

ICER = (Cost Intervention A − Cost Intervention B) / (QALYs Intervention A − QALYs Intervention B)

It can be seen that by dividing the difference in costs of each intervention by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically has a cost effectiveness (CE) threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

An alternative way of presenting the results of economic analyses is in the form of net monetary benefit (NMB), which is calculated as shown in the figure below.

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$$\mathbf{NMB} = \lambda \times \Delta\text{QALYs} - \Delta\text{Costs}$$

Where λ = NICE threshold of £20,000 per QALY

It can be seen that by employing a fixed NICE threshold of £20,000 per QALY and re-arranging the ICER formula it is possible to express both effectiveness and costs in monetary terms. When the calculated result is found to be positive then the benefits are found to outweigh the costs and those interventions that have higher NMBs are preferred to those with lower NMBs.

The base case deterministic results are shown in Table 36. Both FOBT and barium enema are cost effective compared to colonoscopy at a threshold of £20,000 per QALY gained.

Table 37 presents the results in a dominance rank format. In this analysis the tests are rearranged in order of total cost, from cheapest to most expensive. Incremental costs and QALYs are then calculated for each intervention by comparing it against the previous intervention that was found to be cost-effective (at a threshold of £20,000 per QALY). Upon analysis of results using the dominance rank method, FOBT was found to be the most cost-effective test.

Table 36: Base case deterministic results, FOBT and barium enema compared to colonoscopy

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
FOBT	£343,244	- £467,153	809.99	-4.25	£109,860[e]	£15,856,582
Barium Enema	£365,818	-£444,578	810.94	-3.30	£134,681	£15,853,033

Table 37: Base case deterministic results- dominance rank

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
FOBT	£343,244	-	809.99	-	-	£15,856,582
Barium Enema	£365,818	£22,575	810.94	0.95	£22,580	£15,853,033
Colonoscopy	£810,397	£467,153	814.24	4.25	£116,750	£15,474,474

In addition to the deterministic results above, the base case results were also generared probabilisticly. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis. The probabilistic base case results are presented in tables 38 and 39 below showing a comparison against a common baseline (colonoscopy) and a dominance rank, respectively.

As in the deterministic analysis, it can be seen that both FOBT and barium enema are cost effective compared to colonoscopy and that, when using the dominance rank method, FOBT was found to be the most cost-effective test.

Table 38: Base case probabilistic results, FOBT and barium enema compared to colonoscopy

Test	Costs	QALYs	ICER	NMB

[e] When incremental QALYs & Costs are **negative** anything **above** the CE threshold (£20,000 per QALY) is cost-effective.

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	Total	Incr	Total	Incr		
Colonoscopy	£836,201	-	812.12	-	-	£15,407,830
FOBT	£350,045	-£486,157	808.03	-4.17	£116,641	£15,810,627
Barium Enema	£390,076	-£446,125	808.03	-4.17	£107,034	£15,770,593

Table 39: Base case probabilistic results - dominance rank

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
FOBT	£350,045	-	808.03	-	-	£15,810,627
Barium Enema	£390,076	£40,031	808.03	0.00	Dominated	£15,770,593
Colonoscopy	£836,201	£486,157	812.12	4.17	£116,641	£15,407,830

Additional Analysis

Further analysis was undertaken to examine the cost-effectiveness of flexible sigmoidoscopy and CTC. Table 40 shows the ICERs for CTC and flexible sigmoidoscopy compared to colonoscopy. Both investigations were cost-effective compared to colonoscopy.

Table 40: Comparison of flexible sigmoidoscopy and CTC to colonoscopy

Investigation	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
CTC	£710,146	-£100,250	814.38	0.13	Dominant	£15,577,388
Flexible Sigmoidoscopy	£690,542	-£119,855	811.76	-2.48	£48,291[f]	£15,544,691

Upon analysis (using the dominance rank method) including all investigations, FOBT is shown to be the most cost-effective investigation (Table 41).

Table 41: Dominance rank for all investigations

Investigation	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
FOBT	£343,244	-	809.99	-	-	£15,856,582
Barium enema	£365,818	£22,575	810.94	0.95	£23,730	£15,853,033
Flexible Sigmoidoscopy	£690,542	£347,298	811.76	1.77	£196,197	£15,544,691
CTC	£710,146	£ 366,903	814.38	4.39	£83,664	£15,577,388
Colonoscopy	£810,397	£467,153	814.24	4.25	£109,860	£15,474,474

Faecal Immunochemical Tests

In addition to the main analysis, the GDG wanted to explore the use of newer faecal occult blood tests. Faecal immunochemical tests (FIT) are similar to guaiac based FOBT in their design and sample collection however FIT detects globin in stool samples rather than heam. FIT has been associated with a higher sensitivity and specificity than FOBT. The results of the additional analysis are shown in Table 42 below. It can be seen that FIT is cost-effective compared to colonoscopy and when assessed using the dominance rank method it becomes the most cost-effective test.

Update 2015

[f] When incremental QALYs & Costs are **negative** anything **above** the CE threshold (£20,000 per QALY) is cost-effective.

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Table 42: Dominance rank for all investigations

Investigation	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
FIT	£377,839	-£432,558	812.34	-1.90	£227,696	£15,869,038

Sensitivity analysis results

A series of one-way sensitivity analyses were conducted, whereby the value of one input parameter is changed and its effect on the overall outcome is recorded and assessed. The results of the analysis show that small changes in prevalence, cost and diagnostic accuracy result in barium enema becoming the most cost-effective test. The discount rate also has an effect on the overall result however no other parameter resulted in a change to the overall results.

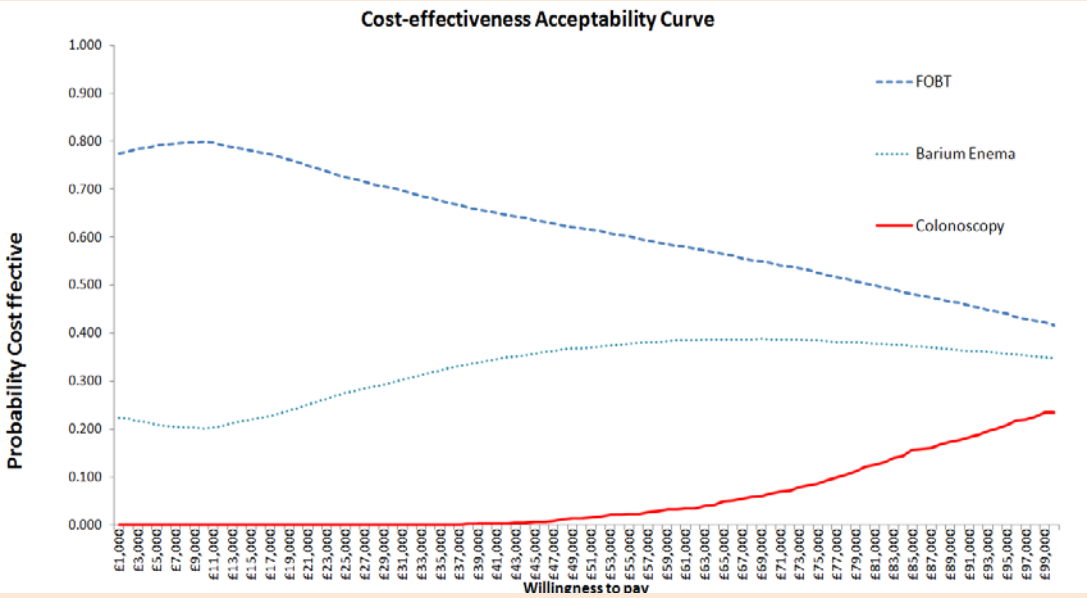
Tests with a high specificity reduce the overall cost of the strategy due to the low number of false positives receiving further unnecessary expensive investigations. Tests with high sensitivity increase the overall number of people diagnosed with cancer thus increasing overall QALYs. FOBT was the most cost-effective investigation because of its low cost and moderately high sensitivity and specificity. The increase in cancer diagnosis between FOBT and the next cheapest, more specific investigation (barium enema) was minimal meaning FOBT was more cost-effective than barium enema.

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values.

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC). The graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis. It can be seen that at a threshold of £20,000 per QALY, FOBT has a high probability of being cost-effective (77%). As the CE threshold increases beyond £20,000 per QALY CTC has a higher probability of being cost-effective.

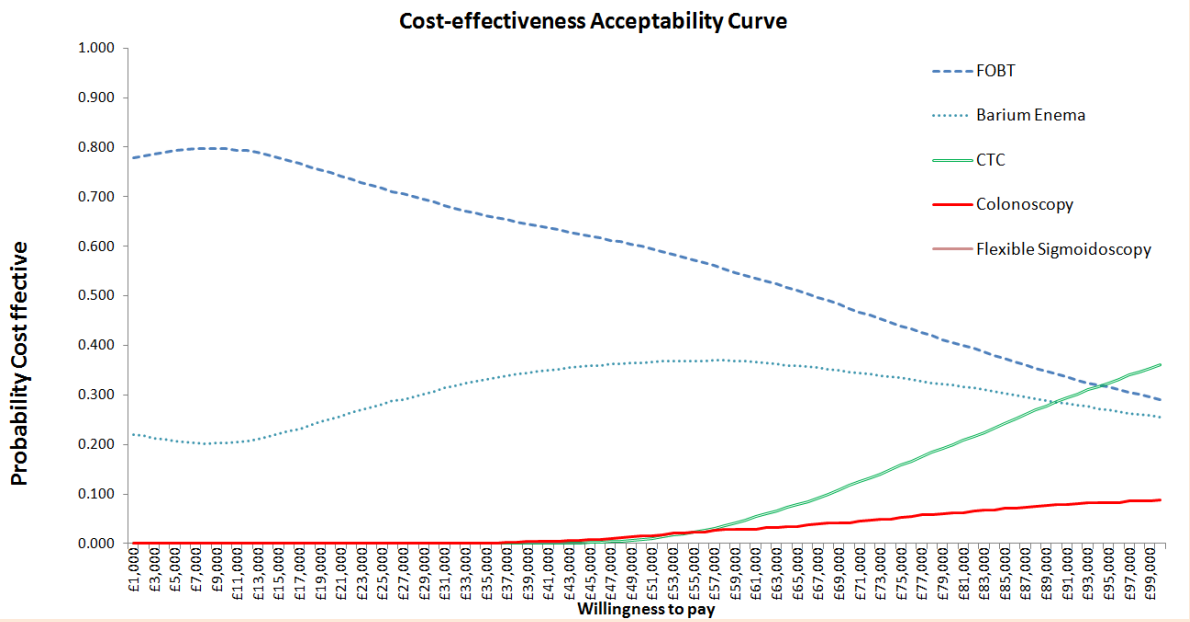
Update 2015

Figure: Cost-effectiveness acceptability curve (CEAC): Base case results



In the figure below CTC and flexible sigmoidoscopy are included in the PSA analysis. It is shown that FOBT is still the most cost-effective test at a threshold of £20,000 per QALY. However, as the CE threshold increases CTC starts to become more cost-effective.

Figure: Cost-effectiveness acceptability curve (CEAC): All included investigations



Conclusion

The results of the analysis suggest that faecal occult blood testing is cost-effective to detect colorectal cancer in people aged 40 years and older with a change in bowel habit in primary care. Barium enema, flexible sigmoidoscopy and computed tomography colonography were all found to be cost-effect compared to colonoscopy however FOBT was the most cost effective for this low risk population.

Update 2015

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 50 and have unexplained rectal bleeding. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged 60 and over and have unexplained iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 60 and have unexplained changes in their bowel habit. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people with a rectal or abdominal mass. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 40 with unexplained weight loss and**

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	abdominal pain. [new 2015] **Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who:** • **have abdominal pain or** • **have weight loss or** • **are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if tests show occult blood in their faeces. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings:** • **abdominal pain or** • **change in bowel habit or** • **weight loss or** • **iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). [new 2015]** **Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. [2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of colorectal cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict colorectal cancer. <u>Investigations in primary care for colorectal cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. Although sensitivity and specificity were reported, the GDG agreed that the most informative outcomes were the positive predictive values (because these gave the risk of a patient harbouring cancer) and the false negative rates (to inform whether a negative test obviated the need for further safety-netting).
Quality of the evidence	<u>Signs and symptoms of colorectal cancer</u> The quality of the evidence as assessed by QUADAS-II varied from low to high for the positive predictive values for the different symptoms. It was noted that Panzuto 2003, included a population that appears to be higher risk than the unselected patients specified in the clinical question, meaning that all the positive predictive values reported in this study were higher than those found in the other included studies for the same symptoms. The GDG also noted several other limitations with the evidence appraised. There was a lack of meta-analyses within different age bands, the studies/subgroup analyses were small, family history was not reported alongside symptoms and all the

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	studies were conducted pre-screening for colorectal cancer. The GDG therefore used caution when making recommendations on the basis of the included evidence. <u>Investigations in primary care for colorectal cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values and false negative rates of all the tests considered, including faecal occult blood tests, and could in no instances be considered of high quality. In addition the GDG noted several limitations with the evidence appraised. The GDG were concerned that the faecal occult blood tests included in the evidence may be out of date as newer faecal occult blood tests are now available. Also that the performance characteristics of the older faecal occult blood tests may differ from those of the newer tests.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with colorectal cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without colorectal cancer who get inappropriately referred whilst maximising the number of people with colorectal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with colorectal cancer outweighed the disadvantages to those without. The GDG considered that the potential benefit of the recommendations will be that more patients harbouring colorectal cancer will qualify for suspected cancer pathway referral, but the GDG also recognised that the potential harms of the recommendations made are that more patients without colorectal cancer will undergo invasive procedures and experience psychological distress. The GDG balanced these harms against the benefits by using a threshold of positive predictive values of 3%, above which the GDG were confident that the advantages of suspected cancer pathway referral in those with cancer outweighed the disadvantages of those without. The GDG noted, based on the evidence, that unexplained rectal bleeding was associated with a positive predictive value above 3%, but that the positive predictive value differed across different age groups. The GDG decided to recommend a suspected cancer pathway referral for patients over 50 years with unexplained rectal bleeding because, they agreed that below 50 years, the PPV of rectal bleeding was unlikely to exceed 3%. The GDG noted, based on the evidence, that unexplained iron-deficiency anaemia was associated with a positive predictive value above 3%, but that the positive predictive value differed across different age groups. The GDG decided to recommend a

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suspected cancer pathway referral for patients over 60 years with unexplained iron-deficiency anaemia because the evidence which reported according to 10-year age band showed lower PPVs below the age of 60. The GDG agreed, based on their clinical experience, that in the other studies, if they had reported by 10 year age band, the PPV below the age of 60 would have been less than 3%.

The GDG noted, based on the evidence, that unexplained change in bowel habit was associated with a positive predictive value above 3%, but that the positive predictive value differed across different age groups. The GDG decided to recommend a suspected cancer pathway referral for patients over 60 years with unexplained change in bowel habit because, they agreed that below 60 years, the PPV of unexplained change in bowel habit was unlikely to exceed 3%.

Whilst the GDG acknowledged that Panzuto (2003) reported a PPV of 13.2 for the symptom of bloating, they also noted that none of the other studies had replicated this high PPV. Given the issues with this study documented earlier, the GDG agreed not to make a recommendation on this symptom.

Based on their clinical experience, the GDG decided to recommend a suspected cancer pathway referral for patients with a rectal or abdominal mass because the GDG agreed that the positive predictive values of either mass were likely to exceed the 3% threshold.

The GDG noted, based on the evidence, that abdominal pain plus weight loss was associated with a positive predictive value above 3%. The GDG also noted that although this positive predictive value was reported for all patients, the youngest age included in the study was 40 years old. Based on their clinical experience, the GDG considered it unlikely that this symptom combination would have a positive predictive value of 3% in people younger than 40 and therefore decided to recommend a suspected cancer pathway referral for people aged over 40.

In addition to this recommendation, the GDG also decided to recommend testing for occult blood in faeces for people presenting with abdominal pain or weight loss, and in people aged below 60 years who present with change in bowel habit or iron-deficiency anaemia, and to recommend a suspected cancer pathway referral for any patients found to have occult blood in their faeces.

Additionally, the GDG noted that the age range and symptomatology in the faecal occult blood test studies did not exactly match the age range/symptomatology for which the GDG made faecal occult blood test recommendations. However, the high positive predictive values of the faecal occult blood test studies were so far above the GDG-adopted 3% threshold, that the GDG considered that they could be applied to different populations and using different biochemical methods/tests.

The GDG agreed that that the potential benefit of recommending testing for occult blood in the faeces will be to

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	filter out those patients with symptoms who are less likely to have colorectal cancer and do not warrant a suspected cancer pathway referral. It will also expedite the diagnosis of people who do have colorectal cancer. The GDG also recognised that the potential harms of the recommendations are that some patients testing positive for occult blood in the faeces will not have colorectal cancer and therefore be exposed to unnecessary investigations and experience psychological distress. The GDG balanced these harms against the benefits by considering that testing for occult blood in the faeces in the specified groups allowed identification of a subgroup above the 3% threshold in whom referral was warranted. The GDG also took into account lay and clinical experience that people wish to be investigated at a lower level of risk and earlier. The GDG also recognised that, although it is much less common, colorectal cancer does occur in people aged below 50 years. They considered, based partly on the evidence and partly on their clinical experience, that in this patient group the positive predictive value of rectal bleeding presenting with either abdominal pain, change in bowel habit, weight loss, or iron-deficiency anaemia was likely to approach 3%. The GDG recognised that testing for occult blood in the faeces would not be an appropriate action for this group as they are already known to have rectal bleeding. The GDG therefore agreed to recommend a suspected cancer pathway referral for patients below 50 years presenting with rectal bleeding in combination with any of these symptoms.
Trade-off between net health benefits and resource use	A de novo health economic model was developed for this topic. The results of the economic analysis were used to inform the recommendations made on occult blood tests in low risk patients. The economic model examined a range of tests available to patients suspected of having colorectal cancer in primary care with low risk symptoms. The results of the model showed that, at the NICE threshold of £20,000 per QALY, guaiac based faecal occult blood tests were the most cost-effective investigation. One-way sensitivity analysis showed that barium enema became the most cost-effective test when the prevalence of cancer in the population increased to 5%. The GDG felt that this would be an unreasonably high prevalence in younger patients with low risk symptoms. In addition, the GDG were concerned that the diagnostic accuracy data included for barium enema was unrealistic. Although the studies included primary care patients the sample sizes were small and the specificity reported was 100% which the GDG felt was unlikely as it is not a definitive test. Probabilistic sensitivity analysis showed that, at the NICE threshold of £20,000 per QALY, guaiac based faecal occult blood tests have a high probability (82%) of being the most cost-effective test in this patient population. Based on this the GDG considered that recommending occult blood tests was an efficient use of NHS resources. Although not originally in the clinical question, the GDG were

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	interested to know if the newer versions of occult blood tests (immunochemical tests) were equally cost-effective in this population. The GDG concluded that there was insufficient primary care evidence on the diagnostic accuracy of these tests to evaluate their direct cost-effectiveness.
Other considerations	The GDG noted that the recommendation to test for occult blood in the faeces will necessitate a change in practice because such tests are not currently available in primary care for symptomatic patients.

9.21 Anal cancer

Anal cancer is generally considered separately from colorectal cancer. The histology is different, with almost all being squamous cell cancers. Just over 1,000 new anal cancers are diagnosed each year in the UK, meaning that a full time GP is likely to diagnose approximately 1-2 people with anal cancer during their career. Five-year survival is around 60%. Anal cancer occurs in both sexes, though nearly two-thirds occur in women.

Several symptoms have been reported, including anal pain, tenesmus and rectal bleeding.

Diagnosis is generally made by direct visualisation (proctoscopy/sigmoidoscopy) and biopsy. Some GPs perform proctoscopy, but biopsies are performed in secondary care.

Clinical questions:

- **What is the risk of anal cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected anal cancer should be done with clinical responsibility retained by primary care?**

Update 2015

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of anal cancer in patients presenting with symptoms in primary care.

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The only included study was associated with a number of bias and validity issues, with the main concerns relating to whether the results are representative of those of UK-based primary care practice and the fact that negative sigmoidoscopy results were not verified or followed up.

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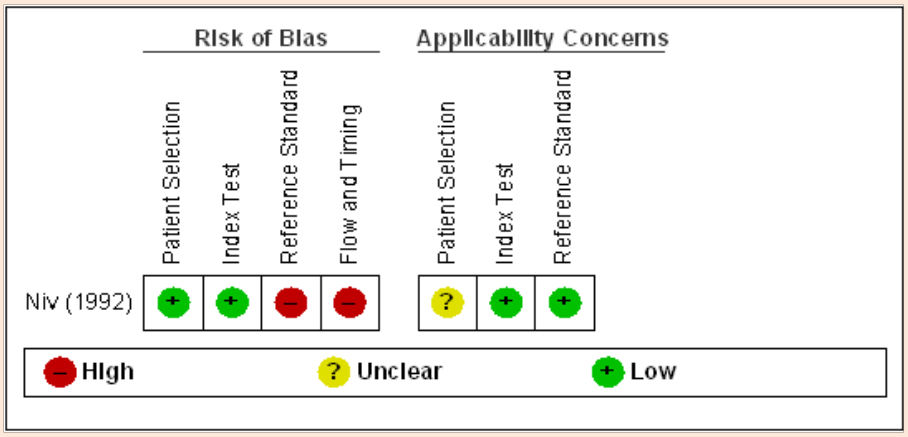

Evidence statement

Sigmoidoscopy (1 study, N = 255) conducted in symptomatic patients presenting in a primary care setting is associated with a positive predictive values of 100%. The included study was associated with 3 bias/applicability concerns (see also Table 43).

Table 43: Anal cancer: Sigmoidoscopy

Study	Test	Prevalence	Sensi-tivity (95% CI)	Speci-ficity (95% CI)	Other results (95% CI)
Niv (1992)	Flexible sigmoidoscopy	5/255	Not reported	Not reported	TP = 4 FN = ≥ 1 TN = ? FP = 0 Positive predictive value = 100% (39.6-100) False negativity rate = cannot be ascertained as negative cases did not appear to be followed up

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

No evidence was found for proctoscopy.

Update 2015

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for anal cancer in people with an unexplained anal mass or unexplained anal ulceration. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of anal cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict anal cancer. No evidence was found for this outcome. Investigations in primary care for anal cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	Signs and symptoms of anal cancer

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	No evidence was found pertaining to the positive predictive values of different symptoms of anal cancer in primary care. <u>Investigations in primary care for anal cancer</u> The evidence for sigmoidoscopy consisted of only one paper of low quality and very limited applicability. No evidence was found pertaining to the diagnostic accuracy of proctoscopy in primary care patients with suspected anal cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathways referral would be to identify those people with anal cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without anal cancer who get inappropriately referred whilst maximising the number of people with anal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with anal cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for anal cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected anal cancer, since diagnosis at an early stage improves the outcome. The GDG noted that 'an unexplained anal mass or ulceration' can be symptoms of anal cancer. The GDG agreed, based on their clinical experience, that had this symptom been studied it would have had a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for these symptoms. The GDG noted the lack of evidence for proctoscopy and the extreme limitations of the evidence for sigmoidoscopy and also noted that neither test is routinely available in UK-based general practices. The GDG considered possible scenarios where these tests might have been useful for the investigation of anal cancer in primary care, but could find none because the assumed positive predictive values would be too low. The GDG therefore decided not to make any recommendations for the primary care investigation of suspected anal cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for an 'unexplained anal mass or ulceration' was likely to be cost-neutral as it is already standard practice.

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Colorectal cancer

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Anal cancer

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10 Breast cancer

Around 50,000 new breast cancers are diagnosed each year in the UK, around a quarter of these following screening mammography. A full time GP is likely to diagnose approximately 1-2 people with breast cancer every year. It is uncommon in males. Five-year survival is 85%, though this figure includes cancers detected by screening as well as those identified after symptoms have occurred.

Several symptoms have been reported, with breast lump being the most common. A malignant breast lump is usually painless, though pain can occur. Nipple symptoms, including change in shape or nipple bleeding, are recognised symptoms, as are skin changes, such as tethering or *peau d'orange*.

A diagnosis of breast cancer is generally made using mammography and fine needle aspiration. This is performed in secondary care.

Clinical questions:

- **What is the risk of breast cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected breast cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note is that 3/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP and a fourth study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Two of the studies also employed reference standards that are subject to an unclear risk of bias, one study only reported episode-(not patient)based analyses, which seems to result in overestimation of the PPVs, and one study had a large amount of missing data; all of which must be born in mind when evaluating the evidence contributed by these studies.

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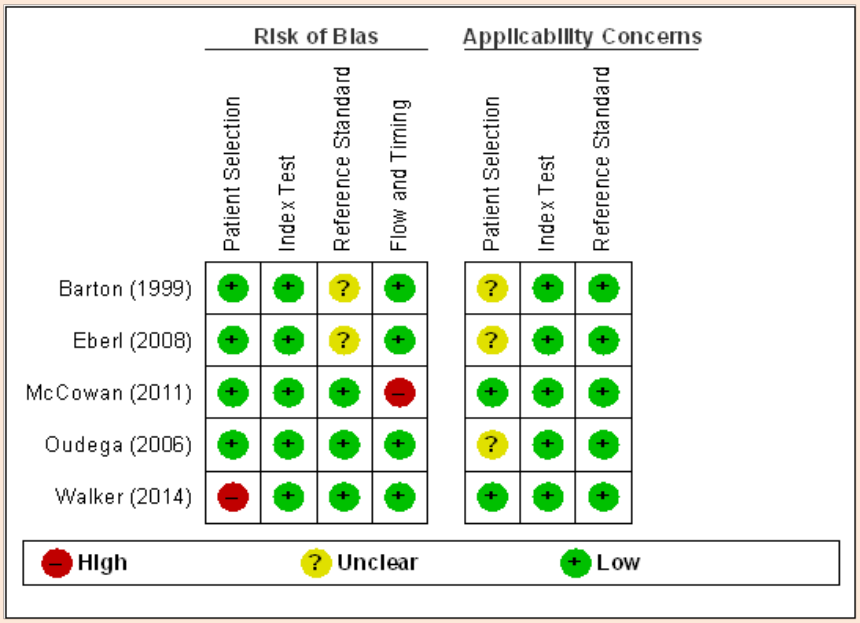

Evidence statement

The positive predictive values for breast cancer of single symptoms presenting in a primary care setting ranged from 0% (for an 'irrregularly shaped discrete breast lump', a 'breast lump with a spongy texture', nipple discharge, nipple eczema, nipple retraction, breast abscess, 'other breast symptom') to 48% (for breast lump in women aged 70+ years; 5 studies, N = 24269), but these extreme PPVs were based on small patient/episode numbers. The studies were subject to 1-2 bias or applicability concerns (see also Table 44).

The positive predictive values for breast cancer of symptom pairs presenting in a primary care setting ranged from 0% (for breast lumpiness with 'skin or nipple change' or breast pain, and for breast pain with 'skin or nipple change') to 100% (for breast mass and 'skin or nipple change'; 2 studies, N = 21239), but these extreme PPVs were based on small patient/episode numbers. The studies were subject to 1-2 bias/applicability concerns (see also Table 45).

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Table 44: Breast cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)% Prevalence
Barton (1999) Episode-based analysis	Breast pain	Women aged 40-79 years	1.8 (0.6-4.9) 4/221 episodes in 372 women
Eberl (2008)	Breast pain	Women aged <25 – 75+ years	0.9 (0.5-1.7) 11/1191
McCowan (2011)	Breast pain	Women aged 25- >80 years	5.9 (1-21.1) 2/34
Walker (2014)	Breast pain	Women aged 40-49 years	0.17 (0.16-0.17)
Walker (2014)	Breast pain	Women aged 50-59 years	0.8 (0.52-1.2)
Walker (2014)	Breast pain	Women aged 60-69 years	1.2 (0.73-2)
Walker (2014)	Breast pain	Women aged 70+ years	2.8 (1.4-5.4)
Barton (1999)	Breast mass	Women aged 40-79	10.7 (6.9-16.1)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)% Prevalence
Episode-based analysis		years	21/196 episodes in 372 women
Eberl (2008)	Breast lump/mass	Women aged <25 – 75+ years	8.1 (6.3-10.4) 60/741
Walker (2014)	Breast lump	Women aged 40-49 years	4.8 (3.6-5.4)
Walker (2014)	Breast lump	Women aged 50-59 years	8.5 (6.7-11)
Walker (2014)	Breast lump	Women aged 60-69 years	25 (17-36)
Walker (2014)	Breast lump	Women aged 70+ years	48 (35-61)
McCowan (2011)	Discrete breast lump	Women aged 25- >80 years	10 (3.7-22.6) 5/50
McCowan (2011)	Discrete breast lump < 2 cm	Women aged 25- >80 years	7.7 (0.4-37.9) 1/13
McCowan (2011)	Discrete breast lump ≥ 2 cm	Women aged 25- >80 years	14.3 (2.5-43.8) 2/14
McCowan (2011)	Discrete breast lump: Round, oblong mass	Women aged 25- >80 years	25 (4.5-64.4) 2/8
McCowan (2011)	Discrete breast lump: Irregular in shape	Women aged 25- >80 years	0 (0-69) 0/3
McCowan (2011)	Discrete breast lump: Mobile	Women aged 25- >80 years	12.5 (2.2-40) 2/16
McCowan (2011)	Discrete breast lump: Tethered to skin or chest wall	Women aged 25- >80 years	40 (7.3-83) 2/5
McCowan (2011)	Discrete breast lump: Smooth texture	Women aged 25- >80 years	18.2 (3.2-52.2) 2/11
McCowan (2011)	Discrete breast lump: Irregular texture	Women aged 25- >80 years	33.3 (6-75.9) 2/6
McCowan (2011)	Discrete breast lump: Spongy texture	Women aged 25- >80 years	0 (0-94.5) 0/1
Walker (2014)	Nipple discharge	Women aged 40-49 years	1.2 (NR)
Walker (2014)	Nipple discharge	Women aged 50-59 years	2.1 (0.81-5.1)
Walker (2014)	Nipple discharge	Women aged 60-69 years	2.3 (NR)
Walker (2014)	Nipple discharge	Women aged 70+ years	23 (NR)
McCowan (2011)	Nipple discharge	Women aged 25- >80 years	0 (0-37.1) 0/9
McCowan (2011)	Nipple discharge: Bloodstained	Women aged 25- >80 years	0 (0-53.7) 0/5
McCowan (2011)	Nipple discharge: Persistent	Women aged 25- >80 years	0 (0-43.9) 0/7
Barton (1999)	Skin or nipple change	Women aged 40-79	3 (0.5-11.3)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)% Prevalence
Episode-based analysis		years	2/67 episodes in 372 women
Eberl (2008)	Nipple complaint	Women aged <25 – 75+ years	1.9 (0.6-5.1) 4/210
McCowan (2011)	Nipple eczema	Women aged 25- >80 years	0 (0-94.3) 0/1
McCowan (2011)	Nipple retraction	Women aged 25- >80 years	0 (0-53.7) 0/5
Walker (2014)	Nipple retraction	Women aged 40-49 years	NR (NR) 4 cases, 0 controls
Walker (2014)	Nipple retraction	Women aged 50-59 years	2.6 (NR)
Walker (2014)	Nipple retraction	Women aged 60-69 years	3.4 (NR)
Walker (2014)	Nipple retraction	Women aged 70+ years	12 (NR)
Barton (1999) Episode-based analysis	Breast lumpiness	Women aged 40-79 years	2.6 (0.1-15.4) 1/38 episodes in 372 women
McCowan (2011)	Breast thickening	Women aged 25- >80 years	11.1 (0.6-49.3) 1/9
McCowan (2011)	Breast abscess	Women aged 25- >80 years	0 (0-94.3) 0/1
Barton (1999) Episode-based analysis	Other breast symptom	Women aged 40-79 years	0 (0-43.9) 0/7 episodes in 372 women
Eberl (2008)	Other breast complaint	Women aged <25 – 75+ years	1.7 (0.7-3.8) 6/361
McCowan (2011)	Other breast symptom (skin nodules, general nodularity)	Women aged 25- >80 years	25 (1.3-78.1) 1/4
McCowan (2011)	Lymphadenopathy	Women aged 25- >80 years	40 (7.3-83) 2/5
Oudega (2006)	Deep vein thrombosis	All patients	0.93 (0.3-2.53) 4/430

CI = Confidence interval. Please note the calculations of the positive predictive values differ between the studies with Barton (1999), Eberl (2008), McCowan (2011) and Oudega (2006) using (TP)/(TP+FP) and Walker (2014) using Bayesian statistics due to the case-control design of this study. No meta-analyses were performed as there were not enough studies for this analysis to be performed with both Barton (1999) and Walker (2014) being ineligible for inclusion due to the episode-based analysis and case-control design, respectively.

Table 45: Breast cancer: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Barton (1999) Episode-based analysis	Breast pain (reported twice in an episode??)	Women aged 40-79 years	1.2 (0.2-4.7)* 2/169 episodes in 372 women
Barton (1999) Episode-based analysis	Breast mass (reported twice in an episode??)	Women aged 40-79 years	10.7 (6.5-16.8)* 17/159 episodes in 372 women

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Barton (1999) Episode-based analysis	Skin or nipple change (reported twice in an episode??)	Women aged 40-79 years	2 (0.1-11.8)* 1/51 episodes in 372 women
Barton (1999) Episode-based analysis	Breast lumpiness (reported twice in an episode??)	Women aged 40-79 years	4 (0.2-22.3)* 1/25 episodes in 372 women
Barton (1999) Episode-based analysis	Breast pain and breast mass	Women aged 40-79 years	6.5 (1.1-22.8) 2/31 episodes in 372 women
Walker (2014)	Breast lump and breast pain	Women aged 40-49 years	4.9 (NR)
Walker (2014)	Breast lump and breast pain	Women aged 50-59 years	5.7 (NR)
Walker (2014)	Breast lump and breast pain	Women aged 60-69 years	6.5 (NR)
Walker (2014)	Breast lump and breast pain	Women aged 70+ years	> 5 (NR)
Barton (1999) Episode-based analysis	Breast pain and skin or nipple change	Women aged 40-79 years	0 (0-26.8) 0/14 episodes in 372 women
Barton (1999) Episode-based analysis	Breast pain and breast lumpiness	Women aged 40-79 years	0 (0-43.9) 0/7 episodes in 372 women
Barton (1999) Episode-based analysis	Breast mass and skin or nipple change	Women aged 40-79 years	100 (5.5-100) 1/1 episodes in 372 women
Barton (1999) Episode-based analysis	Breast mass and breast lumpiness	Women aged 40-79 years	20 (10.5-70.1) 1/5 episodes in 372 women
Barton (1999) Episode-based analysis	Skin or nipple change and breast lumpiness	Women aged 40-79 years	0 (0-94.5) 0/1 episodes in 372 women

*CI = Confidence interval. Please note the calculations of the positive predictive values differ between the studies with Barton (1999) using (TP)/(TP+FP) and Walker (2014) using Bayesian statistics due to the case-control design of this study. * These results are presented in a table (Table 5) entitled "Breast Cancer Diagnosis According to Combinations of Symptoms", it is however unclear what they reflect: Since they are similar, but not identical to those presented as single symptoms, they cannot be that; also, since only 56 women had 2 episodes and 35 women had 3 or more episodes, these results cannot represent a repeat presentation of the same symptom across episodes; which leaves repeat presentations of these symptoms within episodes as an option. However, that is not clearly reported either in the paper, so it cannot be confirmed what exactly these results reflect.*

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The study was associated with a number of bias and validity issues. The following issues compromise the validity and applicability of this study, (1) only about half of the patient population were patients relevant to the current question, to the extent that Dutch primary care is comparable to UK-based primary care, and no subgroup analyses were presented for this group of patients, (2) the results of the ultrasound scan was interpreted non-blinded to the results of the mammography and clinical examination, which biases the accuracy of the outcome measures study, most likely upwards, and (3) the time span

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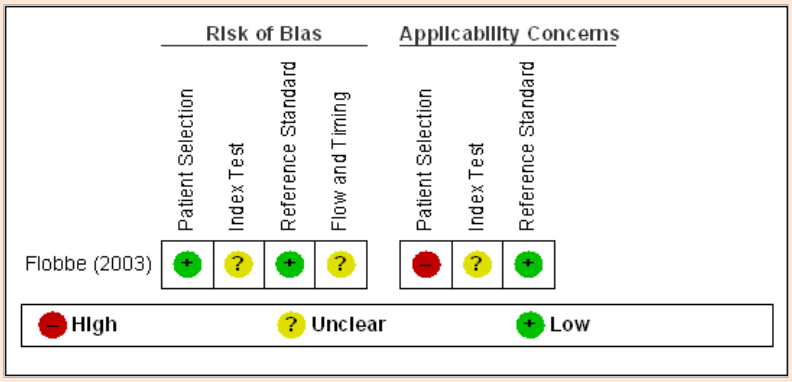
between the index test and reference standard is unclear and the results are therefore compromised to an unknown extent.



Evidence statement

Mammography (1 study, N = 2020 patients/ 3835 breasts) is associated with a sensitivity of 82.9%, a specificity of 91.9%, a positive predictive value of 26.2%, and a false negativity rate of 17.1% for breast cancer. Ultrasound (1 study, N = 2020 patients/ 3835 breasts) is associated with a sensitivity of 87.6%, a specificity of 95.5%, a positive predictive value of 40.4%, and a false negativity rate of 12.4% for breast cancer. The study was associated with 4 bias or applicability concerns (see also Table 46).

Table 46: Breast cancer: Study results

Study	Test	Prevalence	Sensi-tivity (95% CI) %	Speci-ficity (95% CI) %	Other results (95% CI)
Flobbe (2003)	Mammography	129/3835 breasts 127/2020 patients	82.9 (75.1-88.8)	91.9 (90.9-92.7)	TP = 107 FN = 22 TN = 3405 FP = 301 Positive predictive value = 26.2 (22.1-30.8)% Negative predictive value = 99.4 (99-99.6)% False negativity rate = 17.1%
Flobbe (2003)	Ultrasound	129/3835 breasts 127/2020 patients	87.6 (80.4-92.5) %	95.5 (94.8-96.1) %	TP = 113 FN = 16 TN = 3556 FP = 167 These values from the paper are wrong as the total of negatives should be 3706 and not 3723 as is the case here. This means that apart from the sensitivity and false negativity rate, the remaining results for ultrasound should be interpreted with extreme caution. Positive predictive value = 40.4 (34.6-46.4) % Negative predictive value = 99.6 (99.3-99.7)% False negativity rate = 12.4%

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.
No evidence was found for FNA

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer if they are aged 30 and over and have an unexplained breast lump with or without pain. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer if they are aged 50 and over with any of the following symptoms in 1 nipple only:** • **discharge** • **retraction** • **other changes of concern. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer in people aged 30 and over with an unexplained lump in the axilla. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of breast cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict breast cancer. <u>Investigations in primary care for breast cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question.
Quality of the evidence	<u>Signs and symptoms of breast cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of moderate-high quality. The GDG noted that for some of the symptoms the positive predictive values were based on very few patients and that this was likely to make these estimates unreliable. <u>Investigations in primary care for breast cancer</u> The evidence for ultrasound and mammography consisted of only one paper of low quality and very limited applicability. No evidence was found pertaining to the diagnostic performance of fine needle aspiration in primary care patients with suspected breast cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with breast cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without breast cancer who get inappropriately referred whilst maximising the number of people with breast cancer who get appropriately referred. In order to strike an appropriate balance between these

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considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with breast cancer outweighed the disadvantages to those without.

The GDG noted, based on the evidence, that 'any breast lump with or without pain' presenting in a primary care setting was associated with a positive predictive value of above 3% for breast cancer. The GDG also noted that the most reliable evidence came from Walker (2011) which included women aged 40 years or older, and that the positive predictive value (and its confidence interval) for a breast lump in women aged 40-49 years was considerably above 3% in this study, with the remaining positive predictive values increasing in direct proportion to increasing age. The GDG extrapolated downwards from age 40 and did not consider it likely that the positive predictive value for a breast lump would drop sharply below this age. The GDG also noted that breast cancer is extremely rare in people aged below 30 years. On this basis, the GDG decided to recommend that 'any breast lump with or without pain' should prompt a suspected cancer pathway referral in a person aged 30 years or older.

The GDG also noted, based on the evidence, that nipple discharge or nipple retraction are symptoms of breast cancer with positive predictive values that increase with age to the extent that they exceed 3% in women aged 70 years or older and 60 years or older, respectively. However, the GDG also noted that the included studies did not distinguish between unilateral and bilateral breast symptoms and therefore judged that the reported symptoms are most likely to be a mix of unilateral and bilateral symptoms. Moreover, the GDG noted, based on their clinical experience that unilateral symptoms carry a higher risk of breast cancer than bilateral symptoms because breast cancer is usually unilateral. The GDG therefore considered that the positive predictive values presented in the evidence are likely to be higher for unilateral symptoms. The GDG therefore decided to recommend a suspected cancer pathway referral for unilateral nipple discharge or retraction in people aged 50 years or older.

The GDG noted, based on their clinical experience, that other nipple symptoms, such as Paget's disease, can be highly predictive of breast cancer. The GDG therefore decided to recommend a suspected cancer pathway referral for 'other nipple change'. However, in order to make a comprehensive and user-friendly recommendation on nipple symptoms, the GDG decided to include 'other nipple change' in the recommendation already made on nipple symptoms in people aged 50 years or older.

The GDG noted that McCowan (2011) reported a PPV of 11.1 for breast thickening. The GDG noted that this was a difficult symptom to make sense of as it was unclear whether it meant thickening of the skin of the breast, or of the breast tissue itself. The confidence intervals reported in McCowan (2011) for this symptom were also extremely wide, reflecting small numbers. Given these issues the GDG agreed it was better to group all 'changes of concern' in the breast together.

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	The GDG noted that 'an unexplained lump in the axilla' can be a symptom of breast cancer. The GDG agreed, based on their clinical experience, that had this symptom been studied it would have had a positive predictive value of 3% or above. The GDG acknowledged that the chance of an axillary mass being malignant rises with age, but there was uncertainty over the age at which the PPV of this symptom reaches a positive predictive value of 3%. The GDG therefore agreed to use the age cut off of 30 years for this symptom to make this recommendation easier to implement alongside the the other breast recommendation Finally, the GDG noted that the strongest evidence was from studies that only included women. However, although breast cancer is extremely rare in men, the GDG decided to extend the recommendations to men by using the term "people" because there is no evidence to suggest that breast cancer presents differently in women than in men. Due to the lack of good quality evidence, the GDG felt unable to make any recommendations about the investigation of suspected breast cancer in primary care.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that current clinical practice is that most women over 30 with a breast symptom get a suspected cancer pathway referral within 2 weeks. Since the recommendations made in this guideline now cover specific symptoms, the GDG considered this would result in a reduction in the number of referrals and a corresponding cost saving. However, because the new recommendations encompass most of the whomen who currently get referred, the GDG anticipated there would only be a small reduction in costs.
Other considerations	The GDG recognised that people who have already had breast cancer may present with a second primary in the other breast. However, the GDG felt that the recommendations cover this population too as there is no evidence to suggest that they present differently to people with a first primary breast cancer.

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Breast cancer

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11 Gynaecological cancers

11.1 Ovarian cancer

Over 7,000 new ovarian cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with ovarian cancer every 3-5 years. Five year survival is very dependent upon the stage at diagnosis.

Ovarian cancer can present with a number of different symptoms, and there are often multiple symptoms simultaneously. Symptoms include abdominal pain, abnormal vaginal bleeding, loss of weight, loss of appetite and fatigue. The cancer may also present with abdominal distension.

Most ovarian cancers lead to a raised serum CA125, a blood test that can be performed in primary care. Ultrasound, particularly trans-vaginal, can image the ovaries well, and is generally used after a raised CA125 is found, or where there is continuing suspicion despite a normal CA125. This is generally available in primary care. Definitive diagnosis requires biopsy, a secondary care procedure.

Recommendations	**Refer the woman urgently[g] if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). [2011]** **Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month:** • **persistent abdominal distension (women often refer to this as 'bloating')** • **feeling full (early satiety) and/or loss of appetite** • **pelvic or abdominal pain** • **increased urinary urgency and/or frequency. [2011]** **Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit. [2011]** **Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent. [2011]** **Carry out appropriate tests for ovarian cancer in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[h], because IBS rarely presents for the first time in women of this age. [2011]** **Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. [2011]** **If serum CA125 is 35 IU/ml or greater, arrange an ultrasound**

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g An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.
h See the NICE guideline on irritable bowel syndrome in adults

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	scan of the abdomen and pelvis. [2011] **If the ultrasound suggests ovarian cancer, refer the woman urgently[i] for further investigation. [2011]** **For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:** • **assess her carefully for other clinical causes of her symptoms and investigate if appropriate** • **if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent. [2011]**
	These recommendations are from 'Ovarian cancer', NICE clinical guideline 122 (2011). They were formulated by the Ovarian cancer guideline and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/CG122.

11.21 Endometrial cancer

Around 8,000 new endometrial cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with endometrial cancer every 3-5 years. Five year survival is close to 80%.

The most common symptom of endometrial cancer is abnormal vaginal bleeding, particularly after the menopause.

These features of endometrial cancer can also be present in other cancers, especially cervical or ovarian cancer.

The main method of diagnosis is by endometrial biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of endometrial cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected endometrial cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included studies in the figure below. The main issues to note are that one of the studies was conducted in a Dutch primary care setting, which may limit the applicability of the result to UK primary care and this study may also not have accounted for all the patients. Moreover, another study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors of the study may have gone some

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i An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

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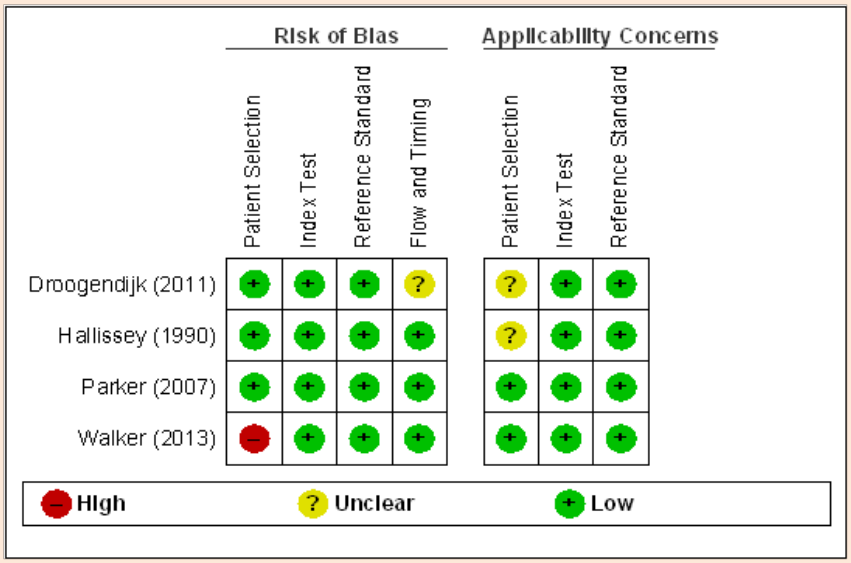
way in counteracting this influence. Finally, the population in one of the studies comprises a mix of 'old' and 'new' investigated or uninvestigated symptoms, and it is unclear how directly applicable this sample is to the current question.



Evidence statement

For uterine cancer the positive predictive values of single symptoms (4 studies, N = 25134) presenting in primary care ranged from 0% (for post-menopausal bleeding in women aged 40-44 years) to 9.6% (for repeated post-menopausal bleeding). The included studies were associated with 0-2 bias/applicability concerns (see also Table 47).

For uterine cancer the positive predictive values of symptom combinations (1 study, N = 12269) presenting in primary care ranged from 0.1% (for high platelets in combination with either abdominal pain, low haemoglobin or high glucose) to 9.1% (for post-menopausal bleeding combined with haematuria). The included study was associated with 1 bias concern (see also Table 48).

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Table 47: Endometrial cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Walker (2013)	Abdominal pain (first presentation to GP)	Women ≥ 55 years	0.1 (0.1-0.1)
Walker (2013)	Abdominal pain (repeated symptom)	Women ≥ 55 years	0.2 (0.1-0.1) As reported, but CI is not correct
Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585
Walker (2013)	Haematuria (first presentation to GP)	Women ≥ 55 years	0.7 (0.5-1)
Walker (2013)	Vaginal discharge (first presentation to GP)	Women ≥ 55 years	1.1 (0.8-1.5)
Parker (2007)	Post-menopausal bleeding	All women	1.7 (1.4-2)
		Women 40-44 years	0 (0-5.9) 0/77
		Women 45-54 years	0.3 (0.2-0.7)
		Women 55-64 years	1.1 (0.9-1.5)
		Women 65-74 years	3.1 (2.4-4.1)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
		Women 75-84 years	5.4 (4-7.2)
		Women ≥ 85 years	3.7 (2-6.7)
Walker (2013)	Post-menopausal bleeding (first presentation to GP)	Women ≥ 55 years	4 (3.2-5.2)
Walker (2013)	Post-menopausal bleeding (repeated symptom)	Women ≥ 55 years	9.6 (6.2-17.8)
Droogendijk	Anaemia	All women	0.63 (0.03-4.01) 1/158
Walker (2013)	Low haemoglobin (test)	Women ≥ 55 years	0.1 (0.1-0.1)
Walker (2013)	High platelets (test)	Women ≥ 55 years	0.1 (0.1-0.1)
Walker (2013)	High glucose (test)	Women ≥ 55 years	0.1 (0.1-0.2)

1 *Walker (2013) calculated the positive predictive values using Bayesian statistics.*

2 **Table 48: Endometrial cancer: Symptom combinations**

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Walker (2013)	Post-menopausal bleeding + haematuria	Women ≥ 55 years	9.1 (NR)
Walker (2013)	Post-menopausal bleeding + vaginal discharge	Women ≥ 55 years	8.3 (NR)
Walker (2013)	Post-menopausal bleeding + abdominal pain	Women ≥ 55 years	2.9 (1.6-5.7)
Walker (2013)	Post-menopausal bleeding + low haemoglobin (test)	Women ≥ 55 years	6.4 (NR)
Walker (2013)	Post-menopausal bleeding + high platelets (test)	Women ≥ 55 years	5.4 (3.1-10.2)
Walker (2013)	Post-menopausal bleeding + high glucose (test)	Women ≥ 55 years	3.4 (1.3-9.5)
Walker (2013)	Abdominal pain + haematuria	Women ≥ 55 years	0.7 (NR)
Walker (2013)	Abdominal pain + vaginal discharge	Women ≥ 55 years	0.5 (0.2-1.3)
Walker (2013)	Abdominal pain + low haemoglobin (test)	Women ≥ 55 years	0.2 (0.1-0.4)
Walker (2013)	Abdominal pain + high platelets (test)	Women ≥ 55 years	0.1 (0.1-0.2)
Walker (2013)	Abdominal pain + high glucose (test)	Women ≥ 55 years	0.3 (0.1-0.5)
Walker (2013)	Vaginal discharge + haematuria	Women ≥ 55 years	2.2 (NR)
Walker (2013)	Vaginal discharge + low haemoglobin (test)	Women ≥ 55 years	0.6 (NR)
Walker (2013)	Vaginal discharge + high platelets (test)	Women ≥ 55 years	1.4 (NR)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Walker (2013)	Vaginal discharge + high glucose (test)	Women ≥ 55 years	0.6 (NR)
Walker (2013)	Haematuria + low haemoglobin (test)	Women ≥ 55 years	2.7 (NR)
Walker (2013)	Haematuria + high platelets (test)	Women ≥ 55 years	1.9 (NR)
Walker (2013)	Haematuria + high glucose (test)	Women ≥ 55 years	1.1 (NR)
Walker (2013)	Low haemoglobin (test) + high glucose (test)	Women ≥ 55 years	0.2 (0.1-0.2)
Walker (2013)	Low haemoglobin (test) + high platelets (test)	Women ≥ 55 years	0.1 (0.1-0.2)
Walker (2013)	High platelets (test) + high glucose (test)	Women ≥ 55 years	0.1 (0.1-0.2)

Walker (2013) calculated the positive predictive values using Bayesian statistics. NR = not reported.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of transvaginal/abdominal ultrasound, pipelle sampling, CA125 or hysteroscopy in patients with suspected endometrial cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Refer women using a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause). [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer in women aged under 55 with post-menopausal bleeding. [new 2015]** **Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with unexplained symptoms of vaginal discharge who:** • **are presenting with these symptoms for the first time or** • **have thrombocytosis or** • **report haematuria. [new 2015]** **Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with visible haematuria and any of the following:** • **low haemoglobin levels or** • **thrombocytosis or** • **high blood glucose levels. [new 2015]**

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Relative value placed on the outcomes considered	<u>Signs and symptoms of endometrial cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict endometrial cancer. <u>Investigations in primary care for endometrial cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of endometrial cancer</u> Although the quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms, the body of evidence as a whole could generally be considered of high quality. <u>Investigations in primary care for endometrial cancer</u> No evidence was found pertaining to the diagnostic accuracy of transvaginal/transabdominal ultrasound, pipelle sampling, CA125 or hysteroscopy in primary care patients with suspected endometrial cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those women with endometrial cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of women without endometrial cancer who get inappropriately referred whilst maximising the number of women with endometrial cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with endometrial cancer outweighed the disadvantages to those without. The GDG noted, based on the evidence, that post-menopausal bleeding presenting in a primary care setting was associated with a positive predictive value of above 3% for endometrial cancer in women aged 55 years and above. They therefore recommended this symptom should prompt a suspected cancer pathway referral. The GDG also noted that strictly-defined post-menopausal bleeding (i.e. unexplained vaginal bleeding more than 12 months after cessation of menstruation due to ovarian failure) is still a concern if it occurs in women younger than 55 years, that a number of medical conditions (including endometrial cancer) present earlier in deprived communities, and that relatively younger women (aged under 55 years) would benefit proportionately more from earlier diagnosis of endometrial cancer. The GDG therefore agreed to also recommend a suspected cancer pathway referral for women aged less than 55 years who present with post-menopausal bleeding. However, due to the lack of evidence, the GDG were only able to recommend that a suspected cancer pathway referral is considered.

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	The GDG noted the absence of evidence for investigations for endometrial cancer in primary care. Based on their clinical experience they considered that whilst ultrasound is an investigation commonly used to diagnose endometrial cancer in secondary care, it could have value as an investigation in primary care to determine if a suspected cancer pathway referral was needed. The GDG considered that the clinical benefits of investigation performed in primary care would be to expedite endometrial cancer diagnosis in women whose symptoms may otherwise not be investigated. The GDG noted, based on the evidence, that vaginal discharge at first presentation or with high platelets or haematuria, as well as haematuria with low haemoglobin, high platelets or high glucose are also associated with an appreciable risk of endometrial cancer in women aged 55 and above. The GDG also noted that haematuria, vaginal discharge and post-menopausal bleeding are not always easily differentiated by the woman The GDG therefore decided to recommend further investigation in primary care with ultrasound for women aged 55 and above for clinical scenarios where urgent referral is not warranted, based on symptoms at presentation, but endometrial cancer is still a small possibility.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendations made for referral for endometrial cancer will be either cost-neutral or associated with a slight decrease in resource use as no recommendation was made for referral for persistent inter-menstrual bleeding, unlike in previous guidance. The GDG noted that the recommendation for ultrasound is likely to result in a cost increase due to an increased number of ultrasound scans performed, but that this increase will be counteracted by the savings associated with more endometrial cancers being diagnosed earlier.
Other considerations	The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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11.3 Cervical cancer

Just below 3,000 new cervical cancers are diagnosed each year in the UK, around three-quarters of these following screening. A full time GP is likely to diagnose one person with cervical cancer approximately every ten years. Five year survival is approximately 65%.

The reported symptoms of cervical cancer include inter-menstrual and post-coital bleeding, vaginal discharge and pain.

A diagnosis of cervical cancer is generally made by biopsy, performed in secondary care.

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Clinical questions:

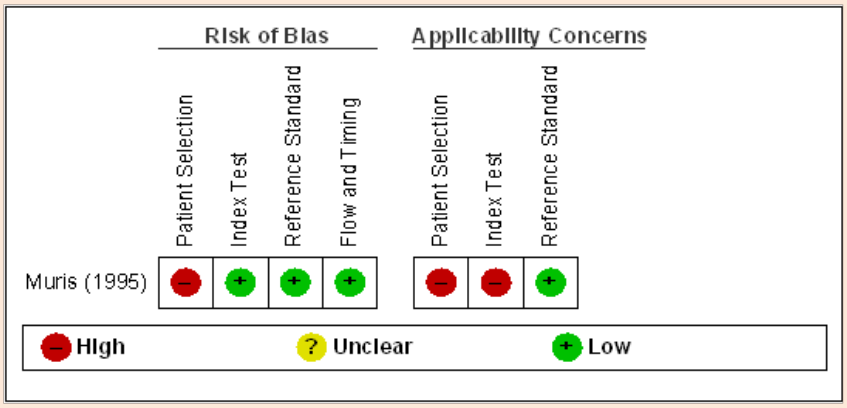
- **What is the risk of cervical cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected cervix cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issues to note are that the study results are compromised by both the non-consecutive/non-random patient selection as well as by the under-specification of the symptom under investigation and the setting, which may not be directly applicable to UK-based primary care.



Evidence statement

Non-acute abdominal complaints presenting in primary care do not appear to be associated with an increased risk of cervical cancer (PPV = 0.5%; 1 study, N = 598). The included study was associated with 3 bias/applicability concerns (see also Table 49).

Table 49: Cervical cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Muris (1995)	Non-acute abdominal complaints	All women	0.5 (0.1-1.6) 3/598: 1 cervix, 2 other cancer of the female genital system

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of cervical smear in patients with suspected cervix cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher

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priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for women if the appearance of their cervix is consistent with cervical cancer. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of cervical cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict cervical cancer. <u>Investigations in primary care for cervical cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of cervical cancer</u> The evidence pertaining to the positive predictive values of different symptoms of cervical cancer in primary care was extremely limited consisting of one low quality study reporting on a patient series of 598 patients, with non-acute abdominal complaints. Only one of these patients had cervical cancer. Therefore the GDG decided to disregard this evidence. <u>Investigations in primary care for cervical cancer</u> No evidence was found pertaining to the diagnostic accuracy of cervical smear in primary care patients with suspected cervical cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those women with cervical cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of women without cervical cancer who get inappropriately referred whilst maximising the number of women with cervical cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with cervical cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that only very little evidence of low quality had been found on the positive predictive values of symptoms for cervical cancer. Despite the limited evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected cervical cancer, since screening does not identify all cervical cancers, leaving some to present symptomatically. The GDG noted that a cervix with an appearance consistent with cervical cancer is likely to be a symptom of cervical cancer. The GDG agreed, based on their clinical experience, that had this symptom been studied it would have had a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for this symptom. The GDG also discussed the likely PPVs for other symptoms, such as

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	inter-menstrual bleeding, post-coital bleeding and vaginal discharge. However the GDG agreed that these were likely to be extremely low as these symptoms are very common and cervical cancer is relatively rare. The GDG therefore decided not to make any further recommendations based on symptoms. Due to the lack of evidence and the fact that there is no other obvious test for a cervix with an appearance consistent with cervical cancer in primary care, the GDG were not able to recommend a particular test beyond visual inspection for the primary care investigation of cervical cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation made for referral for cervical cancer is likely to be either cost-neutral or associated with a slight decrease in resource use as no recommendation was made for referral for persistent inter-menstrual bleeding, unlike in previous guidance.
Other considerations	The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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11.4 Vulval cancer

Over 1,000 new vulval cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with vulval cancer during their career. Most vulval cancers are squamous cell cancers.

Because of its rarity, there are few reports on the clinical features of vulval cancer. It is believed usually to present with a mass or ulceration of the vulva, with vulval itch or redness.

Definitive diagnosis requires biopsy, performed in secondary care.

Clinical questions:

- **What is the risk of vulval cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected vulval cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of vulval cancer in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of biopsy in patients with suspected vulval cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for vulval cancer in women with an unexplained vulval lump, ulceration or bleeding. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of vulval cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict vulval cancer. No evidence was found for this outcome. <u>Investigations in primary care for vulval cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of vulval cancer</u> No evidence was found pertaining to the positive predictive values of different symptoms of vulval cancer in primary care. <u>Investigations in primary care for vulval cancer</u> No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected vulval cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those women with vulval cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of women without vulval cancer who get inappropriately referred whilst maximising the number of women with vulval cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with vulval cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for vulval cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected vulval cancer, since there was no test available in primary care. The GDG noted that an unexplained vulval lump, ulceration or bleeding can be symptoms of vulval cancer. The GDG agreed, based on their clinical experience, that had these symptoms been studied they would have had a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for these symptoms. The GDG also noted that most vulval cancers are skin cancers

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	(squamous cell carcinoma and melanoma), so the recommendations made for these cancers will also be relevant for women with suspected vulval cancer. Due to the lack of evidence, the GDG were not able to make any recommendations about any tests for the primary care investigation of vulval cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for an unexplained vulval lump, ulceration or bleeding is likely to be cost-neutral as it is currently standard practice.
Other considerations	The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

11.5 Vaginal cancer

Over 250 new vaginal cancers are diagnosed each year in the UK, meaning most GPs will not encounter a woman with the disease. Five year survival varies considerably with stage.

Because of its rarity, there are few reports on the clinical features of vaginal cancer. It is believed to present usually with a mass or ulceration within the vagina.

Definitive diagnosis requires biopsy, performed in secondary care.

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Clinical questions:

- **What is the risk of vagina cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected vaginal cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of vulval cancer in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of tests in patients with suspected vaginal cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

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Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for vaginal cancer in women with an unexplained palpable mass in or at the entrance to the vagina. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of vaginal cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict vaginal cancer. No evidence was found on this outcome. <u>Investigations in primary care for vaginal cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of vaginal cancer</u> No evidence was found pertaining to the positive predictive values of different symptoms of vaginal cancer in primary care. <u>Investigations in primary care for vaginal cancer</u> No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected vaginal cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those women with vaginal cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of women without vaginal cancer who get inappropriately referred whilst maximising the number of women with vaginal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with vaginal cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for vaginal cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected vaginal cancer, since there was no test available in primary care. The GDG noted that a palpable mass in the vagina or at the introitus can be symptoms of vaginal cancer. The GDG agreed, based on their clinical experience, that had these symptoms been studied they would have had a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for this symptom. Due to the lack of evidence and the fact that there is no obvious test for vaginal cancer in primary care, the GDG were not able to recommend a particular test for the primary care investigation of vaginal cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic

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	analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for an unexplained palpable mass in the vagina or at the entrance to the vagina is likely to be cost-neutral as it is currently standard practice.
Other considerations	The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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Endometrial cancer

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Hallissey, M.T., Allum, W.H., Jewkes, A.J., Ellis, A.J., Fielding, J.W.L. Early detection of gastric cancer.British Medical Journal 301, 513-515. 1990.

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Walker, S., Hyde, C. & Hamilton, W. (2013) Risk of uterine cancer in symptomatic women in primary care: case-control study using electronic records. British Journal of General Practice, 63: 643-648.

Cervical cancer

Muris, J. W., Starmans, R., Fijten, G. H., Crebolder, H. F., Schouten, H. J., and Knottnerus, J. A. Non-acute abdominal complaints in general practice: diagnostic value of signs and symptoms. British Journal of General Practice 45[395], 313-316. 1995.

Vulval cancer

None

Vaginal cancer

None

12 Urological cancers

12.1 Prostate cancer

Over 41,000 new prostate cancers are diagnosed each year in the UK, so a full-time GP will usually diagnose one new person with prostate cancer each year. Five-year survival is approximately 80%.

Prostate cancer usually presents with lower urinary tract symptoms, including nocturia, urinary frequency, and hesitancy. Haematuria can occur, as can erectile dysfunction. Some prostate cancers present with disseminated disease, typically metastases to bone.

The lower urinary symptoms overlap with those of benign prostatic hyperplasia – and the two conditions can co-exist. Examination of the prostate gland can help to differentiate the two, with hardness of the prostate, individual nodules, or loss of the median sulcus being features suggestive of cancer.

Prostate specific antigen (PSA) testing is generally available in primary care, with age-specific raised values suggestive of cancer. Definitive diagnosis requires biopsy, often guided by imaging. This is performed in secondary care.

Clinical questions:

- **What is the risk of prostate cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected prostate cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP and the 5th study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Three of the studies also employed reference standards that are subject to an unclear risk of bias; all of which must be born in mind when evaluating the evidence contributed by these studies.

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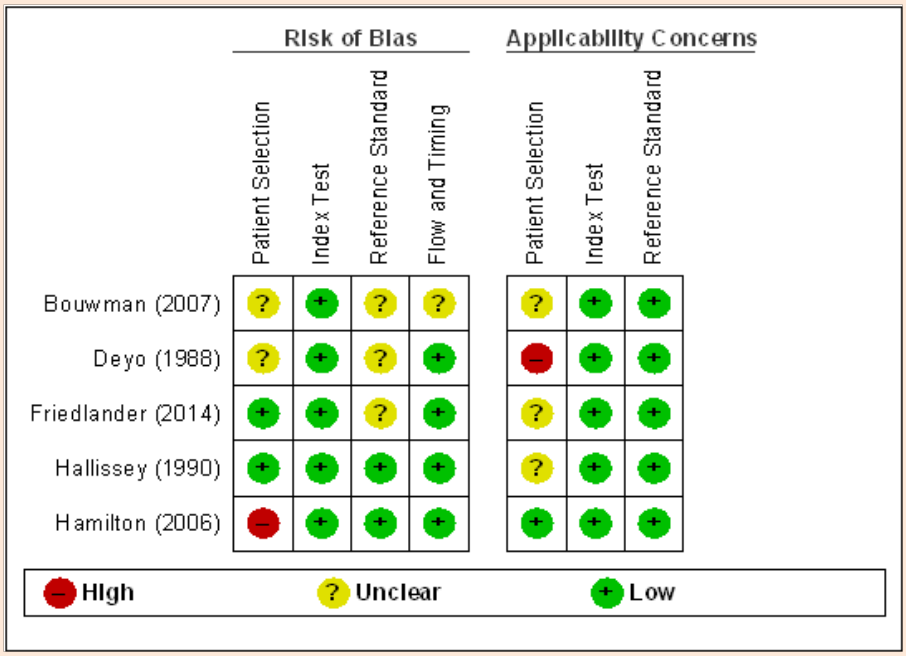

Evidence statement

The positive predictive values for prostate cancer of single symptoms presenting in a primary care setting ranged from 0.08% (for dyspepsia) to 12% (for malignant rectal exam; 5 studies, N = 7440). The studies were associated with 1-4 bias or applicability concerns (see also Table 50).

The positive predictive values for prostate cancer of symptom pairs presenting in a primary care setting ranged from 1.8% (for haematuria + frequency/urgency) to 15% (for nocturia + malignant rectal exam; 1 study, N = 1297). This study was a case-control study (i.e, high risk of bias for patient selection; see also Table 51).

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Table 50: Prostate cancer: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Bouwman (2007)	Urinary symptoms	Males aged ≥ 50 years	7.37 (5-10.7) 26/353
Deyo (1988)	Back pain	Male patients	0.13 (0.007-0.9) 1/750
Friedlander (2014)	Haematuria	All included patients	0.61 (0.36-1.03) 15/2455
Hamilton (2006)	Haematuria	All included patients	1 (0.57-1.8)
Hamilton (2006)	Haematuria (reported twice)	All included patients	1.6 (0.8-3.2)
Hamilton (2006)	Loss of weight	All included patients	0.75 (0.38-1.4)
Hamilton (2006)	Loss of weight (reported twice)	All included patients	2.1 (NR)
Hamilton (2006)	Nocturia	All included patients	2.2 (1.2-3.6)
		Patients 40-69 years	1.1 (NR)
		Patients ≥ 70 years	5.9 (NR)
Hamilton (2006)	Nocturia (reported twice)	All included patients	3.3 (NR)
Hamilton (2006)	Hesitancy	All included patients	3 (1.5-5.5)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Hamilton (2006)	Hesitancy (reported twice)	All included patients	2 (NR)
Hamilton (2006)	Rectal exam: Benign	All included patients	2.8 (1.6-4.6)
		Patients 40-69 years	0.85 (NR)
		Patients ≥ 70 years	8.7 (NR)
Hamilton (2006)	Rectal exam: Malignant	All included patients	12 (5-37)
Hamilton (2006)	Frequency/urgency	All included patients	2.2 (1.1-3.5)
Hamilton (2006)	Frequency/urgency (reported twice)	All included patients	3.1 (1.9-5.5)
Hamilton (2006)	Frequency	Patients 40-69 years	0.61 (NR)
		Patients ≥ 70 years	7.4 (NR)
Hamilton (2006)	Retention	All included patients	3.1 (1.5-6)
		* excluding 39 patients with unsuspected cancer	1.6 (NR)
Hamilton (2006)	Impotence	All included patients	3 (1.7-4.9)
		Patients 40-69 years	1.1 (NR)
		Patients ≥ 70 years	8.4 (NR)
Hamilton (2006)	When PSA was added to a small multivariate analysis (N = 208; N = 137 patients and N = 71 controls) with the following otherwise significant variables: urinary retention, second presentation with loss of weight, impotence, frequency, hesitancy, nocturia, haematuria, and rectal examination, these variables ceased to be significant predictors of prostate cancer while PSA > 4 ng/ml was significant (OR = 29, 95% CI 3.9-220; p = .001).		
Hallissey (1990)	Dyspepsia	All patients	0.08 (0.01-0.3) 2/2585

*CI = Confidence interval. *The authors report that a sub-analysis excluding the 39 patients who had previously unsuspected cancer identified at prostatectomy, showed that the PPVs of symptoms were little changed, other than for retention.*

Table 51: Prostate cancer: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Hamilton (2006)	Haematuria + nocturia	All included patients	1.9 (NR)
Hamilton (2006)	Haematuria + benign rectal exam	All included patients	3.3 (NR)
Hamilton (2006)	Haematuria + malignant rectal exam	All included patients	3.9 (NR)
Hamilton (2006)	Haematuria + frequency/urgency	All included patients	1.8 (0.9-3.9)
Hamilton (2006)	Loss of weight + nocturia	All included patients	12 (NR)
Hamilton (2006)	Loss of weight + benign rectal exam	All included patients	9.4 (NR)
Hamilton (2006)	Loss of weight + frequency/urgency	All included patients	1.8 (NR)
Hamilton (2006)	Nocturia + hesitancy	All included patients	2.8 (NR)
Hamilton (2006)	Nocturia + benign rectal exam	All included patients	3.9 (2.1-7.8)

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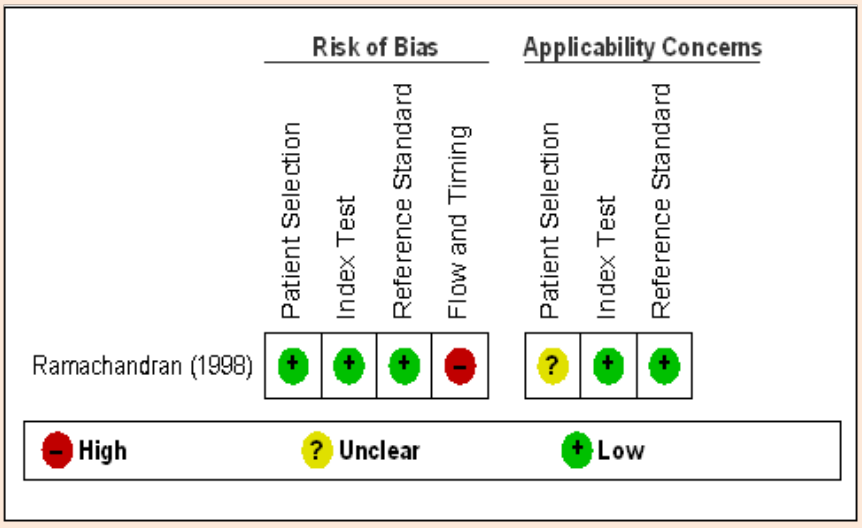
Study	Symptom(s)	Patient group	Positive predictive value (95% CI)%
Hamilton (2006)	Nocturia + malignant rectal exam	All included patients	15 (NR)
Hamilton (2006)	Nocturia + frequency/urgency	All included patients	3.2 (1.9-6)
Hamilton (2006)	Hesitancy + benign rectal exam	All included patients	3.3 (NR)
Hamilton (2006)	Hesitancy + malignant rectal exam	All included patients	10 (NR)
Hamilton (2006)	Hesitancy + frequency/urgency	All included patients	4.7 (NR)
Hamilton (2006)	Benign rectal exam + frequency/urgency	All included patients	4 (2.3-7.4)
Hamilton (2006)	Malignant rectal exam + frequency/urgency	All included patients	13 (NR)

CI = Confidence interval.

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main risk of bias in this study pertains to the ca 20% of missing data in this study. It is not possible to ascertain whether these data are missing in a systematic manner and whether they are likely to substantially influence the test accuracy estimates provided by this study. The only applicability concern identified for this study concerns the underspecification of the patients, that is, it is not clear from, the study whether all the patients were symptomatic patients presenting to primary care, and to the extent they are not from this patient group, the applicability to the current guideline is limited.



Evidence statement

PSA testing (1 study, N = 582) conducted in patients presenting in a primary/hospital care setting is associated with sensitivities that ranged from 77.8-88.9%, specificities that ranged from 70-90.2% and false negativity rates that ranged from 11.1-22.2% for prostate cancer. The study was associated with one bias and one applicability concern (see also Table 52).

Table 52: Prostate cancer: PSA

Study	Test	Prevalence	Sensi-tivity (95% CI)	Speci-ficity (95% CI)	Other results
Ramachandran (1998)	PSA 4 ng/ml	54/582	88.9% (NR)	70% (NR)	False negativity rate = 11.1%
	PSA 5 ng/ml		88.9% (NR)	78% (NR)	False negativity rate = 11.1%
	PSA 6 ng/ml		87% (NR)	82.6% (NR)	False negativity rate = 13%
	PSA 7 ng/ml		83.3% (NR)	86% (NR)	False negativity rate = 16.7%
	PSA 8 ng/ml		83.3% (NR)	88.3% (NR)	False negativity rate = 16.7%
	PSA 9 ng/ml		83.3% (NR)	89% (NR)	False negativity rate = 16.7%
	PSA 10 ng/ml		77.8% (NR)	90.2% (NR)	False negativity rate = 22.2%

No evidence was found for MRI.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their prostate feels malignant on digital rectal examination. [new 2015]** **Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with:** • **any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or** • **erectile dysfunction or** • **visible haematuria. [new 2015]** **Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their PSA levels are above the age-specific reference range. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of prostate cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict prostate cancer. <u>Investigations in primary care for prostate cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. Although sensitivity and specificity were reported, the

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	GDG agreed that the most informative outcomes were the positive predictive values (because these gave the risk of a person harbouring cancer), and the false negative rates (to inform whether a negative test obviated the need for further safety-netting).
Quality of the evidence	<u>Signs and symptoms of prostate cancer</u> The quality of the evidence assessed by QUADAS-II varied with only one of five studies considered to provide high quality evidence. <u>Investigations in primary care for prostate cancer</u> Evidence was only identified on the accuracy of PSA testing. This evidence was assessed by QUADAS-II as not being of high quality. The GDG noted some limitations of the evidence. Firstly, it was not clear whether all patients were symptomatic patients presenting to primary care. Secondly, some data are missing but it is not clear whether this was likely to substantially influence the test accuracy estimates provided. Thirdly, PSA measurement has changed since this study was published. No evidence was found pertaining to the diagnostic performance of MRI in primary care patients with suspected prostate cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those men with prostate cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of men without prostate cancer who get inappropriately referred whilst maximising the number of men with prostate cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with prostate cancer outweighed the disadvantages to those without. However, the GDG noted the evidence which had shown that PSA testing was a reasonably sensitive and specific test for prostate cancer and that a raised PSA level was a significant predictor of prostate cancer. Based on this evidence the GDG decided not to recommend symptoms which should prompt a suspected cancer pathway referral but instead to recommend which symptoms should prompt a PSA test and chose these symptoms based on the positive predictive values presented in the evidence. The results of this PSA test would then determine who needed a suspected cancer pathway referral. By doing this the GDG hoped to refine the group of symptomatic men being referred to those with the greatest chance of having prostate cancer. The GDG noted that Hamilton (2006) had reported loss of weight plus a benign rectal examination to have a PPV of 9.4. The GDG also noted that this PPV was based on very small

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	numbers and no confidence intervals had been calculated for this reason. The GDG agreed that the fact that a rectal examination had been performed, strongly implied that the person also had lower urinary tract symptoms, as it would not be standard practice to perform a rectal examination for loss of weight alone. Given that recommendations had already been made on lower urinary tract symptoms were already (which would encompass people with the symptom combination cited by Hamilton (2006), the GDG agreed that a specific recommendation for this symptom combination was not required. The exception to this was those men whose prostate felt malignant on digital rectal examination. The positive predictive value of a malignant feeling prostate on digital rectal examination was so high above the 3% threshold that even after a normal PSA result, the GDG still considered that urgent referral was justified. For this reason the GDG recommended a digital rectal examination as well as PSA test for all men with relevant symptoms. The GDG noted that there was no strong primary care evidence available on which to base a recommendation for what level of PSA should prompt a suspected cancer pathway referral. They therefore agreed to accept the age-specific reference range. Due to the lack of evidence, the GDG agreed not to make any recommendations on the use of MRI in primary care patients with suspected prostate cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for a malignant prostate on digitial rectal examination is likely to be cost-neutral as it is currently standard practice. The also GDG estimated that the recommendations were likely to result in a moderate increase in PSA testing followed by a smaller increase in suspected cancer pathway referrals. The net effect of this was uncertain but the GDG agreed that any potential increase in costs would be balanced by improvements in the diagnosis of prostate cancer.
Other considerations	The GDG considered whether or not to specify an age range in the recommendations for which symptoms should prompt PSA testing and digital rectal examination, since prostate cancer is less common in younger men. The agreed not to do this as some risk factors, for example ethnicity, might warrant testing at a lower age. The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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12.2 Bladder cancer

Around 10,000 new bladder cancers are diagnosed each year in the UK, meaning that a full time GP is likely to diagnose approximately 1 person with bladder cancer every 3-5 years. It is seen in both sexes, though almost three-quarters of new cases are in males. Five year survival is approximately 55%.

Several symptoms have been reported, with haematuria being the most common. Dysuria and urinary frequency are also features, especially when persistent.

Because haematuria is a symptom of several cancers, investigation strategies may need to consider more than one possible cancer site, such as kidney, prostate or endometrium. Similarly, dysuria and urinary frequency may be misattributed to urinary tract infection, especially in the elderly.

A diagnosis of bladder cancer is generally made by cystoscopy with biopsy, performed in secondary care. Because bladder cancer shares some symptoms with other urological cancers, most haematuria clinics investigate with ultrasound before proceeding to cystoscopy.

Clinical questions:

- **What is the risk of bladder cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected bladder cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note are that one study was conducted in a Belgian primary care population (Bruyninckx, 2003) and another in US primary care setting (Friedlander, 2014) and these studies are therefore only applicable to the extent that the populations are comparable to a UK GP population, another study (Hippisley-Cox 2012) only presented data for 967681 out of 1240722 eligible patients and it is unclear why, a third study (Jones, 2007) report the results for both 6 months and 3 years after first symptom presentation and it is unclear whether 3 years is too long an interval to be confident that the symptom is a result of underlying cancer, similarly, Friedlander (2014) only followed up the included patients for 180 days, which may be too short a time period. The final study (Shephard, 2012) employed a case-control design which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection.

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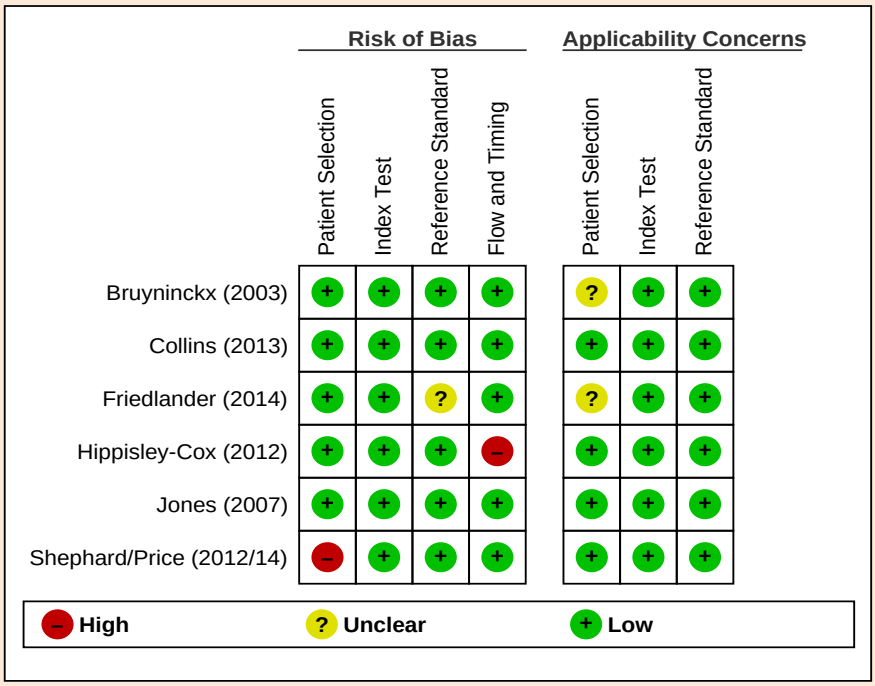

Evidence statement

Haematuria (6 studies, N = 89345) presenting in a primary care setting is associated with overall positive predictive values ranging from 1.34%-10.27% for bladder cancer, which tended to be higher in men (5.47%-14.2%) than in women (2.48%-5.1%; 3 studies, total N = 49327) and to increase with age in men (up 22.1%; 2 studies, total N = 11517) and much less so in women (up to 8.53%; 2 studies, total N = 11517). All the studies were associated with 0-2 bias or applicability concern (see also Tables 53-55).

Haematuria in combination with other symptoms presenting in a primary care setting was associated with positive predictive values ranging from 1.1% (non-visible with raised creatinine in patients ≥ 60 years; 1 study, total N = 26633) to 33.3% (with weight loss in men > 60 years old; 1 study, total N = 409) for bladder cancer. Both studies were associated with 1 bias or applicability concern (see also Table 3).

Other symptoms (than haematuria) presenting alone or in combination with each other (but not haematuria) in a primary care setting were all associated with positive predictive values ≤ 1.5% for bladder cancer (3 studies, total N = 1284137). All the studies were associated with 0-1 bias or applicability concern (see also Table 3).

Table 53: Bladder cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003), Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 6 months)	Haematuria	All patients (N = 70330)	4.43 (2.48-7.79)
Bruyninckx (2003), Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 3 years)	Haematuria	All patients (N = 70330)	4.72 (2.63-8.32)

Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below.

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Table 54: Bladder cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003)	Haematuria	All patients (N = 409)	10.27 (7.6-13.7)
Collins (2013)	Haematuria	All patients (N = 37810)	4.35 (4.1-4.6)
Friedlander (2014)	Haematuria	All included patients (N = 2455)	1.34 (0.94-1.91) 33/2455
Hippisley-Cox (2012)	Haematuria	All patients (N = 18548)	6.48 (6.1-6.8)
Jones (2007, at 6 months),	Haematuria	All patients (N = 11108)	4.2 (3.8-4.6)
Jones (2007, at 3 years),	Haematuria	All patients (N = 11108)	5.7 (5.3-6.2)

Table 55: Bladder cancer: Additional results reported by the individual papers

Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Bruyninckx (2003)	Macroscopic haematuria	Men (all ages)	14.2 (10.1-19.5)
Collins (2013)	Haematuria	Men (all ages)	5.5 (5.2-5.8)
Jones (2007)	Haematuria	Men (all ages) at 6 months	5.47 (4.9-6.1)
Bruyninckx (2003)	Macroscopic haematuria	Men < 40 years	0 (0-12)
Jones (2007)	Haematuria	Men < 45 years at 3 years	0.99 (0.53-1.69)
Bruyninckx (2003)	Macroscopic haematuria	Men 40-59 years	3.6 (.6-13.4)
Jones (2007)	Haematuria	Men 45-54 years at 3 years	4.35 (3.11-5.9)
Jones (2007)	Haematuria	Men 55-64 years at 3 years	8.51 (6.94-10.32)
Bruyninckx (2003)	Macroscopic haematuria	Men > 59 years	22.1 (15.8-30.1)
Jones (2007)	Haematuria	Men 65-74 years at 3 years	11.21 (9.66-12.9)
Jones (2007)	Haematuria	Men 75-84 years at 3 years	10.27 (8.61-12.13)
Jones (2007)	Haematuria	Men ≥ 85 years at 3 years	9.22 (6.43-12.7)
Bruyninckx (2003)	Macroscopic haematuria	Women (all ages)	5.1 (2.5-9.8)
Collins (2013)	Haematuria	Women (all ages)	2.6 (2.3-2.8)
Jones (2007)	Haematuria	Women (all ages) at 6 months	2.48 (2.1-3)
Bruyninckx (2003)	Macroscopic haematuria	Women < 40 years	0 (NR)
Jones (2007)	Haematuria	Women < 45 years at 3 years	.22 (0.05-0.64)
Bruyninckx (2003)	Macroscopic haematuria	Women 40-59 years	6.4 (1.7-18.6)
Jones (2007)	Haematuria	Women 45-54 years at 3 years	1.34 (0.65-2.45)
Jones (2007)	Haematuria	Women 55-64 years at 3 years	3.42 (2.26-4.93)
Bruyninckx (2003)	Macroscopic haematuria	Women > 59 years	8.3 (3.4-17.9)
Jones (2007)	Haematuria	Women 65-74 years at	5.91 (4.42-7.72)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
		3 years	
Jones (2007)	Haematuria	Women 75-84 years at 3 years	6.83 (5.06-8.98)
Jones (2007)	Haematuria	Women ≥ 85 years at 3 years	8.53 (5.6-12.3)
Bruyninckx (2003)	Macroscopic haematuria	All patients < 60 years	2.6 (.9-6.2)
Shephard (2012)	Visible haematuria (coded data only)	All patients 40-59 years	3.1 (1-9.8)
Price (2014)	Visible haematuria (coded and uncoded data)	All patients 40-59 years	1.2 (0.64-2.3)
Shephard (2012)	Visible haematuria (coded data only)	All patients ≥ 60 years	3.9 (3.5-4.6)
Price (2014)	Visible haematuria (coded and uncoded data)	All patients ≥ 60 years	2.8 (2.5-3.1)
Shephard (2012)	Visible haematuria	All patients	Cases: 2595/4915 Controls: 196/21718
Shephard (2012)	Visible haematuria (second attendance)	All patients ≥ 60 years	6.1 (5.1-8.2)
Price (2014)	Non-visible haematuria (coded and uncoded data)	Patients 40-59 years	0.79 (0.11-5.6)
Price (2014)	Non-visible haematuria (coded and uncoded data)	All patients ≥ 60 years	1.6 (1.2-2.1)
Bruyninckx (2003)	Macroscopic haematuria + pain	All patients	5.3 (2.7-9.8)
Bruyninckx (2003)	Macroscopic haematuria + pain	Men > 60 years	17.8 (8.5-32.6)
Shephard (2012)	Visible haematuria + abdominal pain (coded data only)	All patients ≥ 60 years	3.2 (1.9-5.8)
Price (2014)	Visible haematuria + abdominal pain (coded and uncoded data)	All patients ≥ 60 years	2.3 (1.5-3.5)
Price (2014)	Non-visible haematuria + abdominal pain (coded and uncoded data)	All patients ≥ 60 years	1.7 (0.6-4.2)
Bruyninckx (2003)	Macroscopic haematuria without pain	All patients	10.9 (7.3-16)
Bruyninckx (2003)	Macroscopic haematuria without pain	Men > 60 years	18.9 (11.9-28.6)
Bruyninckx (2003)	Macroscopic haematuria + increased frequency of micturition	All patients	7.2 (3.8-12.8)
Bruyninckx (2003)	Macroscopic haematuria + increased frequency of micturition	Men > 60 years	22.6 (10.3-41.5)
Bruyninckx (2003)	Macroscopic haematuria without increased	All patients	13.4 (9.4-18.7)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	frequency of micturition		
Bruyninckx (2003)	Macroscopic haematuria without increased frequency of micturition	Men > 60 years	22 (14.9-31.2)
Bruyninckx (2003)	Macroscopic haematuria + dysuria	All patients	5.6 (2.6-11)
Bruyninckx (2003)	Macroscopic haematuria + dysuria	Men > 60 years	24.1 (11-43.9)
Shephard (2012)	Visible haematuria + dysuria (coded data only)	All patients ≥ 60 years	6.4 (NR as N < 10)
Price (2014)	Visible haematuria + dysuria (coded and uncoded data)	All patients ≥ 60 years	4.1 (2.6-6.3)
Price (2014)	Non-visible haematuria + dysuria (coded and uncoded data)	All patients ≥ 60 years	4.5 (NR)
Bruyninckx (2003)	Macroscopic haematuria without dysuria	All patients	23.6 (17.1-31.5)
Bruyninckx (2003)	Macroscopic haematuria without dysuria	Men > 60 years	21.6 (14.6-30.6)
Bruyninckx (2003)	Macroscopic haematuria + nocturia	All patients	6.3 (2.4-14.8)
Bruyninckx (2003)	Macroscopic haematuria + nocturia	Men > 60 years	12.5 (3.3-33.5)
Bruyninckx (2003)	Macroscopic haematuria without nocturia	All patients	11.2 (8.1-15.2)
Bruyninckx (2003)	Macroscopic haematuria without nocturia	Men > 60 years	23.3 (16.3-32.1)
Bruyninckx (2003)	Macroscopic haematuria + weight loss	All patients	10 (.5-45.9)
Bruyninckx (2003)	Macroscopic haematuria + weight loss	Men > 60 years	33.3 (1.8-87.5)
Bruyninckx (2003)	Macroscopic haematuria without weight loss	All patients	8.3 (5.8-11.5)
Bruyninckx (2003)	Macroscopic haematuria without weight loss	Men > 60 years	18.2 (12.4-26)
Bruyninckx (2003)	Macroscopic haematuria + fatigue	All patients	20.8 (11-35.4)
Bruyninckx (2003)	Macroscopic haematuria + fatigue	Men > 60 years	30 (12.8-54.3)
Bruyninckx (2003)	Macroscopic haematuria without fatigue	All patients	8.9 (6.2-12.4)
Bruyninckx (2003)	Macroscopic haematuria without fatigue	Men > 60 years	20.8 (14.2-29.4)
Bruyninckx (2003)	Macroscopic haematuria with other symptoms	All patients	6.4 (4.3-9.3)
Bruyninckx (2003)	Macroscopic haematuria without other symptoms	All patients	3.9 (2.3-6.4)
Shephard (2012)	Visible haematuria + constipation (coded data only)	All patients ≥ 60 years	2.7 (1.6-4.5)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Price (2014)	Visible haematuria + constipation (coded and uncoded data)	All patients ≥ 60 years	2.2 (1.5-3.4)
Price (2014)	Non-visible haematuria + constipation (coded and uncoded data)	All patients ≥ 60 years	2 (NR)
Shephard (2012)	Visible haematuria + urinary tract infection (coded data only)	All patients ≥ 60 years	4.1 (3-6.2)
Price (2014)	Visible haematuria + urinary tract infection (coded and uncoded data)	All patients ≥ 60 years	2.2 (1.8-2.8)
Price (2014)	Non-visible haematuria + urinary tract infection (coded and uncoded data)	All patients ≥ 60 years	1.4 (0.8-2.4)
Shephard (2012)	Visible haematuria + raised inflammatory markers (coded data only)	All patients ≥ 60 years	5.6 (NR as N < 10)
Price (2014)	Visible haematuria + raised inflammatory markers (coded and uncoded data)	All patients ≥ 60 years	3.3 (2-5.4)
Price (2014)	Non-visible haematuria + raised inflammatory markers (coded and uncoded data)	All patients ≥ 60 years	1.25 (NR)
Shephard (2012)	Visible haematuria + raised creatinine (coded data only)	All patients ≥ 60 years	5.1 (3.4-8.4)
Price (2014)	Visible haematuria + raised creatinine (coded and uncoded data)	All patients ≥ 60 years	2.9 (2.1-3.9)
Price (2014)	Non-visible haematuria + raised creatinine (coded and uncoded data)	All patients ≥ 60 years	1.1 (0.6-2.2)
Shephard (2012)	Visible haematuria + raised white blood cell count (coded data only)	All patients ≥ 60 years	8.8 (NR as N < 10)
Price (2014)	Visible haematuria + raised white blood cell count (coded and uncoded data)	All patients ≥ 60 years	3.7 (2.1-6.3)
Price (2014)	Non-visible haematuria + raised white blood cell count (coded and uncoded data)	All patients ≥ 60 years	3.9 (NR)
Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)
		Men	0.2 (0.2-0.21)
		Women	0.1 (0.1-0.1)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)
Shephard (2012)	Abdominal pain	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	Abdominal pain	All patients	Cases: 358/4915 Controls: 787/21718
Shephard (2012)	Abdominal pain (second attendance)	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	Abdominal pain + dysuria	All patients ≥ 60	0.4 (0.3-0.7)
Shephard (2012)	Abdominal pain + constipation	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Abdominal pain + urinary tract infection	All patients ≥ 60	0.4 (0.3-0.6)
Shephard (2012)	Abdominal pain + raised inflammatory markers	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Abdominal pain + raised creatinine	All patients ≥ 60	0.3 (0.2-0.4)
Shephard (2012)	Abdominal pain + raised white blood cell count	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Dysuria	All patients ≥ 60	0.7 (0.6-0.8)
Shephard (2012)	Dysuria	All patients	Cases: 444/4915 Controls: 209/21718
Shephard (2012)	Dysuria (second attendance)	All patients ≥ 60	1 (0.7-1.5)
Shephard (2012)	Dysuria + constipation	All patients ≥ 60	0.5 (0.3-0.9)
Shephard (2012)	Dysuria + urinary tract infection	All patients ≥ 60	0.7 (0.4-1.1)
Shephard (2012)	Dysuria + raised inflammatory markers	All patients ≥ 60	0.9 (0.5-1.7)
Shephard (2012)	Dysuria + raised creatinine	All patients ≥ 60	0.6 (0.4-1)
Shephard (2012)	Dysuria + raised white blood cell count	All patients ≥ 60	0.9 (0.5-1.9)
Shephard (2012)	Constipation	All patients ≥ 60	0.1 (0.1-.2)
Shephard (2012)	Constipation	All patients	Cases: 286/4915 Controls: 708/21718
Shephard (2012)	Constipation (second attendance)	All patients ≥ 60	0.1 (0.1-0.2)
Shephard (2012)	Constipation + urinary tract infection	All patients ≥ 60	0.5 (0.3-0.7)
Shephard (2012)	Constipation + raised inflammatory markers	All patients ≥ 60	0.2 (0.1-0.2)
Shephard (2012)	Constipation + raised creatinine	All patients ≥ 60	0.2 (0.2-0.3)
Shephard (2012)	Constipation + raised white blood cell count	All patients ≥ 60	0.3 (0.2-0.5)
Shephard (2012)	Urinary tract infection	All patients ≥ 60	0.4 (0.3-0.4)
Shephard (2012)	Urinary tract infection	All patients	Cases: 835/4915 Controls: 705/21718
Shephard (2012)	Urinary tract infection	All patients ≥ 60	0.5 (0.4-1.6)

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Study	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
	(second attendance)		
Shephard (2012)	Urinary tract infection + raised inflammatory markers	All patients ≥ 60	0.4 (0.3-0.7)
Shephard (2012)	Urinary tract infection + raised creatinine	All patients ≥ 60	0.5 (0.3-0.6)
Shephard (2012)	Urinary tract infection + raised white blood cell count	All patients ≥ 60	0.6 (0.4-0.9)
Shephard (2012)	Raised inflammatory markers	All patients ≥ 60	0.1 (0.1-0.2)
Shephard (2012)	Raised inflammatory markers	All patients	Cases: 293/4915 Controls: 717/21718
Shephard (2012)	Raised inflammatory markers + raised creatinine	All patients ≥ 60	0.3 (0.2-0.3)
Shephard (2012)	Raised inflammatory markers + raised white blood cell count	All patients ≥ 60	0.2 (0.1-0.3)
Shephard (2012)	Raised creatinine	All patients ≥ 60	0.1 (0.12-0.14) As reported, but PPV or CI not reported correctly
Shephard (2012)	Raised creatinine	All patients	Cases: 660/4915 Controls: 1668/21718
Shephard (2012)	Raised creatinine + raised white blood cell count	All patients ≥ 60	0.3 (0.2-0.4)
Shephard (2012)	Raised white blood cell count	All patients ≥ 60	0.2 (0.17-0.23)
Shephard (2012)	Raised white blood cell count	All patients	Cases: 250/4915 Controls: 401/21718
Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)
Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)
Collins (2013)	Weight loss	Women	0.1 (0.1-0.2)
Hippisley-Cox (2012)	Weight loss	All patients	0.41 (0.3-0.6)
Collins (2013)	Anaemia	All patients	0.6 (0.5-0.7)
		Men	1.4 (1.1-1.9)
		Women	0.3 (0.3-0.5)
Hippisley-Cox (2012)	Anaemia	All patients	0.69 (0.5-0.9)

NR = Not reported. Please note the calculations of the positive predictive values differ between the studies with Bruyninckx (2003), Hippisley-Cox (2012) and Jones (2007) using (TP)/(TP+FP) and Shephard (2012) using Bayesian statistics due to the case-control design of this study.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of urine cytology, ultrasound, cystoscopy, blood HCG, urine marker NMP22, and urine marker MCM5 in patients with suspected bladder cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 45 and over and have unexplained visible haematuria without urinary tract infection or visible haematuria that persists or recurs after successful treatment of urinary tract infection. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. [new 2015]** **Consider referral for bladder cancer in people aged 60 and over with recurrent or persistent urinary tract infection that is unexplained. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of bladder cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict bladder cancer. <u>Investigations in primary care for bladder cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of bladder cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of high quality. It was noted that the majority of the evidence had merged all urinary tract cancers making it difficult to tease out the specifics related to bladder cancer. The GDG also noted that most of the evidence did not distinguish between visible and non-visible haematuria, but largely grouped these two symptoms together as haematuria. The GDG judged, based on their clinical experience, that most of that evidence was likely to reflect visible haematuria which left them with evidence from one paper about non-visible haematuria. <u>Investigations in primary care for bladder cancer</u> No evidence was found pertaining to the diagnostic performance of ultrasound, urine cytology, cystoscopy, blood HCG or urinary markers NMP22 and MCM5 in primary care patients with suspected bladder cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with bladder cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without bladder cancer who get

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	inappropriately referred whilst maximising the number of people with bladder cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with bladder cancer outweighed the disadvantages to those without. The GDG noted, based on the evidence, that haematuria presenting in a primary care setting was associated with a positive predictive value of above 3% for bladder cancer. They therefore recommended this symptom should prompt a suspected cancer pathway referral. The GDG also noted that, based on the evidence, the positive predictive value of haematuria for bladder cancer increased with age. They therefore agreed to recommend referral for those people aged 45 or over. The GDG agreed, based on their clinical experience that urinary tract infections often cause visible haematuria. They therefore recommended that if visible haematuria persists or recurs after successful treatment of urinary tract infection, a suspected cancer pathway referral should be made. The GDG acknowledged that the positive predictive values associated with urinary tract infections presenting in primary care were inconsistent for bladder cancer and that there was no evidence on recurrent (greater than two) urinary tract infections. However the GDG considered that this was a population in which cancer can be missed and therefore referral should be considered for people with this symptom. The GDG agreed, based on the evidence, to recommend a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer for people aged 60 years and over with unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. The GDG acknowledged that no other symptoms had a high enough positive predictive value for bladder cancer to warrant making recommendations on them. The GDG noted the absence of evidence on investigations in primary care, and that the definitive test for bladder cancer is cystoscopy. However the GDG considered cystoscopy to be best performed by specialists in secondary care and therefore decided to not make any recommendations for investigations for bladder cancer in primary care.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendations on haematuria were likely to be cost saving as the age threshold for referral has been raised for both visible and non-visible haematuria. Investigation of persistent and recurrent urinary tract infections is a revised

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	recommendation and this is likely to increase referrals. The recommendations on non-visible haematuria and recurrent/persistent urinary tract infection in people over 60 are likely to result in a moderate increase in costs. On this basis, the GDG estimated that overall the recommendations were likely to be either cost neutral or a small cost increase. However, they agreed that this balanced against improvements in earlier diagnosis of bladder cancer.
Other considerations	The GDG noted that visible haematuria is a symptom which is common to both renal and bladder cancer. It was therefore, agreed that recommendations for referral of haematuria would need to be consistent for both these cancer sites.

12.31 Renal cancer

Over 10,000 new renal cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with renal cancer every 3-5 years. It is seen in both sexes, though around 60% of new diagnoses are in males. Five year survival is over 55%.

Renal cancer symptoms include haematuria, loin pain, urinary tract infections or a mass in the flank.

The symptoms overlap with other urological cancers, particularly bladder cancer.

Most renal cancers are visible on ultrasound of the kidneys – a test that is available in primary care.

Definitive diagnosis of renal cancer requires histology, performed in secondary care.

Clinical questions:

- **What is the risk of renal cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected renal cancer should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that patient selection is associated with a number of bias or applicability concerns in most of the included studies, with some studies employing non-consecutive or non-random selection of patients and with some studies being employed in settings that are not clearly directly representative of UK-based primary care. Other areas of concern include missing data, compromised reference standards and underspecified presenting symptoms. These issues should all be born in mind when evaluating the evidence along with the fact that a large number of the included cancers were not renal cancers.

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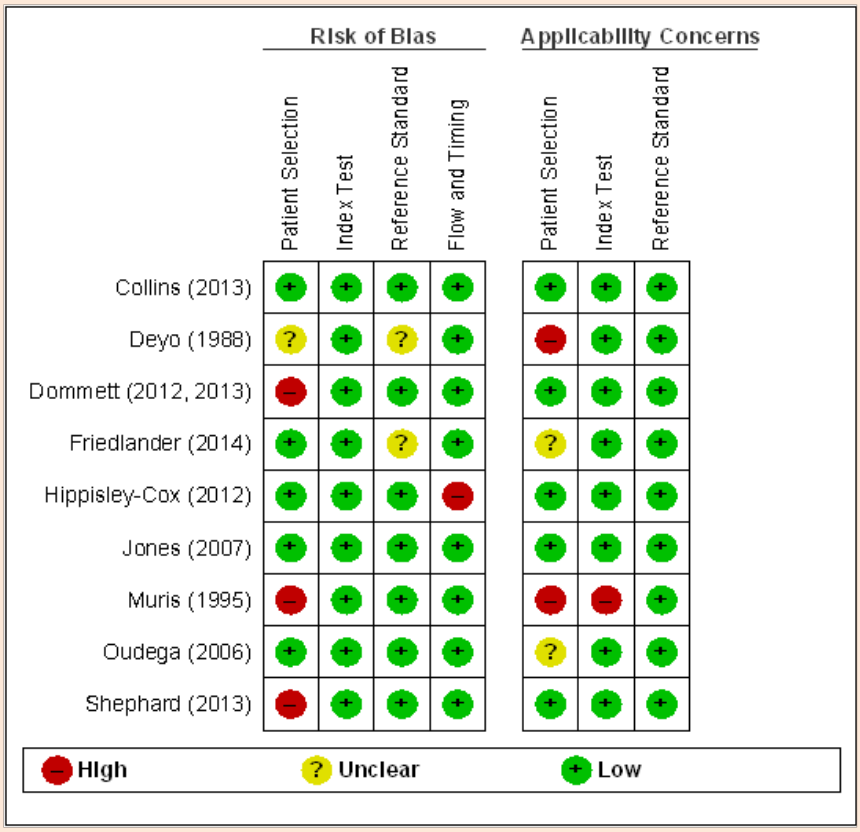

Evidence statement

Patients aged > 14 years

Haematuria (5 studies, N = 87161) presenting in a primary care setting is associated with overall positive predictive values of 0.65-6.48% for renal cancer, which tended to be higher in men (5.47-5.5%) than in women (2.48-2.6%; 2 studies, N = 48918) and to increase with age in men (up to 11.21%; 1 study, N = 11108) and less so in women (up to 8.53%; 1 study, N = 11108). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers. Each of the studies was associated with 0-2 bias concern (see also Tables 56-58).

For renal cancer the positive predictive values of single symptoms (excluding haematuria; 6 studies, N = 344897) presenting in primary care ranged from 0.05% (for back pain) to 1.4% (for anaemia in men). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers and ≤ 3 bias or applicability concerns associated with 4 of the 6 included studies (see also Table 58).

For renal cancer the positive predictive values of symptom combinations (1 study, N = 17240) presenting in primary care ranged from 0.1% (for constipation in combination with either abdominal pain, nausea or lower urinary tract infection) to > 5% (for abdominal pain combined with microcytosis). The included study was associated with 1 bias concern (see also Table 59).

Patients aged < 15 years

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence

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quality is somewhat compromised by the case-control design of the study (see also Tables 60-62).

Table 56: Renal cancer: Meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 6 months)	Haematuria	All patients (N = 69921)	3.05 (1.3-7.01)
Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 3 years)	Haematuria	All patients (N = 69921)	3.3 (1.35-7.84)

Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below

Table 57: Renal cancer: Individual positive predictive values from the meta-analyses

Studies included	Symptom(s)	Patient group	Positive predictive value, % (95% CI)
Collins (2013)	Haematuria	All patients (N = 37810)	4.35 (4.1-4.6)
Friedlander (2014)	Haematuria	All included patients (N = 2455)	0.65 (0.39-1.83) 16/2455
Hippisley-Cox (2012)	Haematuria	All patients (N = 18548)	6.48 (6.1-6.8)
Jones (2007, at 6 months),	Haematuria	All patients (N = 11108)	4.2 (3.8-4.6)
Jones (2007, at 3 years),	Haematuria	All patients (N = 11108)	5.7 (5.3-6.2)

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Table 58: Renal cancer: Patients aged > 14 years: Single symptoms

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)
		Men	0.2 (0.2-0.21)
		Women	0.1 (0.1-0.1)
Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)
Muris (1995)	Non-acute abdominal complaints	All patients	0.11 (0.01-0.7) 1/933
Shephard (2013)	Abdominal pain	Patients ≥ 60 years	0.1 (0.1-0.2) Cases: 350/3149 Controls: 514/14091
Shephard (2013)	Abdominal pain: 2 presentations	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation	Patients ≥ 60 years	0.1 (0.08-0.11) Cases: 194/3149 Controls: 420/14091
Shephard (2013)	Constipation: 2	Patients ≥ 60 years	0.1 (0.06-0.12)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
	presentations		
Shephard (2013)	Lower urinary tract infection	Patients ≥ 60 years	0.1 (0.09-0.12) Cases: 339/3149 Controls: 608/14091
Shephard (2013)	Lower urinary tract infection: 2 presentations	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Fatigue	Patients ≥ 60 years	0.1 (0.09-0.13) Cases: 210/3149 Controls: 405/14091
Shephard (2013)	Fatigue: 2 presentations	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Nausea	Patients ≥ 60 years	0.1 (0.1-0.2) Cases: 171/3149 Controls: 263/14091
Shephard (2013)	Nausea: 2 presentations	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2) Cases: 738/3149 Controls: 993/14091
Shephard (2013)	Thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.3) Cases: 348/3149 Controls: 251/14091
Shephard (2013)	Microcytosis	Patients ≥ 60 years	0.3 (0.2-0.4) Cases: 233/3149 Controls: 158/14091
Deyo (1988)	Back pain	All included patients	0.05 (0.002-0.3) TP = 1, FP = 1974 N = 8 had other types of cancer
Shephard (2013)	Back pain	Patients ≥ 60 years	0.1 (0.07-0.12) Cases: 341/3149 Controls: 901/14091
Shephard (2013)	Back pain: 2 presentations	Patients ≥ 60 years	0.1 (0.07-0.12)
Collins (2013)	Anaemia	All patients	0.6 (0.5-0.7)
		Men	1.4 (1.1-1.9)
		Women	0.3 (0.3-0.5)
Hippisley-Cox (2012)	Anaemia	All patients	0.69 (0.5-0.9)
Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)
Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)
Oudega (2006)	Deep vein thrombosis	All patients	1.16 (0.4-2.9) 5/430
Collins (2013)	Weight loss	Women	0.1 (0.1-0.2)
Hippisley-Cox (2012)	Weight loss	All patients	0.41 (0.3-0.6)
Collins (2013)	Haematuria	Men	5.5 (5.2-5.8)
		Women	2.6 (2.3-2.8)
Shephard (2013)	Visible haematuria	Patients 40-59 years	0.7 (0.4-1.3)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Shephard (2013)	Visible haematuria	Patients ≥ 60 years	1 (0.08-1.3) Cases: 558/3149 Controls: 97/14091
Shephard (2013)	Visible haematuria: 2 presentations	Patients ≥ 60 years	1.2 (0.9-1.8)
Jones (2007)	Haematuria	Men (all ages) at 6 months	5.47 (4.9-6.1)
Jones (2007)	Haematuria	Men < 45 years at 3 years	0.99 (0.53-1.69)
Jones (2007)	Haematuria	Men 45-54 years at 3 years	4.35 (3.11-5.9)
Jones (2007)	Haematuria	Men 55-64 years at 3 years	8.51 (6.94-10.32)
Jones (2007)	Haematuria	Men 65-74 years at 3 years	11.21 (9.66-12.9)
Jones (2007)	Haematuria	Men 75-84 years at 3 years	10.27 (8.61-12.13)
Jones (2007)	Haematuria	Men ≥ 85 years at 3 years	9.22 (6.43-12.7)
Jones (2007)	Haematuria	Women (all ages) at 6 months	2.48 (2.1-3)
Jones (2007)	Haematuria	Women < 45 years at 3 years	0.22 (0.05-0.64)
Jones (2007)	Haematuria	Women 45-54 years at 3 years	1.34 (0.65-2.45)
Jones (2007)	Haematuria	Women 55-64 years at 3 years	3.42 (2.26-4.93)
Jones (2007)	Haematuria	Women 65-74 years at 3 years	5.91 (4.42-7.72)
Jones (2007)	Haematuria	Women 75-84 years at 3 years	6.83 (5.06-8.98)
Jones (2007)	Haematuria	Women ≥ 85 years at 3 years	8.53 (5.6-12.3)

TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 59: Renal cancer: Patients aged ≥ 60 years: Symptom combinations

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Shephard (2013)	Abdominal pain and back pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Abdominal pain and constipation	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Abdominal pain and lower urinary tract infections	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Abdominal pain and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Abdominal pain and nausea	Patients ≥ 60 years	0.2 (0.1-0.2)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
Shephard (2013)	Abdominal pain and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Abdominal pain and thrombocytosis	Patients ≥ 60 years	0.5 (0.3-1)
Shephard (2013)	Abdominal pain and microcytosis	Patients ≥ 60 years	> 5 (NR)
Shephard (2013)	Abdominal pain and visible haematuria	Patients ≥ 60 years	2.8 (NR)
Shephard (2013)	Visible haematuria and back pain	Patients ≥ 60 years	0.7 (0.4-1.3)
Shephard (2013)	Visible haematuria and constipation	Patients ≥ 60 years	1 (NR)
Shephard (2013)	Visible haematuria and lower urinary tract infections	Patients ≥ 60 years	0.6 (0.4-1)
Shephard (2013)	Visible haematuria and fatigue	Patients ≥ 60 years	0.9 (NR)
Shephard (2013)	Visible haematuria and nausea	Patients ≥ 60 years	1.1 (NR)
Shephard (2013)	Visible haematuria and raised inflammatory markers	Patients ≥ 60 years	1.3 (0.7-2.2)
Shephard (2013)	Visible haematuria and thrombocytosis	Patients ≥ 60 years	2.1 (NR)
Shephard (2013)	Visible haematuria and microcytosis	Patients ≥ 60 years	1.5 (NR)
Shephard (2013)	Constipation and back pain	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation and lower urinary tract infections	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2013)	Constipation and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Constipation and nausea	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Constipation and raised inflammatory markers	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Constipation and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.5)
Shephard (2013)	Constipation and microcytosis	Patients ≥ 60 years	0.6 (NR)
Shephard (2013)	Back pain and lower urinary tract infections	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and fatigue	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and nausea	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Back pain and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2013)	Back pain and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Back pain and microcytosis	Patients ≥ 60 years	0.3 (0.1-0.6)
Shephard (2013)	Lower urinary tract	Patients ≥ 60 years	0.2 (0.1-0.3)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI)
	infections and fatigue		
Shephard (2013)	Lower urinary tract infections and nausea	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2013)	Lower urinary tract infections and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Lower urinary tract infections and thrombocytosis	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2013)	Lower urinary tract infections and microcytosis	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2013)	Fatigue and nausea	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2013)	Fatigue and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Fatigue and thrombocytosis	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2013)	Fatigue and microcytosis	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2013)	Nausea and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2013)	Nausea and thrombocytosis	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2013)	Nausea and microcytosis	Patients ≥ 60 years	0.5 (NR)
Shephard (2013)	Raised inflammatory markers and thrombocytosis	Patients ≥ 60 years	0.4 (0.3-0.5)
Shephard (2013)	Raised inflammatory markers and microcytosis	Patients ≥ 60 years	0.7 (0.5-1)
Shephard (2013)	Thrombocytosis and microcytosis	Patients ≥ 60 years	0.6 (0.4-1)

NR = Not reported. TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 60: Positive predictive values for any childhood cancer: All patients[j]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before	All included patients	0.083 (0.067-0.105) Cases: 108/1267

j This table is included in the evidence review for renal cancer because one of the cancers of childhood is renal cancer.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	diagnosis		Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013)	Bruising 0-3 months	All included patients	0.38 (0.09-1.64)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	before diagnosis and ≥ 3 consultations		
Dommett (2013)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.10) Cases: 28/1267 Control: 21/15318
Dommett (2013)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013)	≥ 3 consultations	All included patients	0.02
Dommett (2013)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

The positive predictive values are calculated using Bayesian statistics.

Table 61: Positive predictive values for any childhood cancer: Patients aged 0-4 years[k]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436

k This table is included in the evidence review for renal cancer because one of the cancers of childhood is renal cancer.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
			Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

The positive predictive values are calculated using Bayesian statistics.

Table 62: Positive predictive values for any childhood cancer: Patients aged 5-14 years[l]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831

l This table is included in the evidence review for renal cancer because one of the cancers of childhood is renal cancer.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	diagnosis		Control: 37/10516
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 5-14 years	0.082 (0.053-0.125) Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

The positive predictive values are calculated using Bayesian statistics.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of abdominal ultrasound, urine cytology, x-ray, intravenous pyelogram, or CT scan of the abdomen and pelvis in patients with suspected renal cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for renal cancer if they are aged 45 and over and have unexplained visible haematuria without urinary tract infection or visible haematuria that persists or recurs after successful treatment of urinary tract infection. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of renal cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict renal cancer. <u>Investigations in primary care for renal cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of renal cancer</u> The quality of the evidence as assessed by QUADAS-II varied from low to high for the positive predictive values for the different symptoms. The GDG noted some limitations of the evidence. Firstly, all the evidence with the exception of two papers had

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	merged all urinary tract cancers making it difficult to tease out the specifics related to renal cancer. Secondly, the evidence did not distinguish between visible and non-visible haematuria, but largely grouped these two together as haematuria. The GDG judged, based on their clinical experience, that most of that evidence was likely to reflect visible haematuria. <u>Investigations in primary care for renal cancer</u> No evidence was found pertaining to the diagnostic accuracy of abdominal ultrasound, urine cytology, intravenous pyelogram, abdominal/pelvic CT scan or X-ray in primary care patients with suspected renal cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with renal cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without renal cancer who get inappropriately referred whilst maximising the number of people with renal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with renal cancer outweighed the disadvantages to those without. The GDG noted, based on the evidence, that visible haematuria presenting in a primary care setting was associated with a positive predictive value of above 3% for renal cancer. They therefore recommended this symptom should prompt a suspected cancer pathway referral. The GDG also noted that, based on the evidence, the positive predictive value of visible haematuria for renal cancer increased with age. They therefore agreed to recommend referral for those people aged 45 or over. The GDG agreed, based on their clinical experience that urinary tract infections often cause visible haematuria. They therefore recommended that if visible haematuria persists or recurs after successful treatment of urinary tract infection, a suspected cancer pathway referral should be made. Although the symptoms of abdominal pain and microcytosis had positive predictive values above 3%, the GDG noted that referral for colorectal cancer would normally be the first direction of investigation for these symptoms. They therefore agreed not to make any recommendations for these symptoms related to renal cancer. The GDG noted the absence of evidence for investigations for renal cancer in primary care. Based on their clinical experience they considered that whilst ultrasound is an investigation commonly used to diagnose renal cancer in secondary care, it could have value as an investigation in primary care.

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	The GDG considered that the clinical benefits of renal ultrasound performed in primary care would be to expedite renal cancer diagnosis in people whose symptoms may otherwise not be investigated. However, the GDG recognised that it was difficult to define exactly which symptoms should prompt an ultrasound and consequently some people without renal cancer may also be investigated unnecessarily. The GDG therefore felt unable to make any recommendations on primary care-based investigations for renal cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for visible haematuria is likely to result in a cost decrease because of the introduction of an age limit. However, the recommendation to refer if there is persistent/recurrent urinary tract infection is likely to represent a small to moderate increase in costs. Overall the GDG agreed these were likely to balance each other.
Other considerations	The GDG noted that visible haematuria is a symptom which is common to cancers of the urinary tract. It was therefore, agreed that recommendations for referral of haematuria would need to be consistent for these cancer sites.

12.4 Testicular cancer

Update 2015

Over 2,000 new testicular cancers are diagnosed each year in the UK, so a full-time GP will usually diagnose one new person with testicular cancer during their career. It is atypical in terms of the age-groups affected. The peak age of onset is 30-34 years, although it can occur in older males. It is the commonest cancer in males between 16 and 24 years. Five-year survival is almost 100%.

Testicular cancer usually presents as a change in the shape or texture of the testis. This may be painful. It can present as disseminated disease, particularly with lymph node spread.

Testicular cancer can be seen on ultrasound of the testis, a test available in primary care.

Clinical questions:

- **What is the risk of testicular cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected testicular cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of testicular cancer in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of ultrasound in patients with suspected testicular cancer where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for testicular cancer if they have a non-painful enlargement or change in shape or texture of the testis. [new 2015]** **Consider a direct access ultrasound scan as part of clinical reassessment for testicular cancer in men with unexplained or persistent testicular symptoms. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of testicular cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict testicular cancer. No evidence was found on this outcome. <u>Investigations in primary care for testicular cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of testicular cancer</u> No evidence was found pertaining to the positive predictive values of different symptoms of testicular cancer in primary care. <u>Investigations in primary care for testicular cancer</u> No evidence was found pertaining to the diagnostic accuracy of ultrasound in primary care patients with suspected testicular cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those men with testicular cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of men without testicular cancer who get inappropriately referred whilst maximising the number of men with testicular cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with testicular cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for testicular cancer. Despite the lack of evidence, the GDG considered that it

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	was still important to provide guidance on which symptoms should prompt referral for suspected testicular cancer as it is a very treatable disease and diagnosis at an early stage improves outcome. However, the GDG were aware that most men presenting with scrotal symptoms do not have testicular cancer. They therefore needed to use caution when specifying which symptoms should prompt referral so that excessive referral was avoided. The GDG agreed, based on their clinical experience, that non-painful enlargement or change in shape or texture of the testis were likely to be the typical symptoms of testicular cancer and should prompt a suspected cancer pathway referral. The GDG noted, that although pain can be indicative of cancer, pain in the testes does not often result from testicular cancer. They therefore did not include this symptom in the recommendation as they agreed it would be likely to result in over-referral. The GDG acknowledged that there may be a small number of men with atypical presentations of testicular cancer, who would be missed by this recommendation. However, they agreed that if the symptoms resulted from testicular cancer, they were likely to worsen/persist rather than resolve. The GDG therefore recommended men with persistent or unexplained testicular symptoms be offered clinical reassessment. Due to the lack of evidence, it was not possible to specify what these testicular symptoms were. The GDG noted the lack of evidence on the diagnostic accuracy of ultrasound. However, based on their clinical experience, they noted that ultrasound was an accessible, non-invasive test that could be used to discriminate between malignant and non-malignant disorders of the testes. They therefore agreed to recommend that ultrasound be considered for those men with unexplained or persistent testicular symptoms in order to pick up those men with atypical presentations of testicular cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that referral for men with a non-painful enlargement or change in shape or texture of the testis is already current practice. In addition, ultrasound is a relatively inexpensive test and given the small numbers of men likely to be scanned, this was unlikely to represent a significant additional cost.
Other considerations	The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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12.5 Penile cancer

Penile cancer is rare, with around 500 cases diagnosed each year in the UK. A full time GP is likely to diagnose only one – if any – person with penile cancer during their career. Nearly all are squamous cell cancers.

Penile cancer is usually seen as a raised lesion. Because of its rarity, few studies have reported its clinical features. It can be difficult to differentiate penile cancer from the commoner lesions seen with some sexually transmitted diseases.

It is often possible to diagnose a typical penile cancer visually, but confirmation of the diagnosis is generally made by excision biopsy in secondary care.

Clinical questions:

- **What is the risk of penile cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected penile cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of testicular cancer in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of tests used in patients with suspected penile cancer where the clinical responsibility was retained by primary care.Cost-effectiveness evidence

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer if they have a penile mass or ulcerated lesion, and sexually transmitted infection has been excluded as a cause or a persistent penile lesion after treatment for a sexually transmitted infection has been completed. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer in men with unexplained or persistent symptoms affecting the foreskin or glans. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of penile cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict penile cancer. No evidence was found on this outcome.

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	Investigations in primary care for penile cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	Signs and symptoms of penile cancer No evidence was found pertaining to the positive predictive values of different symptoms of penile cancer in primary care. Investigations in primary care for penile cancer No evidence was found pertaining to the diagnostic accuracy of tests used in primary care patients with suspected penile cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those men with penile cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of men without penile cancer who get inappropriately referred whilst maximising the number of men with penile cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with penile cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for penile cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected penile cancer. The GDG noted that, based on their clinical experience, penile lesions can be a symptom of penile cancer. However they acknowledged that most penile lesions are caused by sexually transmitted infections rather than cancer. They therefore agreed that a suspected cancer pathway referral should only be recommended after sexually transmitted infections had been excluded as the cause of a penile lesion, in order to reduce inappropriate urological referrals. The GDG also agreed that referral should be considered for those men with other unexplained or persistent symptoms of foreskin and/or glans. The GDG discussed whether an age threshold should be included in the recommendations, as penile cancer is rare in men under 60. However it was noted that the demographics of penile cancer may be changing to include younger men. The GDG therefore agreed not to include an age threshold in the recommendations.

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	Due to the lack of evidence, the GDG were not able to recommend a particular test for the primary care investigation of penile cancer. Equally, the GDG were not able to recommend that no tests be done in primary care. Therefore they agreed not to make any recommendations on this issue.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered that the recommendations made were similar to current clinical practice and therefore would not require additional funding. In addition, they noted that penile cancer is very rare and does not affect many men. They therefore agreed the recommendations were likely to be cost-neutral.
Other considerations	The GDG noted that the previous guidance had made specific recommendations about men with Peyronie's disease. It was agreed that this group of men would be covered by the recommendation made and did not require specific mention. The GDG considered the situation for transgendered people, who retain any of the genital organs of their genetic sex. The recommendations for cancers generally found in a single sex, also extend to people who have the organs of that sex, whatever their gender.

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Bladder cancer

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Testicular cancer

None

Penile cancer

None

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13 Skin cancers

13.1 Malignant melanoma of the skin

Just over 13,000 new malignant melanomas are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with malignant melanoma every 3-5 years. Five year survival is 90%.

Malignant melanoma is usually seen as a pigmented lesion on the skin; a number of typical features of the lesion have been described. Rarely, nodular melanomas may occur. The cancer may also present after spread to the regional lymph nodes or wider metastases.

The main method of diagnosis is by excision biopsy, which is performed in secondary care.

Clinical questions:

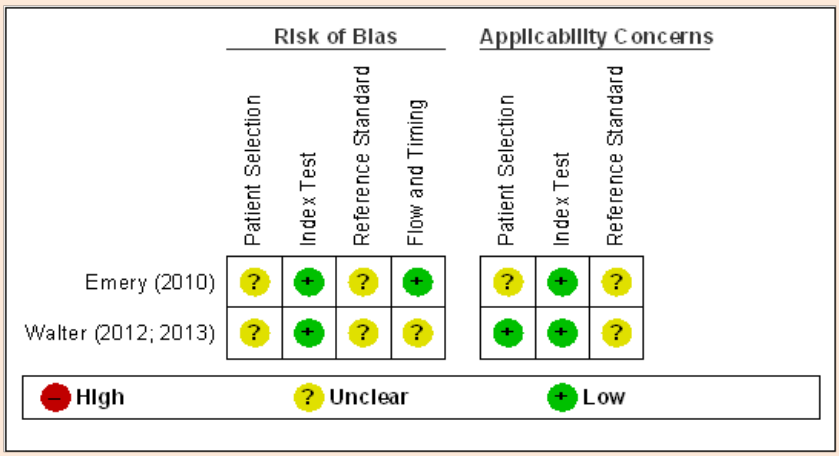
- **What is the risk of malignant melanoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected malignant melanoma should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, (4) the fact that the reference standard did not in all cases match that of the current question, namely histology, and 5) data missing.



Evidence statement

Pigmented skin lesions presenting in a primary care setting are associated with positive predictive values of 0.8-5.1% for malignant melanoma (2 studies, N = 2784 lesions), and the positive predictive values increased proportionally to the number of different risk features the lesions displayed up to 15.7% (1 study, 1436 lesions). The studies were associated with 4 bias/applicability concerns (see also Table 63).

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Table 63: Melanoma: Study results.

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Emery (2010) Lesion-based analysis	Pigmented lesion	All included patients	1.4 (0.8-2.3) 17/1211
		England sample	0.8 (0.3-2) 5/630
		Australia sample	1.9 (1-3.5) 11/581
Walter (2012) Lesion-based analysis	Suspicious pigmented lesions	All included patients	2.3 (1.6-3.2) 36/1573
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Change in size of lesion	All included patients	3.8 (2.5-5.5) 26/693
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Irregular pigmentation	All included patients	4.4 (3.1-6.3) 31/702
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Irregular border	All included patients	5.1 (3.4-7.5) 25/492
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Inflammation	All included patients	4.5 (1.9-10.1) 6/132
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Itch or altered sensation	All included patients	2.3 (1.1-4.4) 9/397
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Lesion larger than other (diameter > 7 mm)	All included patients	3.9 (2.6-5.7) 27/695
Walter (2013) Lesion-based analysis	7PCL: Suspicious pigmented lesions: Oozing/crusting of lesion	All included patients	4.9 (2.1-10.1) 7/144
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 1*	All included patients	2.7 (1.9-3.8) 36/1334
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 2*	All included patients	3.3 (2.4-4.7) 34/1016
Walter (2013)	Original 7PCL: Score ≥ 3*	All included patients	5.1 (3.5-7.4) 29/565

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Lesion-based analysis			
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 4*	All included patients	8.2 (5.2-12.5) 20/245
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 5*	All included patients	12.3 (6.1-22.6) 9/73
Walter (2013) Lesion-based analysis	Original 7PCL: Score ≥ 6*	All included patients	10.5 (1.8-34.5) 2/19
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 1**	All included patients	2.7 (1.9-3.8) 36/1334
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 2**	All included patients	2.9 (2.1-4.1) 36/1221
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 3**	All included patients	3.4 (2.4-4.8) 33/969
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 4**	All included patients	4.8 (3.4-6.8) 33/685
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 5**	All included patients	5.9 (4-8.5) 27/459
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 6**	All included patients	8.3 (5.4-12.6) 21/252
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 7**	All included patients	10.9 (6.7-17.1) 17/156
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 8**	All included patients	15.7 (7.5-29.1) 8/51
Walter (2013) Lesion-based analysis	Weighted 7PCL: Score ≥ 9**	All included patients	8.3 (0.4-40.2) 1/12

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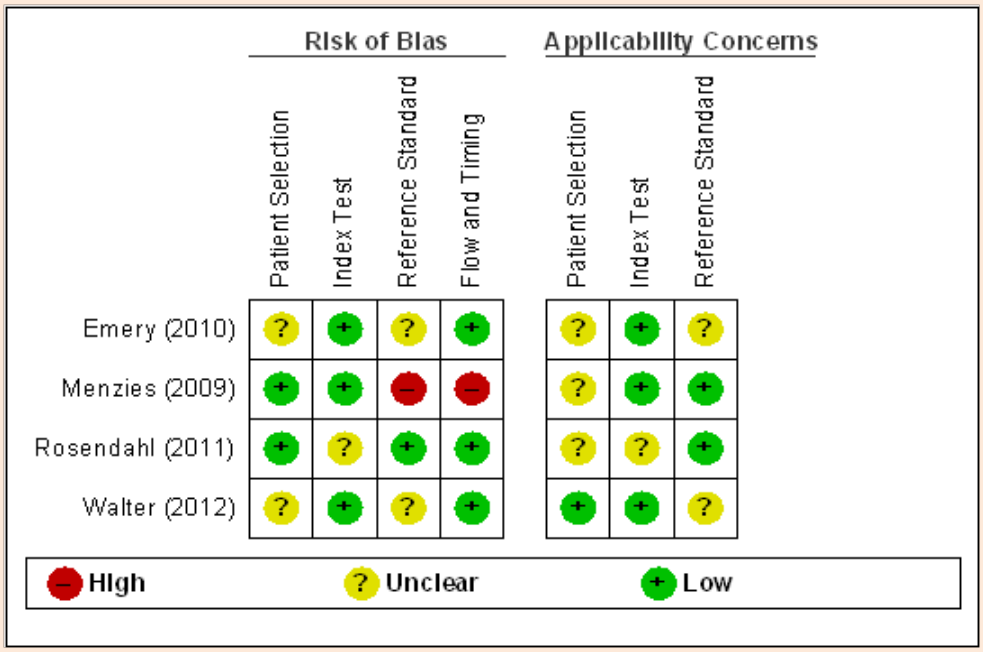
** Original 7PCL consists of 7 items (change in shape, size and/or colour, inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) and each present feature score 1 point. ** The Weighted 7PCL consists of the same 7 items, but these are divided into major (change in shape, size and/or colour) scoring 2 points each and minor (inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) scoring 1 point.*

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study populations may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the criteria for malignancy of the index test are not specified in one case which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole in some cases and not for malignant melanoma separately. The reference standards employed were also subject to high or unclear risk of bias in the majority of the studies.



Evidence statement

SIAscan/MoleMate (2 studies, N = 1977 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 44-100%, specificities ranging between 71.79-95%, positive predictive values ranging between 7.86-52%, and false negativity rates ranging between 0-56% for skin cancer/malignant melanoma. The studies were each associated with 3-4 bias/applicability concerns (see also Table 64).

Dermatoscopy/dermoscopy with and without clinical images or sequential digital dermoscopy imaging (2 studies, N = 794 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 53.1- 82.6%, specificities ranging between 80-92.8%, positive predictive values ranging between 34-44.4%, and false negativity rates ranging between 17.4-46.9% for skin cancer/malignant melanoma. The studies were each associated with 3 bias/applicability concerns (see also Table 65).

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Table 64: Melanoma: SIAscan/MoleMate

Study	Intervention	Prevalence	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	False negativity rate %
Emery (2010)	SIAscan/MoleMate: Moncrieff scoring system	England development set: 24 "suspicious" and 3 melanomas /422 lesions	54 (35-72)	77 (73-81)	12 (7.5-20)	46
Emery (2010)	SIAscan/MoleMate: Primary scare scoring algorithm	England validation set: 6 "suspicious" and 2 melanomas /208 lesions	50 (18-81)	84 (78-88)	9 (3-22)	50
Emery (2010)	SIAscan/MoleMate: Primary scare scoring algorithm	Australia dataset: 45 "suspicious" and 11 melanomas /581 lesions	44 (32-58)	95 (93-97)	52 (38-66)	56
Walter (2012)	SIAscan/MoleMate	18 melanomas/ 766 lesions	100 (78.1-100)	71.79 (68.4-75)	7.86 (4.9-12.3)	0

Table 65: Melanoma: Dermoscopy/dermatoscopy

Study	Intervention	Prevalence	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	False negativity rate %
Menzies (2009)	Dermoscopy	Unclear/331 lesions	53.1 (34.7-70.9)	89 (84.9-92.3)	34 (21.2-48.8)	46.9
Menzies (2009)	Dermoscopy ± sequential digital dermoscopy imaging	Unclear/331 lesions	71.9 (53.3-86.3)	86.6 (82.2-90.3)	36.4 (24.7-49.6)	28.1
Menzies (2009)	Sequential digital dermoscopy imaging	Unclear/149 lesions	72.7 (39-94)	92.8 (87.1-96.5)	44.4 (21.5-69.2)	27.3
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6	80	Not reported	17.4

There was no evidence relating to the diagnostic accuracy of biopsy or ophthalmoscopy for diagnosing malignant melanoma in a primary care setting.

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Cost-effectiveness evidence

Evidence statement

Wilson et al (2012) compared the cost-effectiveness of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm) in addition to usual care (clinical history, naked eye examination and completion of a seven point checklist) in comparison to usual care alone for the diagnosis of potentially suspicious lesions. The authors found that the addition of the Molemate system would increase lifetime costs by £18 and yield an additional 0.01 QALYs per patient. The resulting ICER of £1,896 per QALY falls well below the NICE threshold of £20,000 per QALY and so the base case results suggest that Molemate is a cost-effecitve addition to usual care.

The addition of the Molemate scan also appears to be cost-effective in an alternative analysis in which East of England cancer registry data were used rather than the trial data with an ICER of £3,172 per QALY. Furthermore, a threshold analysis showed that the cost of adding the Molemate scan would have to exceed £290 for it to no longer be considered cost-effective at a threshold of £30,000 per QALY. The true cost of adding the Molemate scan is unlikely to be as high as this and so this too appears to be a strong result.

The probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the addition of the Molemate scan was cost-effective in 60.3% of iterations. This suggests that there is considerable uncertainty, which the authors attribute to uncertainty in the sensitivity and specificity of Molemate versus usual care and the risk of disease progression in undiagnosed melanoma.

While these results appear favourable, further consideration needs to be given to the key effects that are driving the result. The results were primarily driven by the differences in diagnostic accuracy between the two strategies, which were informed by RCT evidence showing that Molemate had higher sensitivity and lower specificity than usual care. However, only the lower specificity result was found to be statistically significant. Indeed, the conclusion drawn from the trial was that Molemate did not add to best application of NICE guidelines in terms of appropriateness of referral.

Furthermore, the implications of the diagnostic accuracy data used in the model is that both appropriate and inappropriate referrals would be increased by using the Molemate system (driven by better sensitivity and poorer specificity, respectively). Therefore, the results of the model essentially suggest that benefits of picking up more cancer through appropriate referral outweigh the costs of making more inappropriate referrals. In other words, a policy of 'over-referring' may be cost-effective.

This interpretation has implications for the cost-effectiveness of the Molemate system itself as it could be argued that the Molemate system is not actually required to achieve such a policy. Being less strict as primary care gatekeepers would very likely lead to similarly cost-effective outcomes without the need for the additional spending on the Molemate system. Indeed, it could be further argued that it would be counter-intuitive to spend money on a system that has only been proven to decrease specificity in comparison to current best practice.

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Table 66: Modified GRADE table showing the included evidence (Wilson et al. 2012) on the cost-effectiveness of adding the molemate system to standard care in patients presenting in primary care with suspected melanoma.

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Wilson et al. 2012 UK study considering NHS and PSS perspective. Cost-utility analysis (CUA)	Patients presenting in primary care with at least one suspicious pigmented lesion.	Standard Care: Lesions assessed by lead clinician following NICE guidelines including clinical history, naked eye examination and completion of 7 point checklist.	£1115	15.098 QALYs	Reference			Threshold Sensitivity Analysis The maximum cost per Molemate scan which would result in an ICER less than £30,000 was found to be £290 per consultation. Deterministic Sensitivity Analysis Use of East of England cancer registry data rather than trial data resulted in an ICER of £3,172 per QALY Probabilistic Sensitivity Analysis 66.1% of iterations led to an ICER below £30,000 per QALY. The molemate system was dominant in 19.6% and dominated in 7.9% of iterations.	Directly Applicable Analysis conducted from a UK Health Service perspective. Results reported as incremental cost per QALY. Minor Limitations Further one-way sensitivity analysis could have been conducted.
		Standard Care (as above) plus the addition of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm)	£1133	15.108 QALYs	£18	0.01 QALYs	£1896 per QALY		

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Recommendations	**Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) if dermatoscopy suggests malignant melanoma of the skin. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for malignant melanoma if they present with a suspicious pigmented skin lesion that has a weighted 7-point checklist score of 3 or more.** **Major features of the lesions (scoring 2 points each):** • **change in size** • **irregular shape** • **irregular colour.** **Minor features of the lesions (scoring 1 point each):** • **largest diameter 7 mm or more** • **inflammation** • **oozing** • **change in sensation.** **[new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of malignant melanoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict malignant melanoma. <u>Investigations in primary care for malignant melanoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. Although sensitivity and specificity were reported, the GDG agreed that the most informative outcomes were the positive predictive values (because these gave the risk of a patient harbouring cancer), and the false negative rates (to inform whether a negative test obviated the need for further safety-netting).
Quality of the evidence	<u>Signs and symptoms of malignant melanoma</u> The evidence consisted of two relatively small studies, and the quality of the evidence was assessed by QUADAS-II as not high quality. The GDG noted the following limitations with the evidence reviewed: the studies were conducted in a setting which was not representative of UK primary care; used lesion-, not patient-based analyses; and/or used a reference standard of questionable reliability. <u>Investigations in primary care for malignant melanoma</u> Evidence was identified for the accuracy of SIAScan/MoleMate and dermoscopy/dermatoscopy with and without clinical images. This evidence was assessed by QUADAS-II as low quality. The GDG noted several limitations with the evidence reviewed. Firstly, the study population of some of the studies were not directly representative of an unselected symptomatic population of patients presenting to UK-based primary care. Secondly, the criteria for malignancy of the index test were not specified in some studies, which may limit its external validity. Thirdly the results presented were lesion-, not patient-based and moreover based on a best case scenario in some of the studies, and therefore likely to

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	be inflated. Fourthly the results were only available for skin malignancy as a whole in some studies and not for malignant melanoma separately. Finally, the reference standard was sub-optimal in some studies, which may also have affected the results. No evidence was identified pertaining to the diagnostic accuracy of biopsy or ophthalmoscopy used in primary care patients with suspected malignant melanoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with malignant melanoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without malignant melanoma who get inappropriately referred whilst maximising the number of people with malignant melanoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with malignant melanoma outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that only very little evidence of questionable quality and/or relevance had been found on the positive predictive values of symptoms of and tests for malignant melanoma. Despite the limited evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected malignant melanoma. The GDG noted, based on their clinical experience, that malignant melanoma is a highly malignant tumour that is, however, very curable when discovered early. The GDG also noted that melanoma is comparatively common in younger people, and that improvements in the early diagnosis of malignant melanoma will be associated with relatively more life years gained. The GDG noted that there was evidence available for both the original (unweighted) and the weighted 7-point checklist, and the GDG agreed that the weighted 7-point checklist is the more widely used. The GDG therefore agreed, based on the evidence, to recommend a suspected cancer pathway referral for people with a score of 3 or greater on the weighted 7-point checklist. The GDG agreed, based on the evidence, that in people with skin lesions, dermatoscopy can differentiate between suspicious and non-suspicious skin lesions, and noted that this differentiation has the potential to result in a more efficient use of the suspected cancer pathway referral system (by only referring those people with skin lesions who are relatively more likely to have a malignancy). The GDG therefore agreed to recommend a suspected cancer pathway referral for people where dermatoscopy suggests malignant melanoma of the skin. The GDG also acknowledged that the use of dermatoscopy requires specialist training and that dermatoscopy is not universally available in UK primary care. The GDG therefore

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	decided to recommend that a suspected cancer pathway referral is considered for people with a skin lesion that is suspicious of malignant melanoma of the skin if dermatoscopy is inappropriate or not available. The GDG agreed not to make any recommendations on the use of biopsy or ophthalmoscopy in primary care patients with suspected malignant melanoma. No recommendation was made on the use of opthalmoscopy in primary care patients with suspected malignant melanoma because the GDG did not have evidence or sufficient experience of ocular melanoma to make a recommendation.
Trade-off between net health benefits and resource use	The GDG noted that one relevant, published economic evaluations had been identified in this area. The GDG noted that there was considerable uncertainty over the results of the Wilson et al. (2012) paper and therefore agreed not to base any recommendations on this evidence. The GDG noted that through using the 7-point checklist, the number of referrals of people who transpire not to have malignant melanoma would probably be reduced. However, there may be more referrals based on dermatoscopy findings. Overall this may result in a small cost increase.

13.2 Squamous cell carcinoma

Update 2015

Approximately 25,000 squamous cell carcinomas of the skin are diagnosed each year, with a full time GP likely to diagnose at least one person with squamous cell carcinoma every 1-2 years. Death from squamous cell carcinoma is rare, with the main advantage from early diagnosis being less extensive treatment. It is seen in both sexes.

Squamous cell carcinoma is usually seen as a raised lesion on the skin; a number of typical features of the lesion have been described.

It is often possible to diagnose a typical squamous cell carcinoma visually, but confirmation of the diagnosis is generally made by excision biopsy in accordance with NICE guidance on Improving Outcomes for People with Skin Tumours including Melanoma.

Clinical questions:

- **What is the risk of squamous cell carcinoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected squamous cell carcinoma should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.

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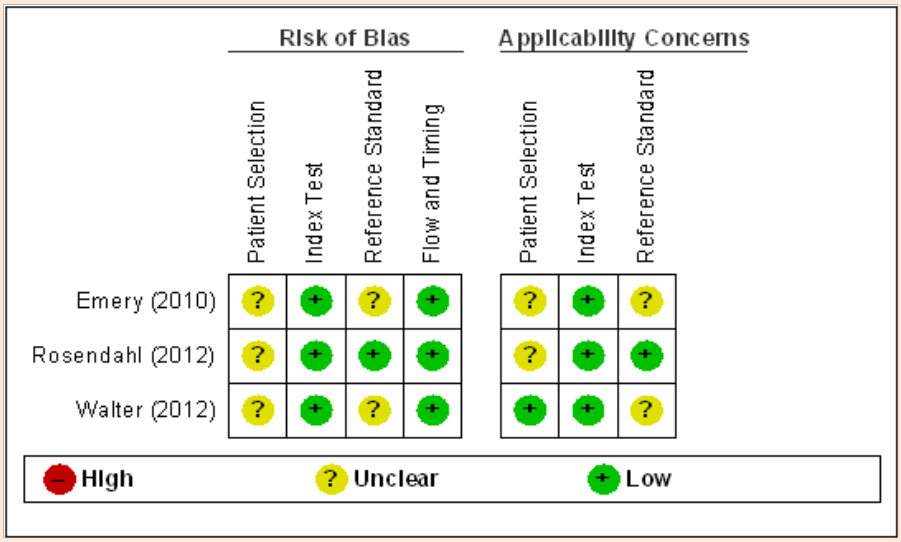

Evidence statement

Pigmented skin lesions (2 studies, N = 2784 lesions) presenting in a primary care setting do not seem to confer a risk of squamous cell carcinoma (1 case observed in total). The studies were associated with 3-4 bias and applicability concerns (See also Table 67).

Non-pigmented raised skin lesions (1 study, N = 206 lesions) presenting in a primary care setting are associated with a positive predictive value of 41.26% for squamous cell carcinoma. The study was associated with 2 bias and applicability concerns (See also Table 67).

Table 67: Squamous cell carcinoma of the skin: Study results.

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Emery (2010) Patient-based analysis	Pigmented lesion	All included patients	0 (0-0.6) 0/858
		England sample	0 (0-1.2) 0/389
		Australia sample	0 (0-1) 0/469
Walter (2012) Lesion, not patient,-based analysis	Suspicious pigmented lesions	All included patients	0.06 (0.003-0.4) 1/1573
Rosendahl (2012) Lesion, not patient,-based analysis	Non-pigmented raised skin lesions	All included patients	SCC total: 41.26 (34.5-48.3) 85/206
			SCC: 15.53 (11-21.4) 32/206
			Keratoacanthoma: 14.08 (9.8-19.8) 29/206
			Bowen disease: 11.65 (7.8-17) 24/206

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
		Females	SCC and KA: 31.81 (21.2-44.6) 21/66
		Males	SCC and KA: 28.57 (21.4-36.9) 40/140
	Non-pigmented raised skin lesions on head and neck	Patients with specific symptom	SCC and KA: 23.33 (15.3-33.7) 21/90
	Non-pigmented raised skin lesions on trunk	Patients with specific symptom	SCC and KA: 14.29 (6.4-27.9) 7/49
	Non-pigmented raised skin lesions on upper extremities	Patients with specific symptom	SCC and KA: 45.16 (27.8-63.7) 14/31
	Non-pigmented raised skin lesions on lower extremities	Patients with specific symptom	SCC and KA: 52.78 (35.7-69.2) 19/36
	Non-pigmented raised skin lesions with monomorphic vascular pattern	Patients with specific symptom	SCC and KA: 26.47 (19.5-34.8) 36/136
	Non-pigmented raised skin lesions with polymorphic vascular pattern	Patients with specific symptom	SCC and KA: 31.71 (18.6-48.2) 13/41
	Non-pigmented raised skin lesions with vessels absent	Patients with specific symptom	SCC and KA: 39.29 (22.1-59.3) 11/28
	Non-pigmented raised skin lesions with vessel morphologic findings: Dots	Patients with specific symptom	SCC and KA: 0 (0-95) 0/1
	Non-pigmented raised skin lesions with vessel morphologic findings: Coils	Patients with specific symptom	SCC and KA: 40 (30.1-49.8) 44/110
	Non-pigmented raised skin lesions with vessel morphologic findings: Serpentine	Patients with specific symptom	SCC and KA: 9.76 (4.6-18.8) 8/82
	Non-pigmented raised skin lesions with vessel morphologic findings: Looped	Patients with specific symptom	SCC and KA: 41.67 (22.8-63.1) 10/24
	Non-pigmented raised skin lesions with vessel arrangement: No arrangement	Patients with specific symptom	SCC and KA: 36.7 (27.8-46.5) 40/109
	Non-pigmented raised skin lesions with vessel arrangement: Radial	Patients with specific symptom	SCC and KA: 41.18 (19.4-66.5) 7/17
	Non-pigmented raised skin	Patients with specific	SCC and KA: 0 (0-

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
	lesions with vessel arrangement: Centered	symptom	30.1) 0/12
	Non-pigmented raised skin lesions with vessel arrangement: Branched	Patients with specific symptom	SCC and KA: 0 (0-12.3) 0/35
	Non-pigmented raised skin lesions with vessel arrangement: Branched and radial	Patients with specific symptom	SCC and KA: 2/2 (TP = 2, FP = 0)
	Non-pigmented raised skin lesions with vessel arrangement: Others	Patients with specific symptom	SCC and KA: 100 (19.8-100) 0/2
	Non-pigmented raised skin lesions and keratin	Patients with specific symptom	SCC and KA: 52.17 (41.6-62.6) 48/92
	Non-pigmented raised skin lesions and ulceration	Patients with specific symptom	SCC and KA: 27.27 (13.9-45.8) 9/33
	Non-pigmented raised skin lesions with white structures: White clods	Patients with specific symptom	SCC and KA: 20 (5.3-48.6) 3/15
	Non-pigmented raised skin lesions with white structures: White structureless zones	Patients with specific symptom	SCC and KA: 47.06 (3.2-61.4) 24/51
	Non-pigmented raised skin lesions with white structures: White circles	Patients with specific symptom	SCC and KA: 58.7 (43.3-72.7) 27/46
	Non-pigmented raised skin lesions with white structures: White lines	Patients with specific symptom	SCC and KA: 6.67 (0.3-34) 1/15
	Non-pigmented raised skin lesions with white structures: White dots (milia)	Patients with specific symptom	SCC and KA: 16.67 (0.9-63.5) 1/6
	Non-pigmented raised skin lesions with white structures: Blood spots	Patients with specific symptom	SCC and KA: 45.61 (32.6-59.2) 26/57
	Non-pigmented raised skin lesions with white structures: Scale	Patients with specific symptom	SCC and KA: 40 (28.7-52.4) 28/70

1 *KA = keratoacanthoma; TP = true positives; FP = false positives*

2

3 *Investigations in primary care*

4 Risk of bias in the included studies

5 The risk of bias and applicability concerns are summarised per study in the figure below. The
6 main issues to note are that the study population may not be directly representative of an
7 unselected symptomatic population of patients presenting to the UK-based GP, that the
8 index test does not specify the criteria for malignancy which may limit its external validity,
9 and that the results presented are based on a best case scenario, and are therefore likely to

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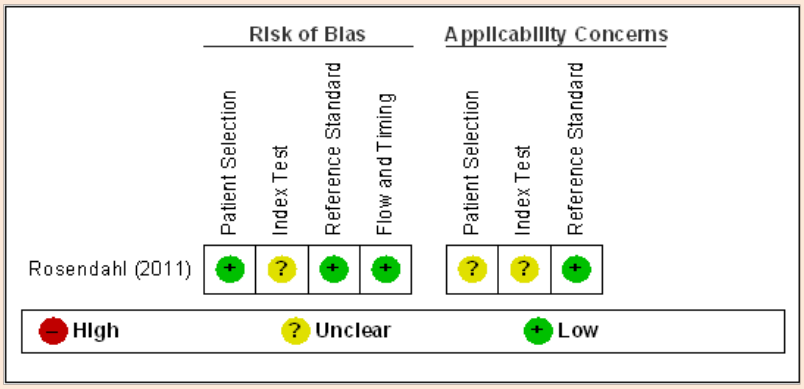
be inflated, and only available for skin malignancy as a whole and not for squamous cell carcinoma separately.



Evidence statement

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for skin malignancy. The study was associated with 1 bias and 2 applicability concerns (See also Table 68).

Table 68: Squamous cell carcinoma of the skin: Study results.

Study	Intervention	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	False negativity rate
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6% (NR)	80% (NR)	NR (NR)	17.4% (NR)

NR = Not reported

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a skin lesion that raises the suspicion of squamous cell carcinoma. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of squamous cell carcinoma The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict squamous cell carcinoma. Investigations in primary care for squamous cell carcinoma The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. Although sensitivity and specificity were reported, the GDG agreed that the most informative outcomes were the positive predictive values (because these gave the risk of a patient harbouring cancer), and the false negative rates (to inform whether a negative test obviated the need for further safety-netting).

Quality of the evidence	<u>Signs and symptoms of squamous cell carcinoma</u> The quality of the evidence was assessed by QUADAS-II as not high quality. The GDG noted the following limitations with the evidence reviewed: some of the studies were conducted in a setting which was not representative of UK primary care; used lesion- not patient-based analyses; and/or focused on pigmented lesions and were not informative about how to recognise a squamous cell carcinoma. Given these limitations, the GDG agreed to disregard this evidence and instead base their recommendations on their clinical opinion, taking into account the natural history of squamous cell carcinoma. <u>Investigations in primary care for squamous cell carcinoma</u> Evidence was only identified on the accuracy of dermatoscopy and clinical images. This evidence was assessed by QUADAS-II as low quality. The GDG noted several limitations with the evidence reviewed. Firstly, the study population may not have been directly representative of an unselected symptomatic population of patients presenting to UK-based primary care. Secondly, the index test did not specify the criteria for malignancy which may limit its external validity. Thirdly the results presented were based on a best case scenario, and therefore likely to be inflated. Fourthly the results were only available for skin malignancy as a whole and not for squamous cell carcinoma separately. No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion used in primary care patients with suspected squamous cell carcinoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with squamous cell carcinoma more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without squamous cell carcinoma who get inappropriately referred whilst maximising the number of people with squamous cell carcinoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with squamous cell carcinoma outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that very little evidence on the positive predictive values of symptoms for squamous cell carcinoma had been found and it was of low quality and questionable relevance. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected squamous cell carcinoma. The GDG noted, based on their clinical experience, that squamous cell carcinomas grow faster than basal cell carcinomas, can metastasise and can have an effect on survival and wellbeing if they grow to be big or disfiguring. However, they noted that, in the absence of appropriate evidence, it is difficult to provide detailed guidance about specific features of a skin lesion that indicates squamous cell carcinoma. The GDG agreed, based on their clinical experience, that a skin

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	lesion which raises the suspicion of squamous cell carcinoma is likely to be a symptom of squamous cell carcinoma, and would probably have a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for this symptom. The GDG agreed not to make any recommendations on the use of dermatoscopy in primary care patients with suspected squamous cell carcinoma due to the very limited and low quality evidence.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation made for referral for squamous cell carcinoma was likely to be cost-neutral as this is already standard practice.
Other considerations	The GDG acknowledged that squamous cell carcinoma is more common in immunosuppressed people, but felt that the recommendation would also be appropriate for this population.

13.3 Basal cell carcinoma

Approximately 75,000 basal cell carcinomas of the skin are diagnosed each year, with a full time GP likely to diagnose at least one person with basal cell carcinoma per year. Death from basal cell carcinoma is exceptionally rare, with the main advantage from early diagnosis being less extensive treatment. It is seen in both sexes.

Basal cell carcinoma is usually seen as a raised lesion on the skin; a number of typical features of the lesion have been described.

It is often possible to diagnose a typical basal cell carcinoma visually, but confirmation of the diagnosis is generally made by excision biopsy in accordance with NICE guidance.

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Clinical questions:

- **What is the risk of basal cell carcinoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected basal cell carcinoma should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.

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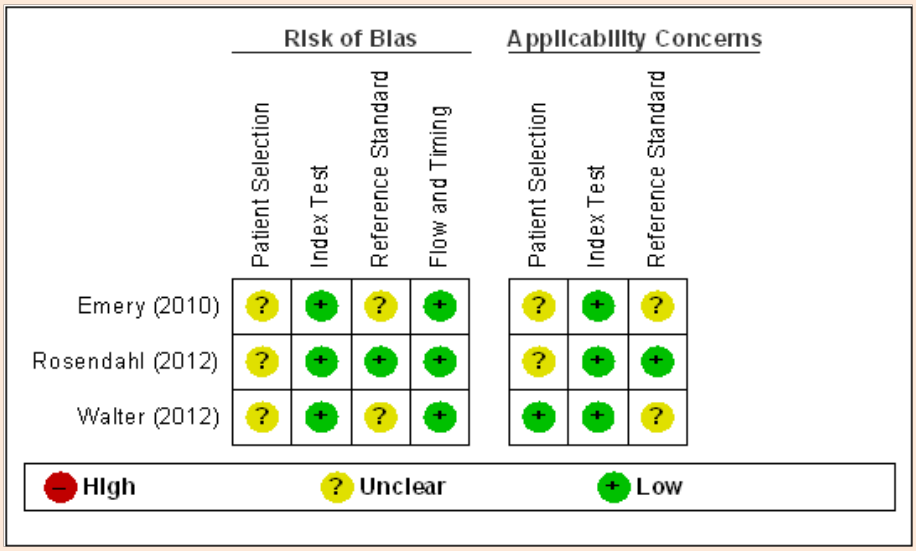

Evidence statement

Pigmented skin lesions (2 studies, N = 2784 lesions) presenting in a primary care setting are associated with positive predictive value of 0.64-1.82% for basal cell carcinoma. The studies were associated with 3-4 bias and applicability concerns (see also Table 69).

Non-pigmented skin lesions (1 study, N = 206 lesions) presenting in a primary care setting are associated with a positive predictive value of 27.18% for basal cell carcinoma. The study was associated with 2 bias and applicability concerns (see also Table 69).

Table 69: Basal cell carcinoma: Study results

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Prevalence
Emery (2010) Lesion, not patient,-based analysis	Pigmented lesion	All included patients	1.82 (1.2-2.8) 22/1211
		England sample	0/630 (0-0.8)
		Australia sample	3.79 (2.4-5.8) 22/581
Walter (2012) Lesion, not patient,-based analysis	Suspicious pigmented lesions	All included patients	0.64 (0.3-1.2) 10/1573
Rosendahl (2010) Lesion, not patient,-based analysis	Non-pigmented raised lesion	All included patients	27.18 (21.3-33.9) 56/206

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study population may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the index test does not specify the criteria for malignancy which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole and not for basal cell carcinoma separately.

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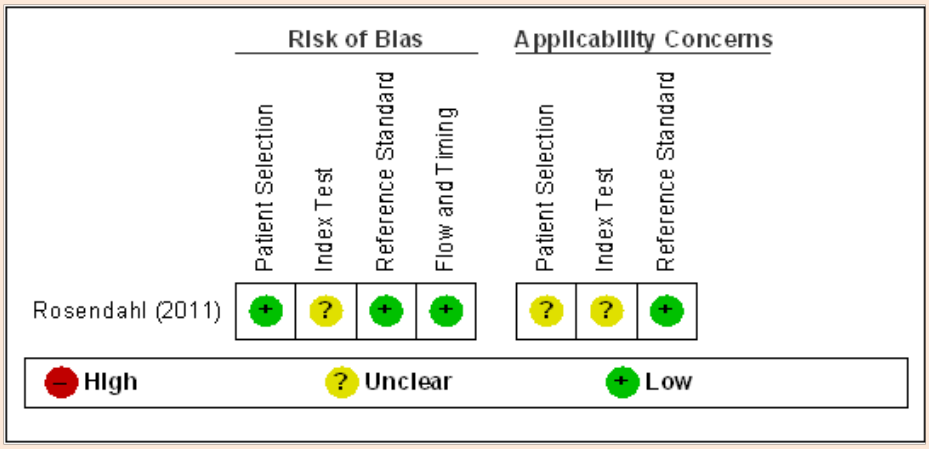

Evidence statement

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for basal cell carcinoma. The study was associated with 1 bias and 2 applicability concerns (see also Table 70).

Table 70: Basal cell carcinoma: Study results

Study	Intervention	Prevalence	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	False negativity rate
Rosendahl (2011)	Clinical images and dermatoscopy	138 malignacies/463 lesions	82.6% (NR)	80% (NR)	NR (NR)	17.4% (NR)

NR = not reported

Update 2015

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider routine referral for people if they have a skin lesion that raises the suspicion of a basal cell carcinoma[m]. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a skin lesion that raises the suspicion of a basal cell carcinoma if there is concern that a delay may have an unfavourable impact, because of factors such as lesion site or size. [new 2015]** **GPs should only excise suspected basal cell carcinomas in accordance with the NICE guideline on improving outcomes for people with skin tumours including melanoma. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of basal cell carcinoma The GDG considered the positive predictive value to be the most

m Typical features of basal cell carcinoma include: an ulcer with a raised rolled edge; prominent fine blood vessels around a lesion; or a nodule on the skin (particularly pearly or waxy nodules).

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	important outcome when identifying which signs and symptoms predict basal cell carcinoma. Investigations in primary care for basal cell carcinoma The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. Although sensitivity and specificity were reported, the GDG agreed that the most informative outcomes were the positive predictive values (because these gave the risk of a patient harbouring cancer), and the false negative rates (to inform whether a negative test obviated the need for further safety-netting).
Quality of the evidence	Signs and symptoms of basal cell carcinoma The quality of the evidence was assessed by QUADAS-II as not high quality. The GDG noted several limitations with the evidence reviewed. Firstly some of the studies were conducted in a setting which was not representative of UK primary care. Secondly, the studies did not present results for each type of skin malignancy, only for malignancy as a whole, making it difficult to ascertain the relevance of the results. Thirdly, the focus of the evidence was on pigmented lesions and not informative about how to recognise a basal cell carcinoma. Given these limitations, the GDG agreed to disregard this evidence and instead base their recommendations on their clinical opinion, taking into account the natural history of basal cell carcinoma. Investigations in primary care for basal cell carcinoma Evidence was only identified on the accuracy of dermatoscopy and clinical images. This evidence was assessed by QUADAS-II as low quality. The GDG noted several limitations with the evidence reviewed. Firstly, the study population may not have been directly representative of an unselected symptomatic population of patients presenting to UK-based primary care. Secondly, the index test did not specify the criteria for malignancy which may limit its external validity. Thirdly the results presented were based on a best case scenario, and therefore likely to be inflated. Fourthly the results were only available for skin malignancy as a whole and not for basal cell carcinoma separately. No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion used in primary care patients with suspected basal cell carcinoma.
Trade-off between clinical benefits and harms	The GDG agreed, based on their clinical experience, that basal cell carcinomas are slow growing, do not often metastasise and have a minimal effect on survival. Given this, the GDG decided that a suspected cancer pathway referral was not an efficient use of resources in people with a suspected basal cell carcinoma. Instead they agreed to recommend that people with a suspected basal cell carcinoma should have a routine referral. The GDG considered that by making these recommendations the referral pathways would be optimised. The GDG recognised that these recommendations could result in a delay in referral for someone with a squamous cell carcinoma that had been misdiagnosed as a basal cell carcinoma but this was unlikely to have significant adverse consequences. The GDG included a recommendation that the referral could be expedited where there was concern that a delay may result in an unfavourable outcome due to the site or size of the lesion. The GDG considered, despite the lack of evidence, that it was

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	commonly accepted that excision was the only definitive test to diagnose a basal cell carcinoma. The GDG discussed that the NICE guidance on Improving Outcomes in Skin Tumours including Melanoma makes recommendations for when excision can and cannot take place in primary care and agreed that these recommendations should be followed, rather than making separate recommendations in this guideline. The GDG considered that aligning with the recommendations in the NICE guidance on Improving Outcomes in Skin Tumours including Melanoma, would help to ensure that basal cell carcinomas were excised to the same high standard, people received more rapid and convenient treatment and the inappropriate removal of skin lesions that were no threat to health (with the associated personal and financial costs) was reduced. The GDG agreed not to make any recommendations on the use of dermatoscopy in primary care patients with suspected basal cell carcinoma.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered that the overall number of patients being referred for investigation of basal cell carcinoma is unlikely to change. However there may be a small increase in the need for suspected cancer pathway referrals for those with lesions in functionally or cosmetically challenging places. The GDG considered that overall this was unlikely to have a major cost impact.

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14 Head and neck cancers

14.1 Laryngeal cancer

Just over 2,000 new laryngeal cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with laryngeal cancer during their career. Five year survival is 70%.

The most common symptom of laryngeal cancer is believed to be hoarseness, sometimes accompanied by other symptoms such as throat pain. However the rarity of this cancer means there are few studies of its clinical features.

The main method of diagnosis is by laryngoscopy and biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of laryngeal cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected laryngeal cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of laryngeal cancer in patients presenting with symptoms in primary care.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of chest x-ray in patients with suspected laryngeal cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for laryngeal cancer in people aged 45 and over with persistent unexplained hoarseness. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for laryngeal cancer in people aged 45 and over with an unexplained lump in the neck. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of laryngeal cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict laryngeal cancer. No evidence was found for this outcome.

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	Investigations in primary care for laryngeal cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	Signs and symptoms of laryngeal cancer No evidence was found pertaining to the positive predictive values of different symptoms of laryngeal cancer in primary care. Investigations in primary care for laryngeal cancer No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected laryngeal cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with laryngeal cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without laryngeal cancer who get inappropriately referred whilst maximising the number of people with laryngeal cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with laryngeal cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for laryngeal cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected laryngeal cancer, since there was no test available in primary care and diagnosis at an early stage improves the outcome. The GDG noted that persistent unexplained hoarseness and an unexplained lump in the neck can be symptoms of laryngeal cancer. The GDG agreed, based on their clinical experience, that had these symptoms been studied they would have had a positive predictive value of 3% or above. The GDG noted that laryngeal cancer is extremely rare in people below 45 years and therefore anticipated that the positive predictive values for persistent unexplained hoarseness and an unexplained lump in the neck were below 3% in people aged less than 45 years old. The GDG therefore agreed to recommend a suspected cancer pathway referral for these symptoms in people aged 45 years and over. Due to the lack of evidence and the fact that there is no obvious test for laryngeal cancer in primary care, the GDG were not able to recommend a particular test for the primary care investigation of laryngeal cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

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	The GDG noted that the recommendations for a suspected cancer pathway referral for persistent unexplained hoarseness and an unexplained lump in the neck in people aged 45 years and over are likely to be associated with a small cost saving as the previous recommendations were for all people whereas the GDG has now imposed the 45 year age-limit.

14.2 Oral cancer

Over 6,500 new oral cancers are diagnosed each year in the UK. Most are diagnosed by dental surgeons. It is seen in both sexes, though two-thirds of new diagnoses are in males. Survival varies considerably.

Oral cancer can present with persistent ulceration, a mass, or abnormal bleeding. Rarely, it can present as advanced disease with regional lymphadenopathy.

Some oral cancers can be recognised visually, but definitive diagnosis requires biopsy, generally in secondary care.

Clinical questions:

- **What is the risk of oral cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected oral cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of oral cancer in patients presenting with symptoms in primary care.

Investigations in primary care

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The study was associated with a number of bias and validity issues. The following issues compromise the validity and applicability of this study, (1) it is unclear (and probably unlikely) that the patient population consists of consecutive or randomly recruited patients (and may therefore bias the results), (2) the study is conducted in the USA in an unclear setting and it is therefore not clearly transferable to UK-based primary care, and (3) the timspan between the index test and reference standard is unclear in all but one patient and the results are therefore compromised to an unknown extent.

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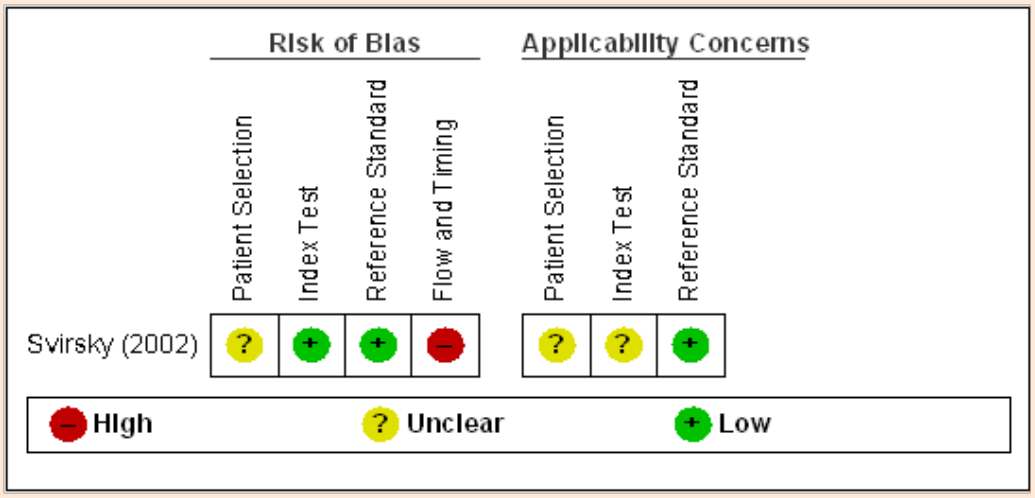

Evidence statement

Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 93.3%, a specificity of 19.1%, a positive predictive value of 5.76%, and a false negativity rate of 6.7% for oral cancer. Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 95.88%, a specificity of 25.37%, a positive predictive value of 38.27%, and a false negativity rate of 4.12% for oral cancer/dysplasia. The study was associated with 4 bias or applicability concerns (see also Table 71).

Table 71: Oral cancer: Study results

Study	Test	Prevalence	Sensi-tivity (95% CI) %	Speci-ficity (95% CI) %	Other results (95% CI)
Svirsky (2002)	Transepithelial oral brush biopsy with a computer-assisted method of analysis	15/298	93.3 (66-99.7)	19.1 (14.8-24.3)	Malignancy: TP = 14 FN = 1 TN = 54 FP = 229 Positive predictive value = 5.76 (3.3-9.7)% Negative predictive value = 98.18 (89-99.9)% False negativity rate = 6.7%
Svirsky (2002)	Transepithelial oral brush biopsy with a computer-assisted method of analysis	97/298	95.88 (89.2-98.7) %	25.37 (19.6-32.1) %	Malignancy and dysplasia: TP = 93 FN = 4 TN = 51 FP = 150 Positive predictive value = 38.27 (32.2-44.7) % Negative predictive value = 92.73 (81.6-97.6)% False negativity rate = 4.12%

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

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Recommendations	**Consider an urgent referral (for an appointment within 2 weeks) for assessment for oral cancer by the community dental service in people with an unexplained lump on the lip or in the oral cavity that has not been assessed by a dental surgeon. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a lump on the lip or in the oral cavity that has been assessed by a dental surgeon to be consistent with oral cancer. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with unexplained ulceration in the oral cavity lasting for more than 14 days. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with a persistent and unexplained lump in the neck. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of oral cancer The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict oral cancer. No evidence was found for this outcome. Investigations in primary care for oral cancer The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question.
Quality of the evidence	Signs and symptoms of oral cancer No evidence was found pertaining to the positive predictive values of different symptoms of oral cancer in primary care. Investigations in primary care for oral cancer The evidence consisted of one study examining the diagnostic performance of transepithelial oral brush biopsy with a computer-assisted method of analysis in 298 patients, which as assessed by QUADAS-II, provided evidence of unclear quality. The GDG noted that the evidence was not applicable to UK-based primary care as it was conducted in the USA using a test that is not appropriate for UK-based primary care due to its requirement of postgraduate training for the physician as well as the requirement of specialist sample handling and testing. The GDG therefore decided to disregard the evidence.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with oral cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of

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	people without oral cancer who get inappropriately referred whilst maximising the number of people with oral cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with oral cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for oral cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected oral cancer as diagnosis at an early stage improves outcome. However, the GDG were aware that most people presenting with oral symptoms do not have oral cancer. They therefore needed to use caution when specifying which symptoms should prompt referral so that excessive referral was avoided. The GDG also recognised that people with oral symptoms may present either to their dental surgeon or their general practitioner, and the importance of assessment by a dental surgeon rather than a general practitioner due to their different areas of expertise. The GDG therefore agreed to reflect this in the recommendations. The GDG noted that unexplained ulceration of more than 14 days duration in the oral cavity, and a persistent and unexplained lump in the neck can be symptoms of oral cancer. The GDG agreed, based on their clinical experience, that had these symptoms been studied it would have had a positive predictive value of 3% or above. The GDG therefore agreed to recommend a suspected cancer pathway referral for these symptoms. The GDG also agreed, based on their clinical experience, that an unexplained lump on the lip or in the oral cavity can be a symptom of oral cancer. They did not, however, consider that the positive predictive value of this symptom was above 3% unless it had been assessed by a dental surgeon to be consistent with oral cancer. The GDG therefore decided to recommend urgent referral for assessment by the community dental service for any person with an unexplained lump on the lip or in the oral cavity which has not been assessed by a dental surgeon, and a suspected cancer pathway referral for any person who has a lump on the lip or in the oral cavity which has been assessed by a dental surgeon to be consistent with oral cancer. Due to the lack of evidence, the GDG decided not to make any recommendations about biopsy in patients with suspected oral cancer who present in primary care.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional

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	economic analysis had been undertaken in this area. The GDG estimated that the recommendations would result in an increase in costs within the community dental service, and a decrease in the number, and therefore cost, of suspected cancer pathway referrals, but were uncertain over net effect.
Other considerations	The GDG noted that NHS dentists are not available in all areas or to all people and frequently also involve payment for the service. The GDG also noted that the community dental service is free, available in all areas, and provides more standardised care than individual dental practitioners, but the GDG recognised that it is currently only set up to treat children and people with special needs and not people with suspected cancer. However, the GDG deemed that although there may be some initial capacity issues whilst the service adjusts to deal with people with suspected cancer, this is unlikely to be a significant problem as the number of people with suspected cancer is small. The GDG decided to prioritise people not incurring costs and the delivery of a higher standard of care and therefore recommended urgent referral to the community dental service. The GDG noted that the prevalence of oral cancer in young people is low, and the GDG therefore considered including an age limit in the recommendations. However, the GDG also noted that cancer presents earlier in deprived communities, so therefore decided against including any age limit in the recommendations in order to avoid missing more cancers in deprived communities.

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14.3 Thyroid cancer

Over 2,500 new thyroid cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1-2 people with thyroid cancer during their career. It is seen in both sexes, though around 70% of new diagnoses are now in females. Five year survival approaches 80%.

Because of its rarity, there are few reports on the clinical features of thyroid cancer. It is believed usually to present with a nodule within the thyroid gland, or as diffuse thyroid swelling. The cancer may also present with regional lymphadenopathy.

Definitive diagnosis requires biopsy, performed in secondary care.

Clinical questions:

- **What is the risk of thyroid cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected thyroid cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

No primary care evidence was identified pertaining to the risk of thyroid cancer in patients presenting with symptoms in primary care.

Investigations in primary care

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No evidence was identified pertaining to the diagnostic accuracy of ultrasound, thyroid function tests, or fine needle aspiration in patients with suspected thyroid cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for thyroid cancer in people with an unexplained thyroid lump. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of thyroid cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict thyroid cancer. No evidence was found for this outcome. <u>Investigations in primary care for thyroid cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of thyroid cancer</u> No evidence was found pertaining to the positive predictive values of different symptoms of thyroid cancer in primary care. <u>Investigations in primary care for thyroid cancer</u> No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected thyroid cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with thyroid cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without thyroid cancer who get inappropriately referred whilst maximising the number of people with thyroid cancer who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with thyroid cancer outweighed the disadvantages to those without. However, in this instance, the GDG acknowledged that no evidence had been found on the positive predictive values of symptoms for thyroid cancer. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected thyroid cancer, since diagnosis at an early stage improves the outcome. The GDG noted that an unexplained thyroid lump can be a symptom of thyroid cancer. The GDG agreed, based on their clinical experience, that had this symptom been studied it would

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	have had a positive predictive value of 3% or above.The GDG therefore agreed to recommend a suspected cancer pathway referral for this symptom. The GDG noted that ultrasound needed to be performed with fine needle aspiration to investigate suspected thyroid cancer, and that fine needle aspiration is not available as a primary care test. The GDG therefore decided not to make any recommendations for the primary care investigation of suspected thyroid cancer.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for a suspected cancer pathway referral for an unexplained thyroid lump is likely to be cost-neutral as it is currently standard practice.

References

Laryngeal cancer

None

Oral cancer

Svirsky, J. A., Burns, J. C., Carpenter, W. M. & et.al. (2002) Comparison of computer-assisted brush biopsy results with follow up scalpel biopsy and histology. Gen Dent, 50: 500-503.

Thyroid cancer

None

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15 Brain and central nervous system cancers

Around 9000 new primary brain and central nervous system cancers are diagnosed each year in the UK, meaning that a full time GP is likely to diagnose approximately 1 person every 3-5 years. It is seen in both sexes, and is one of the commoner cancers in childhood, though it is encountered at all ages. It is also one of the commoner cancers in young people.

Several symptoms have been reported, including new-onset seizures, headache, nausea, drowsiness, visual change and personality change.

A diagnosis of brain and central nervous system cancer (whether primary or secondary) is generally made by imaging using CT or MRI. These diagnostic tests can be performed with the GP retaining clinical responsibility

Clinical questions:

- **What is the risk of brain and central nervous system cancer in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected brain and central nervous system cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that a number of the studies employed case-control (or other non-consecutive, non-randomised) designs which have been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Other issues of concern include that some of the studies were conducted abroad and their direct relevance to UK-based primary care may therefore be limited, that the symptoms were underspecified in one study and therefore of limited use for the present purposes, and that some of the reference standards employed were of questionable quality and applicability.

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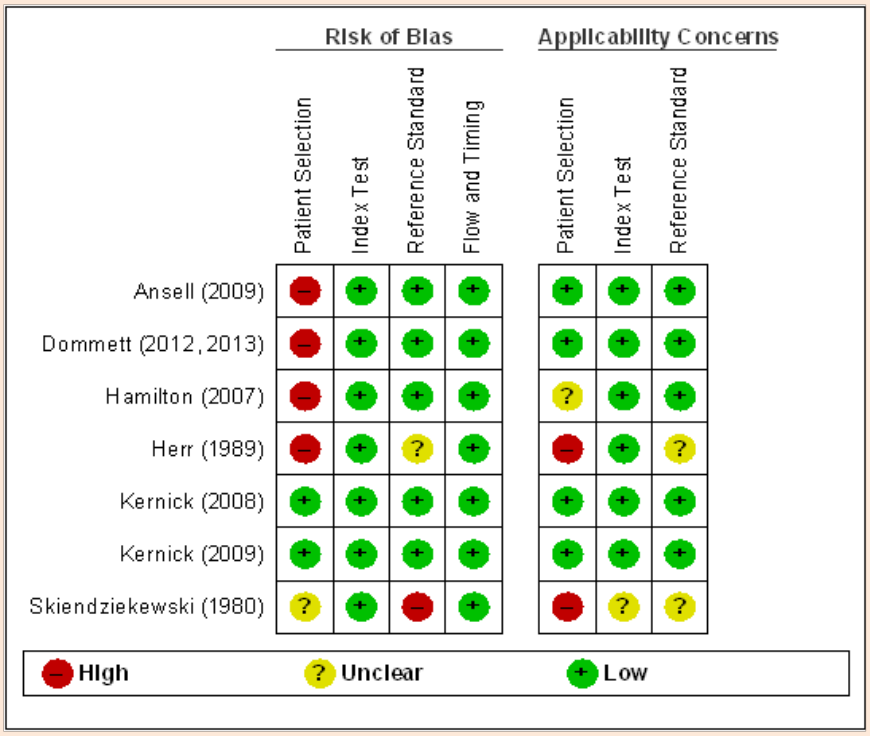

Evidence statement

The positive predictive values of having a brain tumour in adulthood ranged from 0% (for dizziness and/or weakness) to 2.3% (for new-onset seizure in 60-69 year old patients) for symptomatic patients presenting to primary care (4 studies, N = 106588). The included studies were associated with 0-4 bias/applicability concerns each (see also Table 72).

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain or musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) for symptomatic patients aged 0-14 years old presenting to primary care (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 73).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from < 0.013% (for vomiting or headache with anorexia) to 0.15 (for vomiting in combination with unsteadiness) for patients aged 0-14 years old, from 0% (for primary headache) to 0.03% (for undifferentiated headache) for patients aged 5-17 years, and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (3 studies, N = 79910). The evidence quality is somewhat compromised by the case-control design of two of the studies (see also Table 74).

Table 72: Brain & CNS cancer: Study results for adult populations

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Hamilton (2007)	Headache	All included patients	0.09 (0.08-0.1)
Hamilton (2007)	Headache*	Patients 60-69 years	0.12 (NR)
Kernick (2008)	Undifferentiated headache	All included patients	0.15 (0.12-0.19) 97/63921
Kernick (2008)	Undifferentiated headache	Patients < 50 years	0.08 (0.05-0.11) 32/40866
Kernick (2008)	Undifferentiated headache	Patients ≥ 50 years	0.28 (0.22-0.36) 65/23055
Kernick (2008)	Primary headache	All included patients	0.045 (0.023-0.088)

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
			10/21758
Kernick (2008)	Primary headache	Patients < 50 years	0.03 (0.01-0.08) 5/16282
Kernick (2008)	Primary headache	Patients ≥ 50 years	0.09 (0.03-0.23) 5/5476
Hamilton (2007)	Motor loss	All included patients	0.026 (0.024-0.03)
Hamilton (2007)	New-onset seizure	All included patients	1.2 (1-1.4)
Hamilton (2007)	New-onset seizure*	Patients 60-69 years	2.3 (NR)
Hamilton (2007)	Confusion	All included patients	0.2 (0.16-0.24)
Hamilton (2007)	Memory loss	All included patients	0.036 (0.026-0.052)
Hamilton (2007)	Visual disorder	All included patients	0.035 (0.025-0.051)
Hamilton (2007)	Headache + any of the other symptoms reported by Hamilton (2007)	All included patients	0.39 (0.31-0.48)
Herr (1989)	Dizziness	All included patients	0 (0-3.7) 0/125
Skiendziekewski (1980)	Weakness and/or dizziness	All included patients	0 (0-4.4) 0/106
Hamilton (2007)	Weakness	All included patients	0.14 (0.11-0.18)

* *Peak PPVs for these symptoms are in this age group.*

Table 73: Positive predictive values for any childhood cancer: Patients aged 0-14 years[n]

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12	All included patients	0.096 (0.074-0.126)

n This table is included in the evidence review for brain & CNS cancer because one of the cancers of childhood is brain & CNS cancer.

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
	months before diagnosis		Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before	All included patients	Cases: 63/1267

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
	diagnosis		Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 74: Brain & CNS cancer: Positive predictive values for central nervous system**
3 **(CNS) child- or young adulthood cancer tumour**

Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Ansell (2009)	Vomiting and unsteadiness	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.15 (0.01-0.1) 1/654
Ansell (2009)	Vomiting and visual difficulties	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.088 (0.005-0.6) 1/1142
Ansell (2009)	Headache and unsteadiness	All included CNS childhood cancer tumour patients and	0.085 (0.005-0.6) 1/1172

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
		controls aged 0-14 years	
Ansell (2009)	"All other symptom combinations (except vomiting or headache with anorexia) had a predictive probability [of a child having a brain tumour given a visit to a GP with both symptoms] of between 1 in 1500 and 1 in 8000 children". The predictive probabilities of vomiting or headache with anorexia appeared to be even lower.		
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Kernick (2009)	Headache (any type)	All included patients aged 5-17 years	0.03 (0.01-0.05) 13/48575
Kernick (2009)	Primary headache	All included patients aged 5-17 years	0 (0-0.05) 0/9321
Kernick (2009)	Undifferentiated headache	All included patients aged 5-17 years	0.03 (0.02-0.06) 13/38705
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.02 (0.01-0.06)
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%

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Study	Symptom(s)	Patient group	Positive predictive value % (95% CI) Frequency
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

The positive predictive values are calculated using Bayesian statistics.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of CT or MRI scans in patients with suspected brain or CNS cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider an urgent direct access MRI scan of the brain (within 2 weeks) to assess for brain or central nervous system cancer in adults with progressive, sub-acute loss of central neurological function. [new 2015]** **Consider a very urgent referral (for an appointment within 48 hours) for suspected brain or central nervous system cancer in children and young people with newly abnormal cerebellar or other central neurological function. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of brain and central nervous system cancer</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict brain cancer. <u>Investigations in primary care for brain and central nervous system cancer</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of brain and central nervous system cancer</u> The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of moderate-high quality. <u>Investigations in primary care for brain and central nervous system cancer</u> No evidence was found pertaining to the diagnostic performance of brain CT or MRI in primary care patients with suspected brain cancer.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral or very urgent specialist assessment would be to identify those people with brain/central nervous system cancer more

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	rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without brain/central nervous system cancer who get inappropriately referred or assessed whilst maximising the number of people with brain/central nervous system cancer who get appropriately referred or assessed. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those adults with brain/central nervous system cancer outweighed the disadvantages to those adults without. However, in children's cancers, the GDG decided that this threshold was too stringent for the following reasons: 1) the high levels of treatability of these cancers, 2) early diagnosis can reduce mortality and morbidity, and 3) the number of life-years gained. The GDG therefore agreed that referral at lower levels of risk than 3% was justified in children. The GDG noted that in adults none of the positive predictive values exceeded the 3% threshold for referral and that no evidence was available for brain MRI. However, the GDG also noted, based on their clinical experience, that progressive sub-acute loss of central neurological function can be a symptom of brain cancer that can be diagnosed with a brain MRI, but that the positive predictive value for this symptom is unlikely to exceed 3%. In addition brain MRI is superior to brain CT in terms of obtaining diagnostic information (also for potential alternative diagnoses). The GDG therefore decided to recommend an urgent brain MRI for adults with progressive sub-acute loss of central neurological function. The GDG considered that recommending an urgent scan instead of a referral to neurology would result in a faster diagnostic process for adults with a tumour because they will be referred straight to a neurosurgeon after the scan instead of first to neurology, then for a scan and then to neurosurgery. The GDG noted, based on their clinical experience, that'new abnormal cerebellar or other central neurological function in children or young people can be a symptom of brain cancer, which the GDG agreed was serious enough to warrant very urgent attention. However, the GDG did not feel that an immediate admission would be appropriate since there are risks associated with this and it is still unlikely that the child or young person would have cancer. However, the GDG recognised that new abnormal cerebellar or other central neurological function is a worrying symptom and that children have less reserve than adults so the GDG did not want to recommend a suspected cancer pathway referral either. Instead the GDG opted for urgent specialist assessment as this would mean the child or young person would get seen quickly and would get around any issues with weekend cover and differences in local service configuration.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

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	The GDG noted that the recommendations are likely to result in an increase in MRI scanning, a decrease in outpatient appointments and a decrease in GP consultations (due to patients receiving an earlier answer about symptoms and reassurance that they do not have brain cancer, which means they will not re-attend).The GDG agreed that this would not constitute an overall increase in cost, and may even constitute a small decrease in overall costs.

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Brain and CNS cancer

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16 Haematological cancers

16.1 Leukaemia

Over 8,000 new leukaemias are diagnosed each year in the UK. A full time GP is likely to diagnose approximately one person with leukaemia every 3-5 years. There are several subtypes, with the main division being into myeloid leukaemia and lymphoid leukaemia. The leukaemias may be acute, with rapid progression if untreated, or chronic, which may progress over several years. Some chronic leukaemias transform into acute leukaemias, usually after several years. Most forms of leukaemia have high five-year survival, though some subtypes have a poorer prognosis. Leukaemia accounts for a third of all cancers diagnosed in children. It is one of the commoner cancers in young people.

The most common symptoms of leukaemia relate to replacement of the bone marrow by malignant cells, leading to anaemia, reduced normal white cells and thrombocytopaenia. Symptoms therefore include pallor, bruising and a propensity to infection. Many chronic leukaemias are symptomless and are only identified when a full blood count is performed for other reasons.

In many leukaemias the diagnosis can be made on the blood film, though definitive diagnosis usually requires bone marrow biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of leukaemia in adults and children presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected leukaemia should be done with clinical responsibility retained by primary care?**

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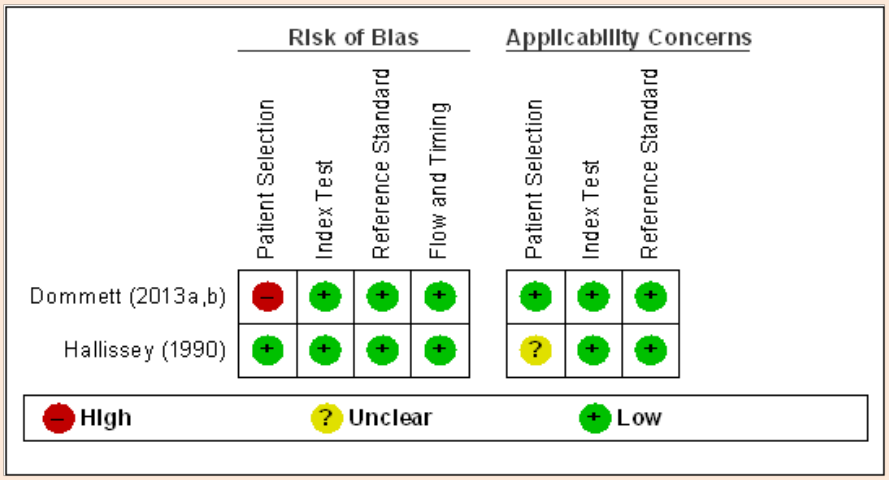
Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included studis in the figure below. One main issue to note is that one study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Another potential threat to the applicability of the findings concerns the fact that the second study employed a patient sample which may not be directly applicable to the current question.



Evidence statement

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years (1 study, N = 30855), and the positive predictive value of having adulthood leukaemia was 0.04% (for dyspepsia) for patients aged > 40 years (1 study, N = 2585) . Both studies were associated with 1 bias/applicability concern (see also Tables 75-76).

Table 75: Leukaemia: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls	0.01 (0-0.01)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		aged 0-14 years	
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 76: Leukaemia: Positive predictive values for teenage and young adult, and adult leukaemia

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799
Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585

The positive predictive values are calculated using Bayesian statistics for Dommett (2013b).

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of white blood cell count in patients with suspected leukemia where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms:** • **pallor** • **persistent fatigue** • **unexplained fever** • **unexplained persistent or recurrent infection** • **generalised lymphadenopathy** • **unexplained bruising**

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	• **unexplained bleeding** • **unexplained petechiae** • **hepatosplenomegaly. [new 2015]** **Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms:** • **pallor** • **persistent fatigue** • **unexplained fever** • **unexplained persistent infection** • **generalised lymphadenopathy** • **persistent or unexplained bone pain** • **unexplained bruising** • **unexplained bleeding. [new 2015]** **Refer children and young people for immediate specialist assessment for leukaemia if they have unexplained petechiae or hepatosplenomegaly. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of leukaemia</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms were predictive of leukaemia. <u>Investigations in primary care for leukaemia</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of leukaemia</u> The quality of the available evidence, as assessed by QUADAS-II, was high. The GDG noted that there was limited evidence, only comprising one study, and that it used a case control design. In addition the evidence related only to children, teenagers and young people. <u>Investigations in primary care for leukaemia</u> No evidence was found pertaining to the diagnostic performance of white blood cell count in primary care patients with suspected leukaemia.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with leukaemia more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without leukaemia who get inappropriately referred whilst maximising the number of people with leukaemia who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above for adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with leukaemia outweighed the disadvantages to those without.

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	The GDG noted that, based on the evidence, no signs or symptoms had a positive predictive value of 3% or above. Consequently they were not able to recommend any signs or symptoms that should prompt a suspected cancer pathway referral for leukaemia. Whilst no evidence had been identified on investigations in primary care for leukaemia, the GDG agreed, based on their clinical experience, that the results of a full blood count would be able to identify leukaemia in the majority of cases. They therefore decided to recommend a set of symptoms which should prompt investigation with a full blood count. The GDG considered that pathways were already in place to deal with people who have an abnormal full blood count suggestive of leukaemia. They therefore decided not to make any recommendations on this. The GDG noted that separate recommendations would need to be made for adults and children/young people as there were slight differences in the symptoms which should prompt investigation between both groups. Since the evidence on the positive predictive values of symptoms only related to children, the GDG agreed to use the symptoms for haematological malignancies recommended in the previous guideline as the basis for their recommendations for adults. These were then amended to make them specific to leukaemia. The recommendations in the previous guideline were also used as the basis for the recommendations on children, supplemented by the evidence found for this question. The GDG noted that unexplained petechia and hepatosplenomegaly in children may indicate severe marrow suppression and were therefore medical emergencies. They therefore agreed to recommend that these children with these symptoms should be have immediate specialist assessment. No similar recommendation was made for adults because they are less likely to be acutely ill with these symptoms.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that there may be a slight increase in the number of full blood counts being performed. However, given that these tests are relatively inexpensive this would probably balance against the reduction in costs associated with more focussed referral of people who have leukaemia.
Other considerations	The GDG acknowledged that Down's syndrome is associated with an increased incidence of acute leukaemia. However the GDG agreed that this risk factor would not affect the clinical considerations on referral or management and therefore different recommendations for those people with Down's syndrome and symptoms of leukaemia were not required.

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16.2 Myeloma

Over 4,500 new myelomas are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 2-3 people with myeloma in their career. Five year survival is nearly 50%. The cancer is an abnormal clone of plasma cells, secreting a specific type of immunoglobulin, called a paraprotein. Paraproteins may be present for many years before true myeloma develops, in the 'monoclonal gammopathy of unknown significance'.

Symptoms arise from two aspects. Destruction of the bone marrow may occur, with bone pain, often in multiple sites such as the ribs, and bone marrow suppression. The paraprotein itself may also lead to complications, such as kidney failure or thrombo-embolism.

Myeloma generally causes considerable elevation of inflammatory markers, such as plasma viscosity or erythrocyte sedimentation rate. Hypercalcaemia can also occur. Paraproteins can be directly measured, and the specific paraprotein identified by protein electrophoresis. Paraproteins are also partially secreted in urine, the Bence Jones protein, which can also be assayed. All these investigations are available to primary care.

Definitive diagnosis generally requires bone marrow biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of myeloma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected myeloma should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are (1) that two of the studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and (2) that two of the studies employed patient selection methods that were not clearly consecutive or random in nature, which, in turn, may result in inflated estimates of the positive predictive values. However, the statistics employed by Shephard (2014) may have gone some way in counteracting this influence.

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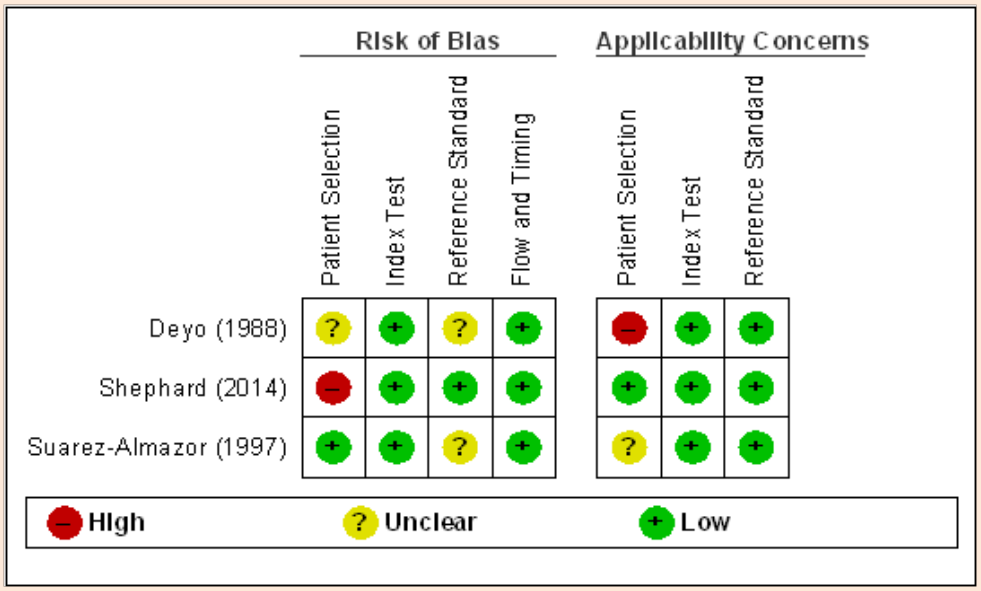

Evidence statement

The positive predictive values for myeloma of single symptoms presenting in a primary care setting ranged from 0% (for 'acute low back pain') to 0.7% (for hypercalcaemia in patients aged ≥ 60 years; 3 studies, N = 17798). The studies were subject to 1-3 bias or applicability concerns (See also Table 77).

The positive predictive values for myeloma of symptom pairs presenting in a primary care setting ranged from 0.1% (for raised creatinine with 'shortness of breath'/ chest infection / joint pain, and for joint pain with 'raised inflammatory markers'/back pain/ 'combined bone pain'/ nausea/fracture/chest pain/ 'shortness of breath', and for 'shortness of breath' with chest infection / chest pain/ fracture/ nausea/ nosebleeds/ back pain/ weight loss, and for chest infection with nosebleeds/nausea, and for chest pain with weight loss; all in patients aged ≥ 60 years) to > 10% (for hypercalcaemia with 'back pain second episode'/ fracture / joint pain/rib pain, and for leucopenia with nosebleeds/fracture; all in patients aged ≥ 60 years; 1 study, N = 14860). The study was subject to 1 bias concern (see also Table 78).

Table 77: Myeloma: Positive predictive values of individual symptoms for myeloma in patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Deyo (1988)	Back pain	All included patients	0.05 (0.003-0.3); 1/1975
Suarez-Almazor (1997)	Acute low back pain	All included patients	0 (0-0.5) or 0.21 (0.04-0.83) 0-2/963 Unclear if diagnosis was prior to symptom
Shephard (2014)	Joint pain	Patients ≥ 60 years	0.05 (0.04-0.06)
Shephard (2014)	Shortness of breath	Patients ≥ 60 years	0.06 (0.05-0.06)
Shephard (2014)	Chest infection	Patients ≥ 60 years	0.06 (0.05-0.06)
Shephard (2014)	Chest pain	Patients ≥ 60 years	0.1 (0.09-0.11)
Shephard (2014)	Fracture	Patients ≥ 60 years	0.1 (0.08-0.12)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Nausea	Patients ≥ 60 years	0.1 (0.08-0.12)
Shephard (2014)	Combined bone pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Nosebleeds	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Back pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Weight loss	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Rib pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Low haemoglobin	Patients ≥ 60 years	0.17 (0.16-0.19)
Shephard (2014)	Leucopenia	Patients ≥ 60 years	0.3 (0.2-0.3)
Shephard (2014)	Low platelets	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Raised inflammatory markers	Patients ≥ 60 years	0.2 (0.18-0.22)
Shephard (2014)	Raised creatinine	Patients ≥ 60 years	0.08 (0.08-0.09)
Shephard (2014)	Raised MVC	Patients ≥ 60 years	0.18 (0.16-0.22)
Shephard (2014)	Hypercalcaemia	Patients ≥ 60 years	0.7 (0.5-1)

Abbreviations: CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives; NR, Not reported.

Table 78: Myeloma: Positive predictive value of symptom combinations for myeloma in patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Joint pain and shortness of breath	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Joint pain and chest infection	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Joint pain and chest pain	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and fracture	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and nausea	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and combined bone pain	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Joint pain and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Joint pain and back pain	Patients ≥ 60 years	0.1 (0.1-0.2)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Joint pain and weight loss	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Joint pain and rib pain	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Shortness of breath and chest infection	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Shortness of breath and chest pain	Patients ≥ 60 years	0.1 (0.05-0.1)
Shephard (2014)	Shortness of breath and fracture	Patients ≥ 60 years	0.1 (0.1-0.3)
Shephard (2014)	Shortness of breath and nausea	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Shortness of breath and combined bone pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Shortness of breath and nosebleeds	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Shortness of breath and back pain	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Shortness of breath and weight loss	Patients ≥ 60 years	0.1 (0.1-0.3)
Shephard (2014)	Shortness of breath and rib pain	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Chest infection and chest pain	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Chest infection and fracture	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Chest infection and nausea	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Chest infection and combined bone pain	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest infection and nosebleeds	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Chest infection and back pain	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Chest infection and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest infection and rib pain	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Chest pain and fracture	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Chest pain and	Patients ≥ 60	0.3 (0.2-0.4)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
	nausea	years	
Shephard (2014)	Chest pain and combined bone pain	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Chest pain and nosebleeds	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Chest pain and back pain	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest pain and weight loss	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Chest pain and rib pain	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Fracture and nausea	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Fracture and combined bone pain	Patients ≥ 60 years	0.8 (NR)
Shephard (2014)	Fracture and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Fracture and back pain	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2014)	Fracture and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Fracture and rib pain	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Nausea and combined bone pain	Patients ≥ 60 years	0.6 (NR)
Shephard (2014)	Nausea and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Nausea and back pain	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2014)	Nausea and weight loss	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nausea and rib pain	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Combined bone pain and nosebleeds	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Combined bone pain and back pain	Patients ≥ 60 years	0.5 (0.3-0.8)
Shephard (2014)	Combined bone pain and weight loss	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Combined bone pain and rib pain	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Nosebleeds and back pain	Patients ≥ 60 years	1.5 (NR)
Shephard (2014)	Nosebleeds and weight loss	Patients ≥ 60 years	0.3 (NR)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Nosebleeds and rib pain	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Back pain and weight loss	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Back pain and rib pain	Patients ≥ 60 years	1.1 (NR)
Shephard (2014)	Weight loss and rib pain	Patients ≥ 60 years	Non-calculable
Shephard (2014)	Back pain first episode and low haemoglobin	Patients ≥ 60 years	0.5 (0.4-0.7)
Shephard (2014)	Back pain first episode and leucopenia	Patients ≥ 60 years	0.6 (0.4-1.2)
Shephard (2014)	Back pain first episode and low platelets	Patients ≥ 60 years	0.7 (0.4-1.3)
Shephard (2014)	Back pain first episode and raised inflammatory markers	Patients ≥ 60 years	0.6 (0.4-0.7)
Shephard (2014)	Back pain first episode and raised creatinine	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Back pain first episode and raised MCV	Patients ≥ 60 years	0.4 (0.3-0.6)
Shephard (2014)	Back pain first episode and hypercalcaemia	Patients ≥ 60 years	4 (NR)
Shephard (2014)	Back pain second episode and low haemoglobin	Patients ≥ 60 years	0.9 (0.6-1.3)
Shephard (2014)	Back pain second episode and leucopenia	Patients ≥ 60 years	2 (NR)
Shephard (2014)	Back pain second episode and low platelets	Patients ≥ 60 years	0.7 (NR)
Shephard (2014)	Back pain second episode and raised inflammatory markers	Patients ≥ 60 years	1.1 (0.7-1.6)
Shephard (2014)	Back pain second episode and raised creatinine	Patients ≥ 60 years	0.5 (0.3-0.7)
Shephard (2014)	Back pain second episode and raised MCV	Patients ≥ 60 years	0.8 (0.4-1.6)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Back pain second episode and hypercalcaemia	Patients ≥ 60 years	>10 (NR)
Shephard (2014)	Shortness of breath and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Shortness of breath and leucopenia	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Shortness of breath and low platelets	Patients ≥ 60 years	0.3 (0.1-0.5)
Shephard (2014)	Shortness of breath and raised inflammatory markers	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Shortness of breath and raised creatinine	Patients ≥ 60 years	0.1 (0.07-0.11)
Shephard (2014)	Shortness of breath and raised MCV	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Shortness of breath and hypercalcaemia	Patients ≥ 60 years	1.5 (NR)
Shephard (2014)	Chest pain and low haemoglobin	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest pain and leucopenia	Patients ≥ 60 years	0.3 (0.1-0.6)
Shephard (2014)	Chest pain and low platelets	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Chest pain and raised inflammatory markers	Patients ≥ 60 years	0.5 (0.3-0.6)
Shephard (2014)	Chest pain and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.2)
Shephard (2014)	Chest pain and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.6)
Shephard (2014)	Chest pain and hypercalcaemia	Patients ≥ 60 years	1.9 (NR)
Shephard (2014)	Chest infection and low haemoglobin	Patients ≥ 60 years	0.2 (0.2-0.3)
Shephard (2014)	Chest infection and leucopenia	Patients ≥ 60 years	0.3 (0.1-0.5)
Shephard (2014)	Chest infection and low platelets	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Chest infection	Patients ≥ 60	0.3 (0.2-0.4)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
	and raised inflammatory markers	years	
Shephard (2014)	Chest infection and raised creatinine	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Chest infection and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Chest infection and hypercalcaemia	Patients ≥ 60 years	2 (NR)
Shephard (2014)	Nosebleeds and low haemoglobin	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2014)	Nosebleeds and leucopenia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Nosebleeds and low platelets	Patients ≥ 60 years	1.2 (NR)
Shephard (2014)	Nosebleeds and raised inflammatory markers	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Nosebleeds and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Nosebleeds and raised MCV	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nosebleeds and hypercalcaemia	Patients ≥ 60 years	NR
Shephard (2014)	Fracture and low haemoglobin	Patients ≥ 60 years	0.3 (0.2-0.4)
Shephard (2014)	Fracture and leucopenia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Fracture and low platelets	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Fracture and raised inflammatory markers	Patients ≥ 60 years	0.4 (0.2-0.6)
Shephard (2014)	Fracture and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Fracture and raised MCV	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Fracture and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Nausea and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Nausea and leucopenia	Patients ≥ 60 years	0.4 (NR)
Shephard (2014)	Nausea and low platelets	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Nausea and	Patients ≥ 60	0.3 (0.2-0.5)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
	raised inflammatory markers	years	
Shephard (2014)	Nausea and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Nausea and raised MCV	Patients ≥ 60 years	0.3 (0.2-0.7)
Shephard (2014)	Nausea and hypercalcaemia	Patients ≥ 60 years	1 (NR)
Shephard (2014)	Combined bone pain and low haemoglobin	Patients ≥ 60 years	0.5 (0.3-1)
Shephard (2014)	Combined bone pain and leucopenia	Patients ≥ 60 years	> 5 (NR)
Shephard (2014)	Combined bone pain and low platelets	Patients ≥ 60 years	0.1 (NR)
Shephard (2014)	Combined bone pain and raised inflammatory markers	Patients ≥ 60 years	0.5 (0.3-0.9)
Shephard (2014)	Combined bone pain and raised creatinine	Patients ≥ 60 years	0.2 (0.1-0.4)
Shephard (2014)	Combined bone pain and raised MCV	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Combined bone pain and hypercalcaemia	Patients ≥ 60 years	1.4 (NR)
Shephard (2014)	Joint pain and low haemoglobin	Patients ≥ 60 years	0.2 (0.1-0.3)
Shephard (2014)	Joint pain and leucopenia	Patients ≥ 60 years	0.3 (NR)
Shephard (2014)	Joint pain and low platelets	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Joint pain and raised inflammatory markers	Patients ≥ 60 years	0.1 (0.1-0.2)
Shephard (2014)	Joint pain and raised creatinine	Patients ≥ 60 years	0.1 (0.05-0.13)
Shephard (2014)	Joint pain and raised MCV	Patients ≥ 60 years	0.2 (NR)
Shephard (2014)	Joint pain and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Rib pain and low haemoglobin	Patients ≥ 60 years	0.9 (NR)
Shephard (2014)	Rib pain and leucopenia	Patients ≥ 60 years	0.5 (NR)

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Study	Symptom(s)	Patient group	PPV % (95% CI) for myeloma; prevalence of myeloma
Shephard (2014)	Rib pain and low platelets	Patients ≥ 60 years	NR
Shephard (2014)	Rib pain and raised inflammatory markers	Patients ≥ 60 years	0.4 (0.2-0.8)
Shephard (2014)	Rib pain and raised creatinine	Patients ≥ 60 years	0.8 (NR)
Shephard (2014)	Rib pain and raised MCV	Patients ≥ 60 years	1.1 (NR)
Shephard (2014)	Rib pain and hypercalcaemia	Patients ≥ 60 years	> 10 (NR)
Shephard (2014)	Weight loss and low haemoglobin	Patients ≥ 60 years	0.4 (0.?-0.7)
Shephard (2014)	Weight loss and leucopenia	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and low platelets	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and raised inflammatory markers	Patients ≥ 60 years	0.6 (0.3-1.1)
Shephard (2014)	Weight loss and raised creatinine	Patients ≥ 60 years	0.5 (NR)
Shephard (2014)	Weight loss and raised MCV	Patients ≥ 60 years	0.6 (NR)
Shephard (2014)	Weight loss and hypercalcaemia	Patients ≥ 60 years	0.5 (NR)

Abbreviations: CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives, NR, Not reported. Shepard (2014) reports that PPVs were not calculated if < 5 cases had the feature(s) and CIs were omitted where < 10 cases or controls had the combined features.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of paraprotein/serum electrophoresis/Bence-Jones protein tests, ESR, X-ray, viscosity or calcium tests in patients with suspected myeloma cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture. [new 2015]** **Offer very urgent protein electrophoresis (within**

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	48 hours) to assess for myeloma in people aged 60 and over with hypercalcaemia or leucopenia and a presentation that is consistent with possible myeloma. [new 2015] **Consider very urgent protein electrophoresis (within 48 hours) to assess for myeloma if the plasma viscosity or erythrocyte sedimentation rate and presentation are consistent with possible myeloma. [new 2015]** **Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) if the results of protein electrophoresis suggest myeloma. [new 2015]**
Relative value placed on the outcomes considered	Signs and symptoms of myeloma The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms were predictive of myeloma. Investigations in primary care for myeloma The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	Signs and symptoms of myeloma The quality of the evidence, as assessed by QUADAS-II, varied for the positive predictive values for the different signs and symptoms and included one study of high quality. Investigations in primary care for myeloma No evidence was found pertaining to the diagnostic performance of paraprotein, serum electrophoresis, Bence-Jones protein (urine test), ESR, viscosity, calcium or X-ray in primary care patients with suspected myeloma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with myeloma more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without myeloma who get inappropriately referred whilst maximising the number of people with myeloma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with myeloma outweighed the disadvantages to those without. The GDG noted that the positive predictive values were below 3% for all single symptoms, but that they were above 3% for a number of symptoms when these were combined with hypercalcaemia or leucopenia. The GDG agreed, based on the evidence, that the symptoms of persistent bone pain, particularly back pain, and

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	unexplained fracture should prompt investigation in primary care in people aged 60 years or older. The GDG also noted that whilst no evidence had been identified on the diagnostic accuracy of investigations in primary care for myeloma, the GDG agreed, that there were several tests available that could be used to identify myeloma. Since myeloma is easily treatable but has one of the worst diagnostic experiences, the GDG decided to recommend those symptoms which should prompt investigation in primary care, to help improve the diagnosis of this cancer. Based on the evidence for signs and symptoms of myeloma and their clinical experience, the GDG identified four tests (full blood count, calcium level and tests for plasma viscosity or erythrocyte sedimentation rate) which increased the likelihood of diagnosing myeloma. They also identified electrophoresis as an investigation that could diagnose myeloma. Since the symptoms recommended to prompt investigation were fairly generic, the GDG agreed to recommend that full blood count, calcium level and tests for plasma viscosity or erythrocyte sedimentation rate should be used first, to try to narrow the patient group to those with cancer, as they were non-invasive, readily available, relatively in-expensive and returned results quickly. If these test results showed an abnormality consistent with myeloma, the GDG agreed that electrophoresis should be performed to diagnose myeloma, and that this should be 'very urgent' to avoid any unnecessary delay for patients who have myeloma. It was noted that although electrophoresis can diagnose myeloma, it is more expensive and time consuming to perform than a full blood count, calcium level and tests for plasma viscosity or erythrocyte sedimentation rate and so would not be appropriate to use it as a first test.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that full blood count, calcium level and tests for plasma viscosity or erythrocyte sedimentation rate were less expensive than electrophoresis. Therefore they recommended that the former be used as the first test since this was likely to be the larger group of people. The GDG considered that the recommendations made could result in some additional costs for increased use of tests, for example electrophoresis. However they agreed this would be balanced by a reduction in costs resulting from decreased emergency admissions, due to earlier diagnosis of myeloma.
Other considerations	The GDG acknowledged that older black men are thought to be at increased risk of myeloma. However the GDG agreed that this risk factor would not affect the clinical considerations on referral or management and therefore different recommendations for older black men with symptoms of leukaemia were not required.

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16.3 Non-Hodgkin's lymphoma

Nearly 13,000 new non-Hodgkin's lymphomas are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with non-Hodgkin's lymphoma every 2-3 years. It is one of the commoner cancers in young people. Five year survival is just under 70%.

The most common symptom of non-Hodgkin's lymphoma is lymphadenopathy, sometimes accompanied by other symptoms such as fever, pruritus, weight loss or night sweats.

These features can also be present in other cancers, especially Hodgkin's lymphoma or lymph node spread from other cancer sites.

The main method of diagnosis is by biopsy, which is performed in secondary care.

Clinical questions:

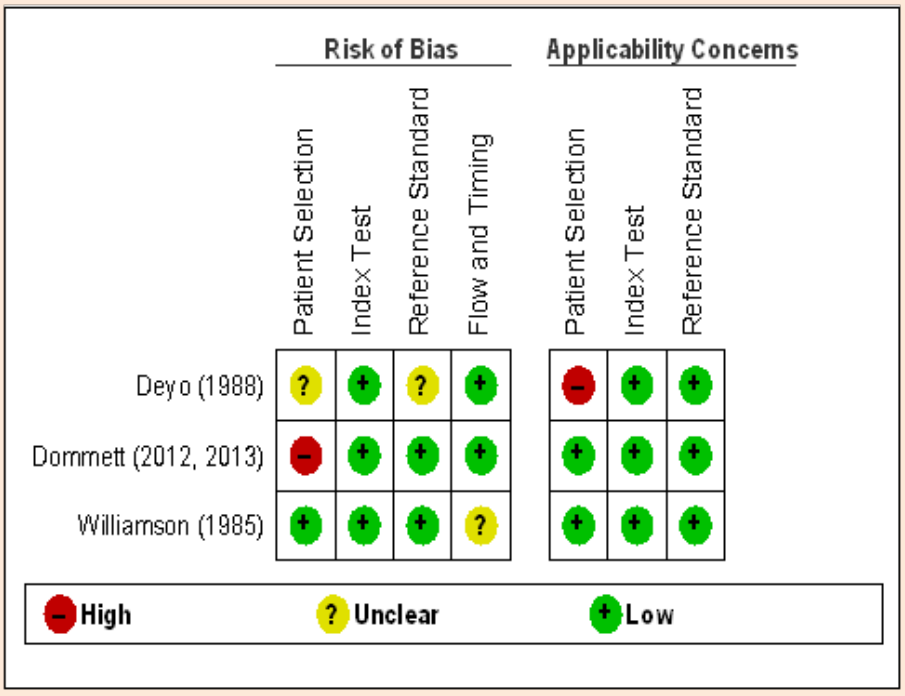
- **What is the risk of non-Hodgkin's lymphoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected non-Hodgkin's lymphoma cancer should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



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Evidence statement

Adult and mixed age populations

Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin's/Non-Hodgkin's lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 79).

Children and teenagers and young people

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 80-81).

Table 79: Non-Hodgkin's lymphoma: Adult and mixed age populations

Study	Symptom(s)	Patient group	Result
Deyo (1988)	Back pain	All included patients	0.1 (0.02-0.41) 2/1975 7 had other types of cancer: lymphoma (NOS): N = 2, unknown primary: N = 1, Prostate: N = 1, retroperitoneal liposarcoma: N = 1, lung cancer: N = 1, renal cell: N = 1, multiple myeloma: N = 1, mucinous adenocarcinoma (of gallbladder?): N = 1
Williamson (1985)	Lymphadenopathy	All included patients	0.8 (0.1-3.2) TP = 2, FP = 247 Cancer: Hodgkin's: N = 1 Adenocarcinoma: N = 1

TP = True positives, FP = False positives.

Table 80: Non-Hodgkin's lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months	All included leukemia/lymphoma	0.43 (0.06-3.15)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
	before diagnosis	patients and controls aged 0-14 years	
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 81: Non-Hodgkin's lymphoma: Positive predictive values for teenage and young adult lymphoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding	All included lymphoma patients and controls	0.0279 (0.0152-0.0515)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	abdomen	aged 15-24 years	Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, chest X-ray or LDH in patients with suspected non-hodgkin's lymphoma cell cancer where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of non-Hodgkin's lymphoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict non-Hodgkin's lymphoma. <u>Investigations in primary care for non-Hodgkin's lymphoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of non-Hodgkin's lymphoma</u> The quality of the available evidence, as assessed by QUADAS-II, was very low for the adult population and low for the children and young adult population. The GDG noted some limitations with the evidence. Firstly, not all studies were representative of UK primary care practice.

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	Secondly, not all patients were included in the analyses. Thirdly, there were a limited number of cases in the studies and there was no distinction between Hodgkin's lymphoma, non-Hodgkin's lymphoma and leukaemia. Investigations in primary care for non-Hodgkin's lymphoma No evidence was found pertaining to the diagnostic accuracy of chest X-rays, CT scans, ultrasound or LDH in primary care patients with suspected non-Hodgkin's lymphoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with non-Hodgkin's lymphoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without non-Hodgkin's lymphoma who get inappropriately referred whilst maximising the number of people with non-Hodgkin's lymphoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with non-Hodgkin's lymphoma outweighed the disadvantages to those without. The GDG noted that the symptoms reported in the evidence all had positive predictive values below 3%. However, the GDG also acknowledged that there are no investigations available in primary care for suspected non-Hodgkin's lymphoma. They therefore agreed, despite the low positive predictive values, that the appropriate action for people presenting with signs and symptoms of non-Hodgkin's lymphoma would be a suspected cancer pathway referral. The GDG agreed, based on their clinical experience, that the majority of patients with non-Hodgkin's lymphoma, present with lymphadenopathy. They also agreed that splenomegaly, fever, night sweats, pruritis and weight loss were commonly associated with non-Hodgkin's lymphoma, particularly when presenting alongside lymphadenopathy. The GDG therefore recommended that these symptoms should prompt a suspected cancer pathway referral. Shortness of breath (resulting from a mediastinal mass) was identified as a peripheral symptom, less classically associated with non-Hodgkin's lymphoma. However the GDG agreed it was important to include this symptom in the recommendation to try to raise awareness of this association. The GDG noted that although the evidence reported the symptoms of bruising and pallor in children and young people, these symptoms were more likely to result from leukaemia than non-Hodgkin's lymphoma. They therefore agreed that these symptoms should not be included in the recommendations.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

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	The GDG noted that the recommendations made were essentially a refinement of those in previous guidance and were unlikely to result in a substantial change to current practice. They therefore considered there would be minimal additional costs from implementing these recommendations.

16.41 Hodgkin's lymphoma

Just below 2,000 new Hodgkin's lymphomas are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with Hodgkin's lymphoma during their career. It is one of the commoner cancers in young people. Five year survival is 85%.

The most common symptom of Hodgkin's lymphoma is lymphadenopathy, sometimes accompanied by other symptoms such as fever, pruritus, weight loss or night sweats.

These features can also be present in other cancers, especially non-Hodgkin's lymphoma or lymph node spread from other cancer sites.

The main method of diagnosis is by biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of Hodgkin's lymphoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected Hodgkin's lymphoma should be done with clinical responsibility retained by primary care?**

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Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

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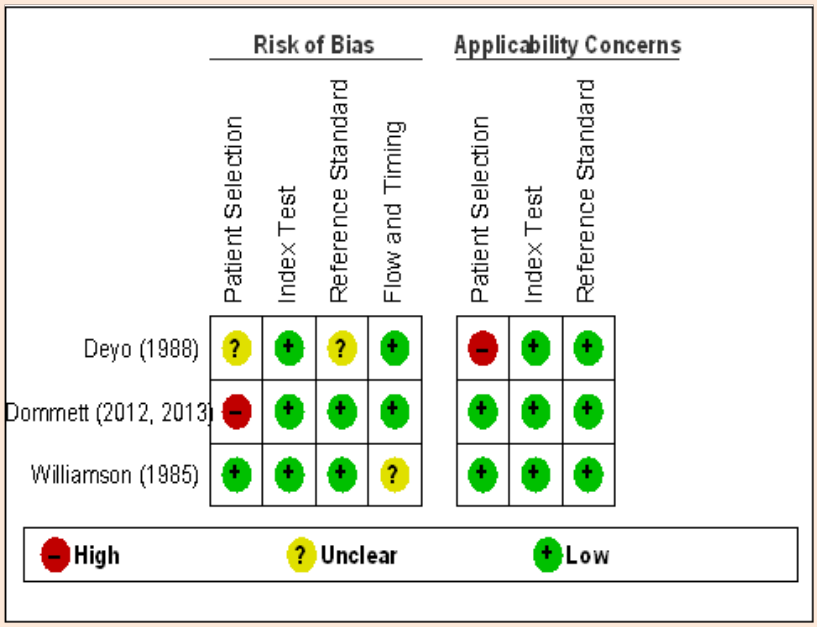

Evidence statement

Adult and mixed age populations

Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin's/Non-Hodgkin's lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 82).

Children and teenagers and young people

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 83-84).

Table 82: Hodgkin's lymphoma: Adult and mixed age populations

Study	Symptom(s)	Patient group	PPVs (95% CI)
Deyo (1988)	Back pain	All included patients	0.1 (0.02-0.41) 2/1975 7 had other types of cancer: lymphoma (NOS): N = 2, unknown primary: N = 1, Prostate: N = 1, retroperitoneal liposarcoma: N = 1, lung cancer: N = 1, renal cell: N = 1, multiple myeloma: N = 1, mucinous adenocarcinoma (of

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Study	Symptom(s)	Patient group	PPVs (95% CI)
			gallbladder?): N = 1
Williamson (1985)	Lymphadenopathy	All included patients	0.8 (0.1-3.2) TP = 2, FP = 247 Cancer: Hodgkin's: N = 1 Adenocarcinoma: N = 1

TP = True positives, FP = False positives.

Table 83: Hodgkin's lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma	0.01 (0-0.01)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		patients and controls aged 0-14 years	
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 84: Hodgkin's lymphoma: Positive predictive values for teenage and young adult lymphoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT scan, ultrasound or LDH in patients with suspected Hodgkin's lymphoma where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy.**

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	When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. [new 2015]
Relative value placed on the outcomes considered	Signs and symptoms of Hodgkin's lymphoma The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict Hodgkin's lymphoma. Investigations in primary care for Hodgkin's lymphoma The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	Signs and symptoms of Hodgkin's lymphoma The quality of the available evidence, as assessed by QUADAS-II, was very low for the adult population and low for the children and young adult population. The GDG noted some limitations with the evidence. Firstly, not all studies were representative of UK primary care practice. Secondly, not all patients were included in the analyses. Thirdly, there were a limited number of cases in the studies and there was no distinction between Hodgkin's lymphoma, non-Hodgkin's lymphoma and leukaemia. Investigations in primary care for Hodgkin's lymphoma No evidence was found pertaining to the diagnostic accuracy of chest X-rays, CT scans, ultrasound or LDH in primary care patients with suspected Hodgkin's lymphoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with Hodgkin's lymphoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without Hodgkin's lymphoma who get inappropriately referred whilst maximising the number of people with Hodgkin's lymphoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with Hodgkin's lymphoma outweighed the disadvantages to those without. The GDG noted that the symptoms reported in the evidence all had positive predictive values below 3%. However, the GDG also acknowledged that there are no investigations available in primary care for suspected Hodgkin's lymphoma. They therefore agreed, despite the low positive predictive values, that the appropriate action for people presenting with signs and symptoms of Hodgkin's lymphoma would be a suspected cancer pathway referral. The GDG agreed, based on their clinical experience, that the majority of patients with Hodgkin's lymphoma, present with

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	lymphadenopathy. They also agreed that fever, night sweats, pruritis and weight loss were commonly associated with Hodgkin's lymphoma, particularly when presenting alongside lymphadenopathy. The GDG therefore recommended that these symptoms should prompt a suspected cancer pathway referral. Alcohol-induced lymph node pain was identified as a rare symptom that was only associated with Hodgkin's lymphoma and should therefore be included in the recommendations. Shortness of breath (resulting from a mediastinal mass) was identified as a peripheral symptom, less classically associated with Hodgkin's lymphoma. However the GDG agreed it was important to include this symptom in the recommendation to try to raise awareness of this association. The GDG noted that although the evidence reported the symptoms of bruising and pallor in children and young people, these symptoms were more likely to result from leukaemia than Hodgkin's lymphoma. They therefore agreed that these symptoms should not be included in the recommendations.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendations made were essentially a refinement of those in previous guidance and were unlikely to result in a substantial change to current practice. They therefore considered there would be minimal additional costs from implementing these recommendations.

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17 Sarcomas

17.1 Bone sarcoma

Around 500 new bone sarcomas are diagnosed each year in the UK, meaning that a full time GP is unlikely to diagnose more than one bone sarcoma during their career. It is seen in both sexes, and is one of the commoner cancers in children, teenagers and young people.

Pain and loss of function of the affected limb are thought to be the main presenting symptoms of bone sarcoma. However the rarity of this cancer means there are few studies of its clinical features.

Because of the rarity of bone sarcoma, there is no standard diagnostic pathway for primary care. Plain X-ray may show abnormalities suggestive of the sarcoma.

Clinical questions:

- **What is the risk of bone sarcoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected bone sarcoma should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP. In the case of Pharisa (2009) whose sample consisted of patients presenting as emergencies, the symptom spectrum is likely to be of the more severe kind than those typically seen by a GP in the UK, but in the other cases (e.g., presentations to physiotherapists, chiropractors and hospital-based walk-in and family clinics) it is unclear how the patients differ from those of primary current interest. Dommett (2012, 2013a,b) only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Finally, two studies employed reference standards that are at some (unknown level of) risk of failing to identify all patients with cancer, which means that the relevant PPVs may be underestimated (to the extent that the reference standards have failed to identify patients with cancer).

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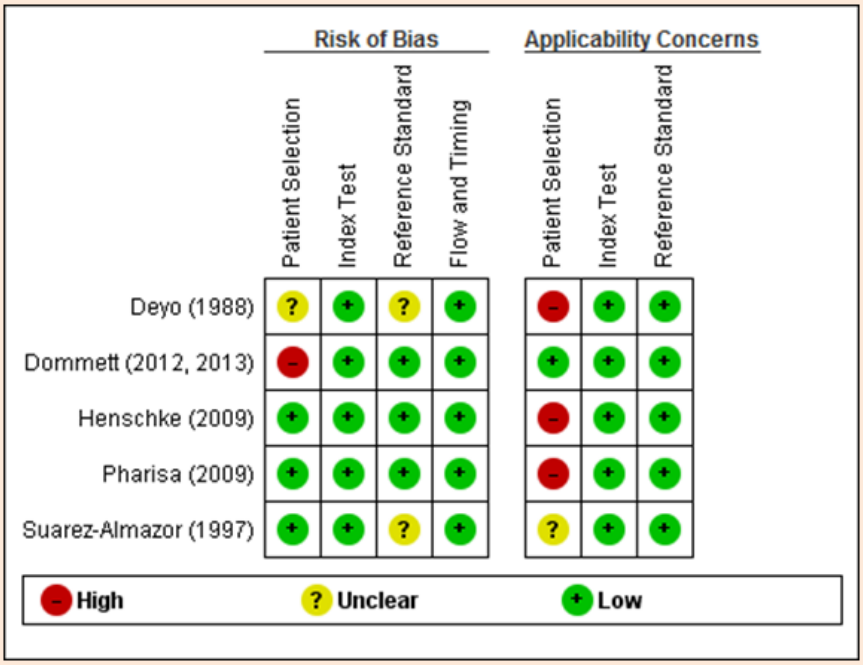

Evidemce statement

Adult patients

Acute low back pain alone (2 studies, N = 2135) or in combination with other single risk factors/symptoms (1 study, N = 19-281), and back pain (1 study, N = 1975) presenting in a primary care setting do not appear to confer an increased risk of bone sarcoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 85).

Children, teenage and young adult patients

The positive predictive values of having childhood or young adulthood bone sarcoma tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 86).

Neck pain (1 study, N = 170) presenting in a primary care setting does not appear to confer an increased risk of bone sarcoma, although the study population is not directly representative of the typical unselected symptomatic UK GP population (see also Table 86).

Table 85: Bone sarcoma: Patients aged > 14-15 years

Study	Symptom(s)	Patient group	PPVs (95% CI); prevalence
Deyo (1988)	Back pain	All included patients	0 (0-0.2) 0/1975 None had bone sarcoma, but N = 9 had other types of cancer
Suarez-Almazor (1997)	Acute low back pain	All included patients	TP = 0-1, FP = 962-963 Unclear if diagnosis prior to symptom
Henschke (2009)	Acute low back pain	All included patients	0 (0-0.4)

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Study	Symptom(s)	Patient group	PPVs (95% CI); prevalence
			0/1172 None had cancer
Henschke (2009)	Acute low back pain + age at onset < 20 years or > 55 years	Subgroup with both symptoms	0 (0-1.7) 0/281 None had cancer
Henschke (2009)	Acute low back pain + previous history of cancer	Subgroup with both symptoms	0 (0-9.6) 0/46 None had cancer
Henschke (2009)	Acute low back pain + tried bed rest, but no relief	Subgroup with both symptoms	0 (0-2.4) 0/192 None had cancer
Henschke (2009)	Acute low back pain + unexplained weight loss	Subgroup with both symptoms	0 (0-69) 0/3 None had cancer
Henschke (2009)	Acute low back pain + insidious onset	Subgroup with both symptoms	0 (0-2.3) 0/202 None had cancer
Henschke (2009)	Acute low back pain + systemically unwell	Subgroup with both symptoms	0 (0-15.5) 0/27 None had cancer
Henschke (2009)	Acute low back pain + constant progressive non-mechanical pain	Subgroup with both symptoms	0 (0-13) 0/33 None had cancer
Henschke (2009)	Acute low back pain + sensory level altered from trunk down	Subgroup with both symptoms	0 (0-20.9) 0/19 None had cancer

TP = True positives, FP = False positives.

Table 86: Bone sarcoma: Positive predictive values for child- or young adulthood bone tumour/soft tissue sarcoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone tumour/soft tissue sarcoma patients and	0 (0-0)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		controls aged 0-14 years	
Dommett (2013b)	Lump mass swelling	All included bone tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included bone tumour/soft tissue sarcoma patients and controls aged 15	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included bone tumour/soft tissue sarcoma patients and controls aged 15	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included bone tumour/soft tissue sarcoma patients and controls aged 15	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438
Pharisa (2009)	Neck pain	Children ≤ 16 years	TP = 0, FP = 170 None had cancer

The positive predictive values are calculated using Bayesian statistics. TP = true positives, FP = false positives

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of x-ray, calcium or alkaline phosphatase in patients with suspected bone sarcoma where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider an urgent direct access X-ray (within 2 weeks) to assess for bone sarcoma in children and young people with unexplained bone swelling or pain. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people if an X-ray suggests the possibility of bone sarcoma. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of bone sarcoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict bone sarcoma. <u>Investigations in primary care for bone sarcoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of bone sarcoma</u>

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	The quality of the evidence assessed by QUADAS-II varied, with the majority of studies providing moderate quality evidence. The GDG noted some limitations of the evidence. Firstly, the majority of studies employed samples of patients that were not directly representative of UK-based primary care. Secondly, some of the studies used a non-rigorous reference standard that may have failed to identify patients with cancer with the consequence that the positive predictive values may be underestimated. Thirdly, the largest and most applicable study did not distinguish between bone and soft tissue sarcoma, but grouped them together in their analyses. Bone sarcoma-specific positive predictive values were therefore not available in this study. <u>Investigations in primary care for bone sarcoma</u> No evidence was found pertaining to the diagnostic performance of X-ray, calcium, and alkaline phosphatase in primary care patients with suspected bone sarcoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with bone sarcoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without bone sarcoma who get inappropriately referred whilst maximising the number of people with bone sarcoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults, with a lower threshold potentially pertaining to children. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with bone sarcoma outweighed the disadvantages to those without. However, the GDG noted that none of the positive predictive values in the evidence were sufficiently high to warrant a suspected cancer pathway referral. The GDG therefore decided not to recommend a suspected cancer pathway referral for any specific symptoms of bone sarcoma. However, based on their clinical experience, the GDG agreed that in people in whom an X-ray suggests the possibility of bone sarcoma, the positive predictive value is likely to be above 3%. The GDG therefore decided to recommend a suspected cancer pathway referral for this group. The GDG also noted, based on their clinical experience, that although there is some risk of false positive results, bone sarcoma will be evident on X-ray which is a relatively cheap and easy test to perform; that bone swelling and pain can be symptoms of bone sarcoma; and that although bone sarcoma is a rare cancer the risk of bone sarcoma is higher in children and young people than in adults. The GDG therefore decided to recommend an urgent X-ray for any child or young adult with unexplained bone swelling or pain. However, although the recommendation focuses on children and young people, the GDG noted that it does not preclude clinicians following the same instructions for adults.

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	The GDG discussed children with an unexplained limp and noted that this symptom could not be investigated with an X-ray. The GDG noted that any child presenting with a limp would be referred to a secondary care specialist and therefore a recommendation for this symptom is not needed. The GDG also noted that it is also likely that a child presenting with a limp will be referred for other concerns primarily, and not bone sarcoma. Due to the lack of evidence, the GDG agreed not to make any recommendations on the use of calcium, and alkaline phosphatase in primary care patients with suspected bone sarcoma
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG estimated that the recommendations were likely to result in an increase in X-rays, which would be offset by a decrease in paediatric referrals, overall resulting in a net cost saving and improved patient experience.

17.2 Soft tissue sarcoma

Update 2014

Just over 3,000 new soft tissue sarcomas are diagnosed each year in the UK. A full time GP is likely to diagnose approximately 1 person with soft tissue sarcoma during their career. They occur in connective tissue, so can occur in many parts of the body. Five year survival is highly dependent on the specific site.

The rarity of this cancer means there are few studies of its clinical features. It is believed that most present with a mass, which may be painless, and may become quite large.

The main method of diagnosis is by biopsy, which is performed in secondary care.

Clinical questions:

- **What is the risk of soft tissue sarcoma in patients presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected soft tissue sarcoma should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting the influence of the latter.

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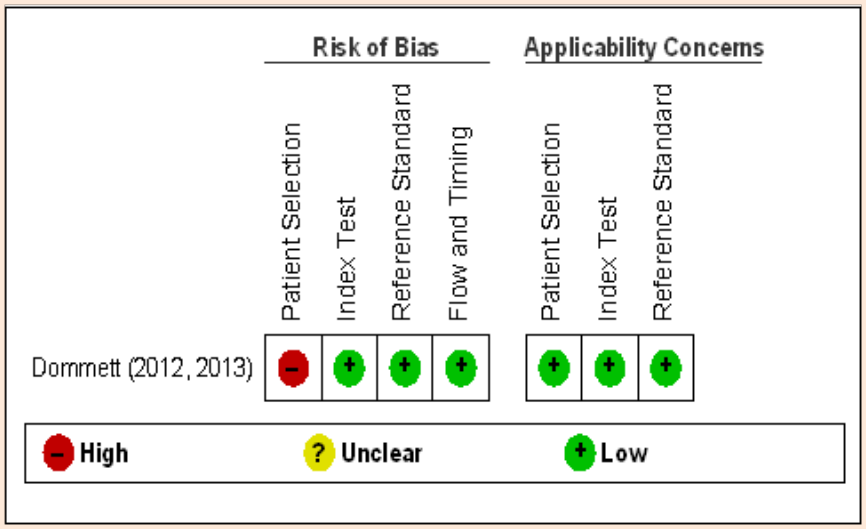

Evidence statement

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 87).

Table 87: Soft tissue sarcoma: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal	All included lymphoma	0.0093 (0.0058-

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	symptoms	patients and controls aged 15-24 years	0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Investigations in primary care

No primary care evidence was identified pertaining to the diagnostic accuracy of ultrasound in patients with suspected soft tissue sarcoma where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for soft tissue sarcoma in people with an unexplained lump that is increasing in size. [new 2015]** **Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people if they have ultrasound scan findings that are suggestive of soft tissue sarcoma or if ultrasound findings are uncertain and clinical concern persists. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of soft tissue sarcoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict soft sarcoma. <u>Investigations in primary care for soft tissue sarcoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found for any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of soft sarcoma</u> The evidence consisted of one study (published in 3 papers), proving evidence of high quality as assessed by QUADAS-II. However the study did not distinguish between bone and soft tissue sarcoma, but grouped them together in the analyses. Soft tissue sarcoma-specific positive predictive values were therefore not available in this study. <u>Investigations in primary care for soft tissue sarcoma</u>

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	No evidence was found pertaining to the diagnostic performance of ultrasound in primary care patients with suspected soft tissue sarcoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those people with soft tissue sarcoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without soft tissue sarcoma who get inappropriately referred whilst maximising the number of people with soft tissue sarcoma who get appropriately referred. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those with soft tissue sarcoma outweighed the disadvantages to those without. However, the GDG noted that none of the positive predictive values in the evidence were above 3% and that soft tissue sarcoma is a rare cause of the symptoms. GDG therefore decided not to recommend a suspected cancer pathway referral for any specific symptoms of soft tissue sarcoma. However, based on their clinical experience, the GDG agreed that in people in whom an ultrasound is consistent with soft tissue sarcoma or clinical concern persists, the positive predictive value is likely to be above 3%. The GDG therefore decided to recommend a suspected cancer pathway referral for these groups. The GDG also noted, based on their clinical experience, that soft tissue sarcoma will be evident on ultrasound, which is a relatively cheap and easy test to perform, and that an unexplained lump increasing in size can be a symptom of soft tissue sarcoma. The GDG therefore decided to recommend an urgent ultrasound in people with an unexplained lump that is increasing in size.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG estimated that the recommendations were likely to result in an increase in ultrasound scans, which would be offset by a decrease in suspected cancer pathway referrals, overall resulting in a net cost saving and improved patient experience.

Update 2014

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Bone sarcoma

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18 Childhood cancers

18.1 Cancers affecting children and young people

A variety of cancers can affect both children and young people, and some of the more common cancers in children and young people fit into that category. The recommendations for these cancers are included within other chapters. For recommendations on brain and central nervous system cancers see chapter 15; for recommendations on leukaemia see section 16.1; for recommendations on bone sarcoma see section 17.1,

Three cancers almost entirely restricted to children are given their own specific recommendations in this chapter.

18.2 Neuroblastoma

Neuroblastoma is a rare cancer, generally occurring in young children. It is the commonest cancer in the first year of life, though there are only around a hundred cases annually in the UK, so most GPs will not diagnose one. It is a tumour of neuroendocrine origin, so can originate in several different organs, particularly in the abdomen. Five year survival depends upon the precise histology but is between 50-90%.

The symptoms are thought to be a mass, though because of its rarity there are very few reports of its clinical features.

Paediatric referral is required for imaging and biopsy.

Clinical questions:

- **What is the risk of retinoblastoma, neuroblastoma and Wilm's tumour in children presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected retinoblastoma, neuroblastoma and Wilm's tumour in children should be done with clinical responsibility retained by primary care?**

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

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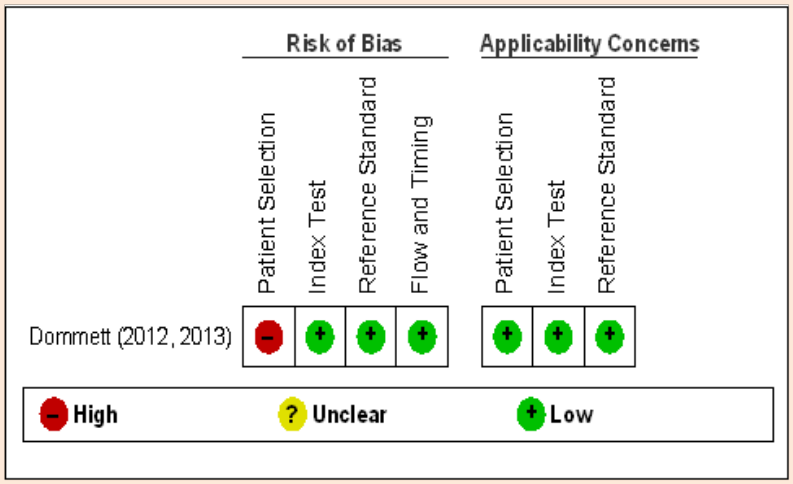

Evidence statement

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 88-90).

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 91-93).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old , and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 94).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 95).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and 'lump mass swelling below neck excluding abdomen') for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 96).

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Table 88: Positive predictive values for any childhood cancer: Patients aged 0-14 years[o]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318

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o This table is included in the evidence review for neuroblastoma because neuroblastoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 89: Positive predictive values for any childhood cancer: Patients aged 0-4 years[p]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency

p This table is included in the evidence review for neuroblastoma because neuroblastoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 90: Positive predictive values for any childhood cancer: Patients aged 5-14**
3 **years[q]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561

q This table is included in the evidence review for neuroblastoma because neuroblastoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 5-14 years	0.082 (0.053-0.125) Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 91: Positive predictive values for leukaemia/lymphoma childhood cancer[r]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)

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r This table is included in the evidence review for childhood cancers because both are cancers of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 92: Positive predictive values for teenage and young adult leukaemia[s]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls	0.0038 (0.003-0.0048)

s This table is included in the evidence review for childhood cancers because leukaemia is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		aged 15-24 years	Cases: 74/143 Controls: 125/1799

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 93: Positive predictive values for teenage and young adult lymphoma[t]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

3 *The positive predictive values are calculated using Bayesian statistics.*

4 **Table 94: Positive predictive values for central nervous system (CNS) child- or young**
5 **adulthood cancer tumour[u]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer	0.04 (0.02-0.07)

t This table is included in the evidence review for childhood cancers because lymphoma is a cancer of childhood.
u This table is included in the evidence review for childhood cancers because CNS cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		tumour patients and controls aged 0-14 years	
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.02 (0.01-0.06)
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

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1 *The positive predictive values are calculated using Bayesian statistics.*

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Table 95: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma[v]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Table 96: Positive predictive values for childhood abdominal cancer tumour[w]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.01-0.12)
Dommett (2013a)	Lump mass swelling	All included abdominal	0.03 (0.00-0.23)

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v This table is included in the evidence review for childhood cancers because both are cancers of childhood.
w This table is included in the evidence review for childhood cancers because abdominal cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
	below neck excluding abdomen 0-3 months before diagnosis	cancer patients and controls aged 0-14 years	
Dommett (2013a)	Weight loss 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.02 (0.00-0.1)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.01-0.02)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.00-0.01)
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)

Investigations in primary care

No primarycare evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm's tumour where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for neuroblastoma in children with a palpable abdominal mass or unexplained enlarged abdominal organ. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of neuroblastoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict neuroblastoma. <u>Investigations in primary care for neuroblastoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of neuroblastoma</u> No evidence was found pertaining to the positive predictive values of different symptoms of neuroblastoma in primary care. However, evidence was found on the positive predictive values of symptoms of 'any' childhood cancer, of which the GDG

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	considered, some would have been neuroblastomas. Investigations in primary care for neuroblastoma No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected neuroblastoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those children with neuroblastoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of children without neuroblastoma who get inappropriately referred whilst maximising the number of children with neuroblastoma who get appropriately referred. In general in adult cancers, in order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. However, in children's cancers, the GDG decided that this threshold was too stringent for the following reasons: 1) the high levels of treatability of these cancers, 2) early diagnosis can reduce mortality and morbidity, and 3) the number of life-years gained. The GDG therefore agreed that referral for symptoms with positive predictive values lower than 3% was justified. However the GDG also acknowledged that no evidence had been found on the positive predictive values of symptoms for neuroblastoma. Despite the limited evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected neuroblastoma, since there was no test available in primary care. The GDG discussed what symptoms should prompt a suspected cancer pathway referral. They noted that the study included in the evidence by Dommett (2012, 2013a, b) had examined the positive predictive values for the symptoms recommended in previous guidance and they were all very low for childhood cancer as a whole, and therefore would be even lower for neuroblastoma. Moreover, the GDG noted that almost all symptoms were more common and less worrying and should therefore prompt investigation with routine tests. The exception to this was abdominal mass which was only reported in cases and not controls. The GDG noted that it can be difficult to determine which abdominal organ is enlarged in children on palpation. The GDG also noted that any abdominal mass (regardless of affected organ) is rare, and that, based on their clinical experience, a palpable abdominal mass or unexplained enlarged abdominal organ can be a symptom of neuroblastoma, which the GDG agreed is serious enough to warrant very urgent attention. However, the GDG did not feel that an immediate admission would be appropriate since there are risks associated with this and it is still unlikely that the child would have cancer. Equally, the GDG recognised that a mass is a worrying symptom and that children have less reserve than adults so the GDG did not want to recommend a suspected cancer pathway referral either. Instead the GDG opted for very urgent specialist assessment (with an appointment within 48 hours) as this would mean the child would get seen quickly and

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	would get around any issues with weekend cover and differences in local service configuration. Due to the lack of evidence and the fact that there is no obvious test for neuroblastoma in primary care, the GDG were not able to recommend a particular test for the primary care investigation of neuroblastoma.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for very urgent specialist assessment for a palpable abdominal mass or unexplained enlarged abdominal organ is likely to be cost-neutral as it is currently standard practice. However, there may be a small cost increase as a result of making the recommendations 'very urgent' and extending it to children of all ages. The GDG agreed that this increase is likely to be small because of the rarity of the symptoms, and the absence of recommendations for any other symptoms or investigations in primary care.
Other considerations	The GDG noted that no recommendations were made for teenagers and young people, but also that most neuroblastomas occur in children under 5 years old, so it is unlikely that teenagers and young people would have a neuroblastoma. Teenagers and young people were therefore not explicitly mentioned in the recommendation. However, the GDG ensured that wording of the recommendation would not stop teenagers and young people from being referred, and also noted that abdominal mass in teenagers and young people is already covered by the recommendations made for the other cancers. The GDG also noted that neuroblastoma is more common in boys than in girls, however as the GDG decided that they would take the same course of action regardless of the sex of the child, they did not make any differential recommendations.

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18.3 Retinoblastoma

Retinoblastoma is a very rare cancer, almost all occurring in young children. Around 50 cases occur annually in the UK, so most GPs will not diagnose one. It has a very high cure rate, with five year survival almost 100%. Around a third of cases are bilateral.

The symptoms are thought to be of an abnormal reflection through the pupil, which appears white; rather than red. Because of its rarity there are very few reports of its clinical features.

No standard investigative pathway exists. Ophthalmological or paediatric referrals are currently the commonest pathways.

Clinical questions:

- **What is the risk of retinoblastoma, neuroblastoma and Wilm's tumour in children presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected retinoblastoma, neuroblastoma and Wilm's tumour in children should be done with clinical responsibility retained by primary care?**

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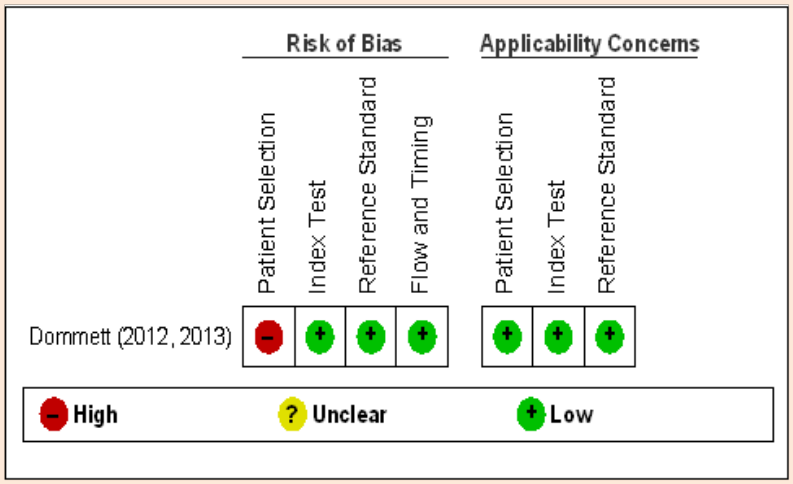
Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



Evidence statement

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 97-99).

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 100-102).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old , and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 103).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N =

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30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 104).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and 'lump mass swelling below neck excluding abdomen') for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 105).

Table 97: Positive predictive values for any childhood cancer: Patients aged 0-14 years[x]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months	All included patients	0.3 (0.09-0.99)

x This table is included in the evidence review for retinoblastoma because retinoblastoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	before diagnosis and ≥ 3 consultations		
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3	All included patients	0.06 (0.03-0.1)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	months before diagnosis		Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

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The positive predictive values are calculated using Bayesian statistics.

Table 98: Positive predictive values for any childhood cancer: Patients aged 0-4 years[y]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

The positive predictive values are calculated using Bayesian statistics.

Table 99: Positive predictive values for any childhood cancer: Patients aged 5-14 years[z]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert	Patients aged 5-14	0.056 (0.047-0.068)

y This table is included in the evidence review for retinoblastoma because retinoblastoma is a cancer of childhood.
z This table is included in the evidence review for retinoblastoma because retinoblastoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	symptom 0-3 months before diagnosis	years	Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 5-14 years	0.082 (0.053-0.125) Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 100: Positive predictive values for leukaemia/lymphoma childhood cancer[aa]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls	0.35 (0.05-2.65)

aa This table is included in the evidence review for childhood cancers because both are cancers of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		aged 0-14 years	
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 101: Positive predictive values for teenage and young adult leukaemia[bb]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia	0.0151 (0.004-

bb This table is included in the evidence review for childhood cancers because leukaemia is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		patients and controls aged 15-24 years	0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799

The positive predictive values are calculated using Bayesian statistics.

Table 102: Positive predictive values for teenage and young adult lymphoma[cc]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Table 103: Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour[dd]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer	0.07 (0.02-0.24)

cc This table is included in the evidence review for childhood cancers because lymphoma is a cancer of childhood.

dd This table is included in the evidence review for childhood cancers because CNS cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		tumour patients and controls aged 0-14 years	
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.02 (0.01-0.06)
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

1 *The positive predictive values are calculated using Bayesian statistics.*

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Table 104: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma[ee]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Table 105: Positive predictive values for childhood abdominal cancer tumour[ff]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.01-0.12)
Dommett (2013a)	Lump mass swelling	All included abdominal	0.03 (0.00-0.23)

ee This table is included in the evidence review for childhood cancers because both are cancers of childhood.
ff This table is included in the evidence review for childhood cancers because abdominal cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
	below neck excluding abdomen 0-3 months before diagnosis	cancer patients and controls aged 0-14 years	
Dommett (2013a)	Weight loss 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.02 (0.00-0.1)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.01-0.02)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.00-0.01)
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)

Investigations in primary care

No primarycare evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm's tumour where the clinical responsibility was retained by primary care.

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	Consider urgent referral (for an appointment within 2 weeks) for ophthalmological assessment for retinoblastoma in children with an absent red reflex. [new 2015]
Relative value placed on the outcomes considered	<u>Signs and symptoms of retinoblastoma</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict retinoblastoma. No evidence was found for this outcome. <u>Investigations in primary care for retinoblastoma</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes
Quality of the evidence	<u>Signs and symptoms of retinoblastoma</u> No evidence was found pertaining to the positive predictive values of different symptoms of retinoblastoma in primary care. <u>Investigations in primary care for retinoblastoma</u>

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	No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected retinoblastoma.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those children with retinoblastoma more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of children without retinoblastoma who get inappropriately referred whilst maximising the number of children with retinoblastoma who get appropriately referred. In general in adult cancers, in order to strike an appropriate balance between these considerations, the GDG has agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. However, in children's cancers, the GDG decided that this threshold was too stringent for the following reasons: 1) the high levels of treatability of these cancers, 2) early diagnosis can reduce mortality and morbidity, and 3) the number of life-years gained. The GDG therefore agreed that referral for symptoms with positive predictive values lower than 3% was justified. However the GDG also acknowledged that no evidence had been found on the positive predictive values of symptoms for retinoblastoma. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected retinoblastoma, since there was no test available in primary care. The GDG noted, based on their clinical experience, that an absent red reflex can be a symptom of retinoblastoma, which the GDG agreed was serious enough to warrant action. The GDG agreed that the most appropriate action would be urgent ophthalmological assessment (with an appointment within 2 weeks), rather than a suspected cancer pathway referral, as this assessment would reduce any delay associated with multiple, serial referrals. In addition, it would allow flexibility in where the referral was made (either to opthamology or paediatrics) depending on how services were set up locally. The GDG discussed whether other symptoms should prompt a suspected cancer pathway referral, but noted that the study included in the evidence by Domment (2012, 2013a, b) had examined the positive predictive values for the symptoms recommended in previous guidance, and they were all very low. The GDG therefore decided not to make any further symptom-based recommendations. Due to the lack of evidence and the fact that there is no obvious test for retinoblastoma in primary care, the GDG were not able to recommend a particular test for the primary care investigation of retinoblastoma.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendation for urgent ophthalmological assessment for an absent red reflex was likely to be associated with a small decrease in net health resource

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	use because the recommendation was more focussed than those in previous guidance. In addition retinoblastoma is a rare cancer so does not affect many people.
Other considerations	The GDG noted that there is variation in the red reflex among different ethnic groups and this may mean a higher rate of referrals for children in certain ethnic groups. The GDG, however, still felt that the recommendation was appropriate as a higher rate of referral was unlikely to disadvantage these children.

18.41 Wilms tumour

Wilm's tumour is a very rare cancer of childhood, affecting the kidney. It is an embryonal tumour, though usually affects children aged 1-3 years. Fewer than 50 cases occur in the UK annually, meaning most GPs will not encounter a child with one. Five-year survival is approximately 90%.

Because of its rarity, there are few reports on the clinical features of Wilm's tumour. It is believed to present usually with an abdominal mass, sometimes accompanied by pain or haematuria.

Definitive diagnosis requires imaging and biopsy, performed in secondary care.

Clinical questions:

- **What is the risk of retinoblastoma, neuroblastoma and Wilm's tumour in children presenting in primary care with symptom(s)?**
- **Which investigations of symptoms of suspected retinoblastoma, neuroblastoma and Wilm's tumour in children should be done with clinical responsibility retained by primary care?**

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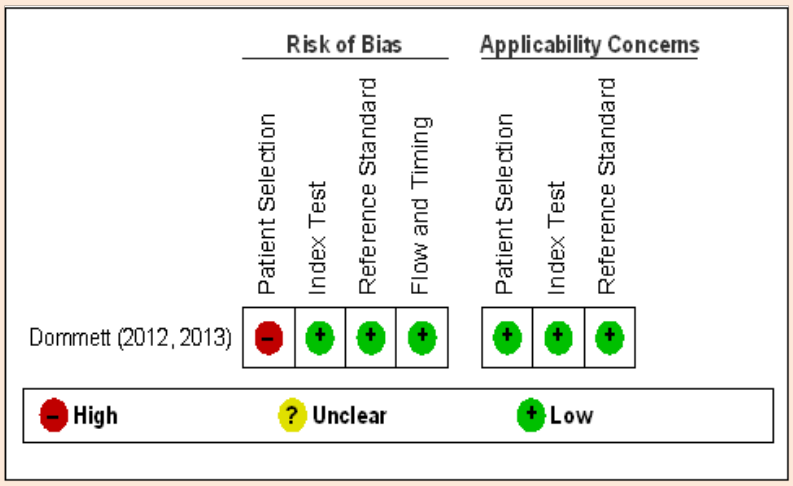
Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.



Evidence statement

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 106-108).

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for 'lump mass swelling below the neck excluding the abdomen') to 0.5034% (for 'lump mass swelling head and neck') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 109-111).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old , and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 112).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 113).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and 'lump mass swelling below neck excluding abdomen') for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 114).

Table 106: Positive predictive values for any childhood cancer: Patients aged 0-14 years[gg]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months	All included patients	0.064 (0.051-0.082)

gg This table is included in the evidence review for Wilm's tumour because Wilm's tumour is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	before diagnosis		Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3	All included patients	Cases: 54/1267

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	months before diagnosis		Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

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1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 107: Positive predictive values for any childhood cancer: Patients aged 0-4**
3 **years[hh]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 0-4 years	0.093 (0.077-0.113) Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12	Patients aged 0-4	0.061 (0.037-0.1)

hh This table is included in the evidence review for Wilm's tumour because Wilm's tumour is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	months before diagnosis	years	Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

The positive predictive values are calculated using Bayesian statistics.

Table 108: Positive predictive values for any childhood cancer: Patients aged 5-14 years[ii]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months	Patients aged 5-14	0.082 (0.053-0.125)

ii This table is included in the evidence review for Wilm's tumour because Wilm's tumour is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	before diagnosis	years	Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 109: Positive predictive values for leukaemia/lymphoma childhood cancer[jj]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls	0.03 (0.01-0.06)

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jj This table is included in the evidence review for childhood cancer because both are cancers of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		aged 0-14 years	
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 110: Positive predictive values for teenage and young adult leukaemia[kk]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799

3 *The positive predictive values are calculated using Bayesian statistics.*

4 **Table 111: Positive predictive values for teenage and young adult lymphoma[ll]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515)

kk This table is included in the evidence review for childhood cancer because leukaemia is a cancer of childhood.
ll This table is included in the evidence review for childhood cancer because lymphoma is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
			Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Table 112: Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour[mm]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer	0.02 (0.01-0.06)

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mm This table is included in the evidence review for childhood cancer because CNS cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		tumour patients and controls aged 0-14 years	
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

The positive predictive values are calculated using Bayesian statistics.

Table 113: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma[nn]

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft	0 (0-0)

nn This table is included in the evidence review for childhood cancer because both are cancers of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		tissue sarcoma patients and controls aged 0-14 years	
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 114: Positive predictive values for childhood abdominal cancer tumour[oo]**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.01-0.12)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.00-0.23)
Dommett (2013a)	Weight loss 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.02 (0.00-0.1)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.01-0.02)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.00-0.01)

oo This table is included in the evidence review for childhood cancer because abdominal cancer is a cancer of childhood.

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)

Investigations in primary care

No primarycare evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm's tumour where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for Wilm's tumour in children with a palpable abdominal mass or unexplained enlarged abdominal organ. [new 2015]** **Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for Wilm's tumour in children with unexplained visible haematuria. [new 2015]**
Relative value placed on the outcomes considered	<u>Signs and symptoms of Wilm's tumour</u> The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict Wilm's tumour <u>Investigations in primary care for Wilm's tumour</u> The GDG identified sensitivity, specificity, positive predictive values and false negative rates as relevant outcomes to this question. No evidence was found on any of these outcomes.
Quality of the evidence	<u>Signs and symptoms of Wilm's tumour</u> No evidence was found pertaining to the positive predictive values of different symptoms of Wilm's tumour in primary care. However, evidence was found on the positive predictive values of symptoms of 'any' childhood cancer, of which the GDG considered, some would have been Wilm's tumour. <u>Investigations in primary care for Wilm's tumour</u> No evidence was found pertaining to the diagnostic accuracy of tests in primary care patients with suspected Wilm's tumour.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those children with Wilm's tumour more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the

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number of children without Wilm's tumour who get inappropriately referred whilst maximising the number of children with Wilm's tumour who get appropriately referred.

In general in adult cancers, in order to strike an appropriate balance between these considerations, the GDG has agreed to recommend referral for those symptoms with a positive predictive value of 3% or above. However, in children's cancers, the GDG decided that this threshold was too stringent for the following reasons: 1) the high levels of treatability of these cancers, 2) early diagnosis can reduce mortality and morbidity, and 3) the number of life-years gained. The GDG therefore agreed that referral for symptoms with positive predictive values lower than 3% was justified. However the GDG also acknowledged that no evidence had been found on the positive predictive values of symptoms for Wilm's tumour.

Despite the limited evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected nephroblastoma/Wilm's tumour, since there was no test available in primary care.

The GDG discussed what symptoms should prompt a suspected cancer pathway referral. They noted that the study included in the evidence by Dommett (2012, 2013a, b) had examined the positive predictive values for the symptoms recommended in previous guidance and they were all very low for childhood cancer as a whole, and therefore would be even lower for Wilm's tumour. Moreover, the GDG noted that almost all symptoms were more common and less worrying and should therefore prompt investigation with routine tests.

The exception to this was abdominal mass which was only reported in cases and not controls. The GDG noted that it can be difficult to determine which abdominal organ is enlarged in children on palpation. The GDG also noted that any abdominal mass (regardless of affected organ) is rare, but that, based on their clinical experience, a palpable abdominal mass or unexplained enlarged abdominal organ can be a symptom of Wilm's tumour, which the GDG agreed is serious enough to warrant very urgent attention. The GDG also noted, based on the evidence, that the positive predictive values for 'urinary symptoms' for childhood cancer were very low. However, the GDG also noted that, based on their clinical experience, unexplained visible haematuria can be a symptom of Wilm's tumour, which the GDG agreed is serious enough to warrant very urgent attention.

The GDG did not feel that an immediate admission would be appropriate since there are risks associated with this and it is still unlikely that the child would have cancer. However, the GDG recognised that a mass and unexplained visible haematuria are worrying symptoms and that children have less reserve than adults so the GDG did not want to recommend a suspected cancer pathway referral either. Instead the GDG opted for very urgent specialist assessment (within 48 hours) as this would mean the child would get seen quickly and would get around any issues with weekend cover and differences in local service configuration.

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	The GDG discussed whether other symptoms should prompt referral suspected cancer pathway referral, but noted that the study included in the evidence by Domment (2012, 2013a, b) had examined the positive predictive values for the symptoms recommended in previous guidance, and they were all very low. Moreover, the GDG noted that these symptoms were all more common and less worrying symptoms and should therefore prompt investigation with routine tests. The GDG therefore decided not to make any further symptom-based recommendations. Due to the lack of evidence and the fact that there is no obvious test for Wilm's tumour in primary care, the GDG were not able to recommend a particular test for the primary care investigation of Wilm's tumour.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG noted that the recommendations for very urgent specialist assessment for a 'palpable abdominal mass or unexplained enlarged abdominal organ' and 'unexplained visible haematuria' are cost-neutral as it is standard practice. However, there may be a small cost increase as a result of making the recommendations 'very urgent' and extending it to children of all ages, but this increase is likely to be small because of the rarity of the symptoms, and the absence of recommendations for any other symptoms or investigations in primary care.
Other considerations	The GDG noted that no recommendations were made for teenagers and young people, because Wilm's tumour is much less likely to be the cause of an abdominal mass in these age groups and haematuria is more likely result from other causes.

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18.5 Non-site specific symptoms in children

The GDG noted that children with cancer often present with advanced disease. This is complicated by the variation in presentation in different ages. In some cases concerns have been raised earlier or on several occasions by parents. The GDG believed that it was important that cancer was considered as a potential diagnosis when children present with symptoms that are not particularly suggestive of cancer but where there was significant or persistent parental concern.

Clinical evidence

Signs and symptoms

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

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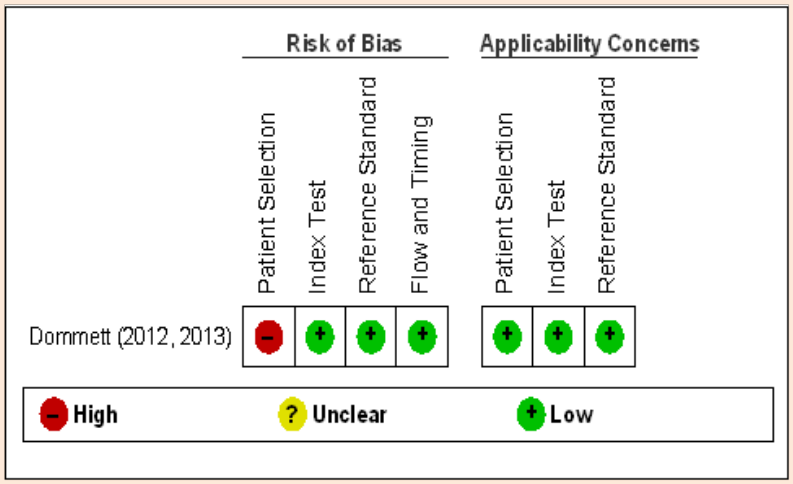

Evidence statement

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 115-117).

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 118-120).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old , and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 121).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 122).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and 'lump mass swelling below neck excluding abdomen') for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 123).

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Table 115: Positive predictive values for any childhood cancer: Patients aged 0-14 years

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	All included patients	0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	All included patients	0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	All included patients	0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318
Dommett (2012)	Headache 0-12 months before diagnosis	All included patients	0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318
Dommett (2013a)	Headache 0-3 months before diagnosis	All included patients	0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318
Dommett (2013a)	Headache 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.22)
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	All included patients	0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included patients	0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.2 (0.1-0.39)
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	All included patients	0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis	All included patients	0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318
Dommett (2013a)	Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.3 (0.09-0.99)
Dommett (2012)	Fatigue 0-12 months before diagnosis	All included patients	0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis	All included patients	0.07 (0.04-0.12) Cases: 42/1267 Control: 24/15318
Dommett (2013a)	Fatigue 0-12 months before diagnosis and ≥ 3 consultations	All included patients	0.12 (0.06-0.23)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Back pain 0-12 months before diagnosis	All included patients	0.088 (0.06-0.128) Cases: 40/1267 Control: 73/15318
Dommett (2012)	Bruising 0-12 months before diagnosis	All included patients	0.08 (0.054-0.118) Cases: 38/1267 Control: 76/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included patients	0.08 (0.05-0.13) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Bruising 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.38 (0.09-1.64)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included patients	0.41 (0.12-1.34) Cases: 33/1267 Control: 18/15318
Dommett (2013a)	Pallor 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included patients	0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.76 (0.1-5.7)
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included patients	0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.15 (0.07-0.32)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Bleeding 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.11 (0.04-0.31)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included patients	0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations	All included patients	0.23 (0.07-0.77)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included patients	0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318
Dommett (2013a)	Pain 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.14 (0.07-0.31)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included patients	0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations	All included patients	0.13 (0.08-0.19)
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	All included patients	0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318
Dommett (2013a)	≥ 3 consultations	All included patients	0.02
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included patients	Cases: 54/1267 Control: 236/15318
Dommett (2013a)	Upper respiratory tract infection 0-3 months before diagnosis	All included patients	Cases: 143/1267 Control: 942/15318
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included patients	Cases: 86/1267 Control: 105/15318
Dommett (2013a)	Cough 0-3 months before diagnosis	All included patients	Cases: 77/1267 Control: 654/15318
Dommett (2013a)	Rash 0-3 months before diagnosis	All included patients	Cases: 63/1267 Control: 555/15318
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included patients	Cases: 60/1267 Control: 137/15318
Dommett (2013a)	Abdominal mass 0-3 months before diagnosis	All included patients	Cases: 48/1267 Control: 0/15318
Dommett (2013a)	Fever 0-3 months before diagnosis	All included patients	Cases: 49/1267 Control: 166/15318
Dommett (2013a)	Eye swelling 0-3 months before diagnosis	All included patients	Cases: 39/1267 Control: 238/15318
Dommett (2013a)	Shortness of breath 0-3 months before diagnosis	All included patients	Cases: 35/1267 Control: 221/15318
Dommett (2013a)	Constipation 0-3 months before diagnosis	All included patients	Cases: 26/1267 Control: 61/15318
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	All included patients	2.19 (0.295-17.034) Cases: 14/1267 Control: 1/15318

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 116: Positive predictive values for any childhood cancer: Patients aged 0-4**
3 **years**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 0-4 years	0.081 (0.059-0.112) Cases: 96/436 Control: 55/4802
Dommett (2012)	Any NICE alert	Patients aged 0-4	0.093 (0.077-0.113)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
	symptom 0-12 months before diagnosis	years	Cases: 124/436 Control: 248/4802
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.076 (0.054-0.107) Cases: 43/436 Control: 105/4802
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 0-4 years	0.135 (0.055-0.335) Cases: 8/436 Control: 11/4802
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 0-4 years	0.061 (0.037-0.1) Cases: 20/436 Control: 61/4802
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 0-4 years	0.198 (0.099-0.399) Cases: 16/436 Control: 15/4802
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 0-4 years	0.087 (0.048-0.16) Cases: 15/436 Control: 32/4802
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 0-4 years	0.186 (0.047-0.742) Cases: 4/436 Control: 4/4802
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 0-4 years	0.155 (0.086-0.279) Cases: 20/436 Control: 24/4802
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 0-4 years	0.739 (0.159-3.496) Cases: 8/436 Control: 2/4802
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 0-4 years	1.286 (0.161-10.569) Cases: 7/436 Control: 1/4802

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 117: Positive predictive values for any childhood cancer: Patients aged 5-14**
3 **years**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Any NICE alert symptom 0-3 months before diagnosis	Patients aged 5-14 years	0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516
Dommett (2012)	Any NICE alert symptom 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.066-0.084) Cases: 303/831 Control: 581/10561
Dommett (2012)	Neurological symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516
Dommett (2012)	Headache 0-12 months before diagnosis	Patients aged 5-14 years	0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2012)	Lymphadenopathy 0-12 months before diagnosis	Patients aged 5-14 years	0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516
Dommett (2012)	Lump/mass/swelling 0-12 months before diagnosis	Patients aged 5-14 years	0.154 (0.099-0.24) Cases: 40/831 Control: 37/10516
Dommett (2012)	Fatigue 0-12 months before diagnosis	Patients aged 5-14 years	0.082 (0.053-0.125) Cases: 32/831 Control: 56/10516
Dommett (2012)	Back pain 0-12 months before diagnosis	Patients aged 5-14 years	0.075 (0.05-0.111) Cases: 36/831 Control: 69/10516
Dommett (2012)	Bruising 0-12 months before diagnosis	Patients aged 5-14 years	0.049 (0.029-0.084) Cases: 18/831 Control: 52/10516
Dommett (2012)	Urinary symptoms 0-12 months before diagnosis	Patients aged 5-14 years	0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516
Dommett (2012)	Hepatosplenomegaly 0-12 months before diagnosis	Patients aged 5-14 years	Cases: 7/831 Control: 0/10516

The positive predictive values are calculated using Bayesian statistics.

Table 118: Positive predictive values for leukaemia/lymphoma childhood cancer

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bruising 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.53 (0.07-3.91)
Dommett (2013a)	Pallor 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.43 (0.06-3.15)
Dommett (2013a)	Lump mass swelling head and neck 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.35 (0.05-2.65)
Dommett (2013a)	Fatigue 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.07 (0.03-0.15)
Dommett (2013a)	Lymphadenopathy 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.06 (0.04-0.11)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.05 (0.02-0.13)
Dommett (2013a)	Bleeding 0-3 months	All included	0.03 (0.01-0.08)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
	before diagnosis	leukemia/lymphoma patients and controls aged 0-14 years	
Dommett (2013a)	Pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.03 (0.01-0.06)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.02 (0.01-0.03)
Dommett (2013a)	Fever 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	≥ 3 consultations	All included leukemia/lymphoma patients and controls aged 0-14 years	0.01 (0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 119: Positive predictive values for teenage and young adult leukaemia

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013b)	Bruising	All included leukaemia patients and controls aged 15-24 years	0.0117 (0.004-0.0343) Cases: 9/143 Controls: 5/1799
Dommett (2013b)	Fatigue	All included leukaemia patients and controls aged 15-24 years	0.0121 (0.0052-0.0282) Cases: 15/143 Controls: 8/1799
Dommett (2013b)	Lymphadenopathy	All included leukaemia patients and controls aged 15-24 years	0.0151 (0.004-0.0578) Cases: 7/143 Controls: 3/1799
Dommett (2013b)	≥ 3 consultations	All included leukaemia patients and controls aged 15-24 years	0.0038 (0.003-0.0048) Cases: 74/143 Controls: 125/1799

The positive predictive values are calculated using Bayesian statistics.

Table 120: Positive predictive values for teenage and young adult lymphoma

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling head and neck	All included lymphoma patients and controls aged 15-24 years	0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013b)	Lump mass swelling below neck excluding abdomen	All included lymphoma patients and controls aged 15-24 years	0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350
Dommett (2013b)	Lymphadenopathy	All included lymphoma patients and controls aged 15-24 years	0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350
Dommett (2013b)	'Lump mass swelling head and neck', 'lymphadenopathy' and 'lump mass swelling below neck excluding abdomen' combined as a single symptom	All included lymphoma patients and controls aged 15-24 years	0.0903 (0.057-0.1425)
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350

The positive predictive values are calculated using Bayesian statistics.

Table 121: Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Abnormal movement 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.11 (0.03-0.35)
Dommett (2013a)	Visual symptoms 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.07 (0.02-0.24)
Dommett (2013a)	Vomiting 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.04 (0.02-0.07)
Dommett (2013a)	Headache 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.02-0.06)
Dommett (2013a)	Pain 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.03 (0.01-0.08)
Dommett (2013a)	Seizure 0-3 months before diagnosis	All included CNS childhood cancer tumour patients and	0.02 (0.01-0.06)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
		controls aged 0-14 years	
Dommett (2013a)	≥ 3 consultations	All included CNS childhood cancer tumour patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013b)	Seizure	All included CNS patients and controls aged 15-24 years	0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906
Dommett (2013b)	Headache	All included CNS patients and controls aged 15-24 years	0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906
Dommett (2013b)	Vomiting	All included CNS patients and controls aged 15-24 years	0.0116 (0.0041-0.031) Cases: 11/154 Controls: 5/1906
Dommett (2013b)	Pain	All included CNS patients and controls aged 15-24 years	0.0029 (0.0014-0.006) Cases: 11/154 Controls: 20/1906
Dommett (2013b)	Visual symptoms	All included CNS patients and controls aged 15-24 years	Cases: 8.4% Controls: 0%
Dommett (2013b)	≥ 3 consultations	All included CNS patients and controls aged 15-24 years	0.0023 (0.0019-0.0029) Cases: 73/154 Controls: 165/1906

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 122: Positive predictive values for child- or young adulthood bone cancer**
3 **tumour/soft tissue sarcoma**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.03 (0.01-0.14)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0.01 (0-0.01)
Dommett (2013a)	Trauma 0-3 months before diagnosis	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI) Frequency
Dommett (2013a)	≥ 3 consultations	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years	0 (0-0)
Dommett (2013b)	Lump mass swelling	All included bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years	0.0415 (0.0124-0.1392) Cases: 19/196 Controls: 3/2438
Dommett (2013b)	Musculoskeletal symptoms	All included lymphoma patients and controls aged 15-24 years	0.0093 (0.0058-0.0151) Cases: 37/196 Controls: 26/2438
Dommett (2013b)	Chest pain	All included lymphoma patients and controls aged 15-24 years	0.0027 (0.001-0.0077) Cases: 5/196 Controls: 12/2438
Dommett (2013b)	≥ 3 consultations	All included lymphoma patients and controls aged 15-24 years	0.003 (0.0024-0.0037) Cases: 86/196 Controls: 189/2438

1 *The positive predictive values are calculated using Bayesian statistics.*

2 **Table 123: Positive predictive values for childhood abdominal cancer tumour**

Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
Dommett (2013a)	Bleeding 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.01-0.12)
Dommett (2013a)	Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.03 (0.00-0.23)
Dommett (2013a)	Weight loss 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.02 (0.00-0.1)
Dommett (2013a)	Abdominal pain 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.01-0.02)
Dommett (2013a)	Musculoskeletal symptoms 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0.01 (0.00-0.01)
Dommett (2013a)	Childhood infection 0-3 months before diagnosis	All included abdominal cancer patients and controls aged 0-14 years	0 (0-0)
Dommett (2013a)	≥ 3 consultations	All included abdominal	0 (0-0)

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Study	Symptom(s)	Patient group	Positive predictive value (95% CI)
		cancer patients and controls aged 0-14 years	

Investigations in primary care

No primarycare evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm's tumour where the clinical responsibility was retained by primary care.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Take into account the insight and knowledge of parents and carers when considering making a referral for suspected cancer in a child or young person. Consider referral for children if their parent or carer has persistent concern or anxiety about the child's symptoms, even if the symptoms are most likely to have a benign cause. [2015]**
Relative value placed on the outcomes considered	The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict childhood cancer.
Quality of the evidence	The quality of the evidence as assessed by QUADAS-II was of high quality.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt urgent investigation or referral would be to identify those people with cancer more rapidly. However, the GDG recognised the importance of recommending the "right" symptoms, in order to minimise the number of people without cancer who get inappropriately referred or assessed whilst maximising the number of people with cancer who get appropriately referred or assessed. In order to strike an appropriate balance between these considerations, the GDG agreed to recommend referral for those symptoms with a positive predictive value of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those adults with cancer outweighed the disadvantages to those adults without. However, in children's cancers, the GDG decided that this threshold was too stringent for the following reasons: 1) the high levels of treatability of these cancers, 2) early diagnosis can reduce mortality and morbidity, and 3) the number of life-years gained. The GDG therefore agreed that referral at lower levels of risk (than 3%) was justified in children, and for these reasons and in order to be internally consistent, the GDG decided to make recommendations for generic symptoms of children's cancers according to the same rules. The GDG noted that all the positive predictive values for which no cancer site-specific recommendations had been made were very low. However, the GDG also noted that the positive

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	predictive value of parental concern had not been studied, which, based on their clinical experience, the GDG agreed was sufficiently high to warrant recommendation(s). The GDG therefore decided to retain two of the recommendations from previous guidance. The GDG also decided not to retain any of the remaining recommendations for the generic symptoms of children's cancer because they were either good clinical practice that was not specific to cancer; contrary to the available evidence (which had been published after the previous guidance); about risk factors or covered elsewhere (in the patient information topic).
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. Parental concern is traditionally regarded as an important factor, but has not been subjected to research. Therefore the GDG considered that his recommendation would not make a material change to the number of referrals made in this clinical situation. Consequently the GDG estimated that there would be no change in cost.

References

Neuroblastoma, Retinoblastoma, Wilm's tumour & Non-site specific symptoms in children

Dommett, R. M., Redaniel, M. T., Stevens, M. C. G., Hamilton, W., and Martin, R. M. Features of childhood cancer in primary care: A population-based nested case-control study. British Journal of Cancer 106[5], 982-987. 2012.

Dommett, R. M., Redaniel, T., Stevens, M. C. G., Martin, R. M., and Hamilton, W. Risk of childhood cancer with symptoms in primary care: A population-based case-control study. British Journal of General Practice; DOI:10.3399/bjgp13X660742. 2013a.

Dommett, R. M., Redaniel, M. T., Stevens, M. C. G., Hamilton, W., and Martin, R. M. Features of cancer in teenagers and young adults in primary care: A population-based nested case-control study. British Journal of Cancer 2329-2333. 2013b.

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19 Non-site-specific symptoms

Some symptoms or symptom combinations may be features of several different cancers. For some of these symptoms, the risk for each individual cancer may be low but the total risk of any cancer may be high. The GDG felt that it was important to examine the evidence for such instances for two main reasons. The first was for equity, in that the GDG believed that a symptom which was above the 3% PPV threshold was important, even if more than one cancer site was possible. Secondly, patients with these non-site specific symptoms often are referred to multiple specialists before their cancer is identified; it was hoped that by identifying which cancers are relevant to these symptoms, and more streamlined diagnostic pathway could be created.

Clinical evidence

Abdominal pain

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in some of the studies, with some studies also conducted in populations that are not clearly directly relevant to the current question and the quality of others suffering from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other issues to note concern missing data, the influence of which on the results is difficult to determine.

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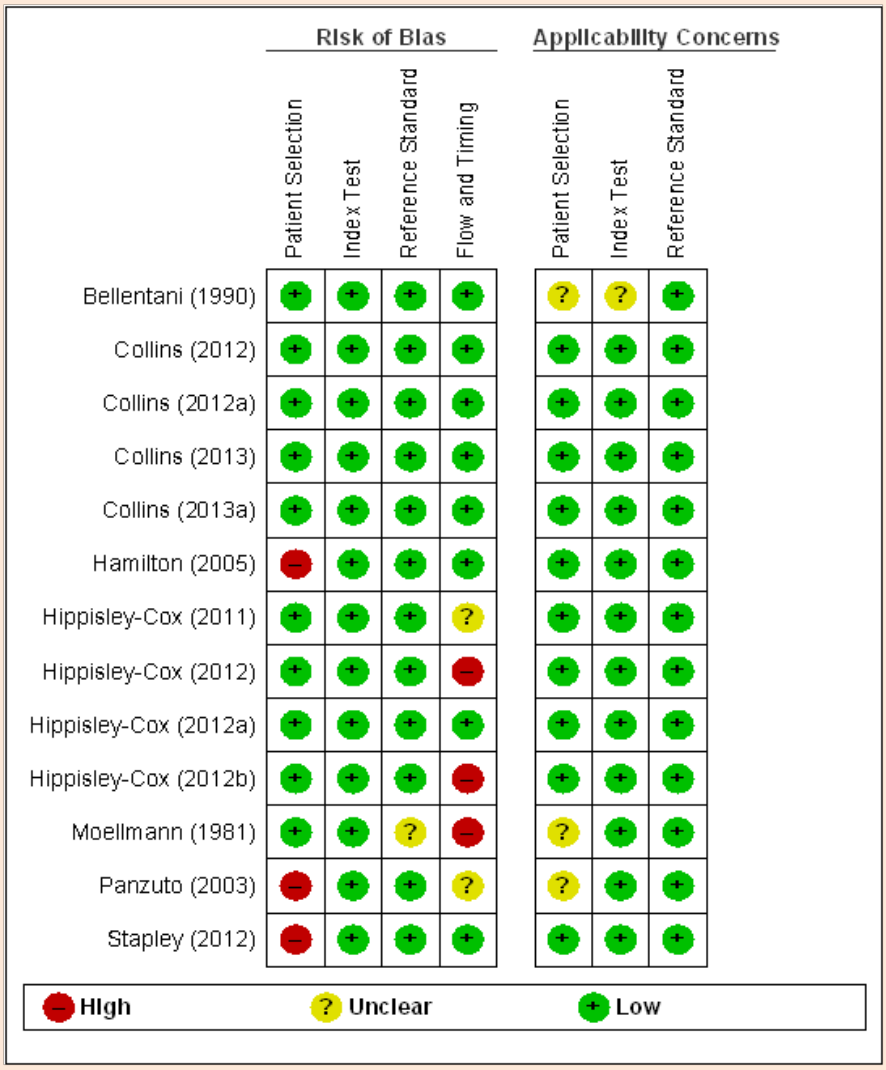

Evidence statement

Abdominal pain (9 studies, N = 6248014) presenting in a primary care setting is associated with an overall positive predictive value of 2.364% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 124).

Table 124: Non-site specific symptoms of concern: Calculation of overall positive predictive value of abdominal pain for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.2 (0.2-0.2)
Colorectal	Various*	30	84	1.524
Oesophagus/ stomach	Meta-analysis	varied	varied	0.34 (0.16-0.71)
Pancreatic	Hippisley-Cox (2012)	30	84	0.3 (0.3-0.4)
Sum				2.364

** Used an average.*

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Table 125: Non-site specific symptoms of concern: Positive predictive values for abdominal pain

Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/ renal		Collins (2013)	Abdominal pain	All patients	0.11 (0.1-0.13)	both	30	84
Bladder/ renal		Collins (2013)	Abdominal pain	Men	0.2 (0.2-0.21)	men	30	84
Bladder/ renal		Collins (2013)	Abdominal pain	Women	0.1 (0.1-0.1)	women	30	84
Bladder/ renal		Hippisley-Cox (2012)	Abdominal pain	All patients	0.2 (0.2-0.2)	both	30	84
Colorectal		Hamilton (2005)	Abdominal pain (reported once)	All patients	1.1 (0.9-1.3) Cases: 148/349 Controls: 163/1744	both	40	no upper limit
Colorectal		Hamilton (2005)	Abdominal pain	Patients 40-69 years	0.65 (NR)	both	40	69
Colorectal		Hamilton (2005)	Abdominal pain	Patients ≥ 70 years	2 (NR)	both	70	no upper limit
Colorectal		Hamilton (2005)	Abdominal pain (reported twice)	All patients	3 (1.8-5.2)	both	40	no upper limit
Colorectal		Hamilton (2005)	Abdominal pain and abdominal tenderness	All patients	1.4 (0.3-2.2)	both	40	no upper limit

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Colorectal		Hamilton (2005)	Abdominal tenderness (reported once)	All patients	1.1 (0.8-1.5) Cases: 62/349 Controls: 67/1744	both	40	no upper limit
Pancreatic		Collins (2013a)	Abdominal pain	All patients	0.14 (0.12-0.15)	both	30	84
Pancreatic		Collins (2013a)	Abdominal pain	Women	0.1 (0.09-0.12)	women	30	84
Pancreatic		Collins (2013a)	Abdominal pain	Men	0.19 (0.16-0.22)	men	30	84
Pancreatic		Hippisley-Cox (2012b)	Abdominal pain	All patients	0.3 (0.3-0.4)	both	30	84
Pancreatic		Stapley (2012)	Abdominal pain	All patients	0.2 (0.19-0.22)	both	40	no upper limit
Pancreatic		Stapley (2012)	Abdominal pain	Patients ≥ 60 years	0.3 (0.3-0.4)	both	60	no upper limit
Pancreatic		Stapley (2012)	Abdominal pain (attended ≥ twice)	Patients ≥ 60 years	1 (0.8-1.2)	both	60	no upper limit
META-ANALYSES (1) Colorectal								
Colorectal		Meta-analysis	Abdominal pain	N = 371703 patients/4 studies	2.04 (0.53-7.55)	both	2 studies 30-84, 1 study 18-87, 1 study NR Individual study details provided below	
Colorectal		Meta-analysis	Abdominal pain	N = 371480; w/o Panzuto	1.02 (0.38-2.69)	both	2 studies 30-84, 1 study NR Individual study details provided below	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
				(2003)				
The 4 studies below are those included in the meta-analysis reported in the cells above:								
Colorectal		Bellentani (1990)	Abdominal pain	All patients (N = 254)	3.9 (2-7.3)	both	NR	NR
Colorectal		Collins (2012)	Abdominal pain	All patients (N = 245989)	0.5 (0.5-0.5)	both	30	84
Colorectal		Hippisley-Cox (2012a)	Abdominal pain	All patients (N = 125237)	0.7 (0.6-0.7)	both	30	84
Colorectal		Panzuto (2003)	Abdominal pain	All patients (N = 223)	13.5 (9.4-18.8)	both	18	87
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Colorectal		Collins (2012)	Abdominal pain	Men 30-84 years	0.6 (0.6-0.7)	men	30	84
Colorectal		Collins (2012)	Abdominal pain	Women 30-84 years	0.4 (0.4-0.5)	women	30	84
META-ANALYSES (2) Oesophageal								
Oesophagus/ stomach	2 combining gastro-oesophageal and 1 reporting on osephageal cancer separately	Meta-analysis	Abdominal pain	N = 3389979/3 studies	0.23 (0.14-0.36)	both	2 studies 30-84, 1 study 40- >90 Individual study details provided below.	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under stomach, avoid double counting it):								
Oesophageal /stomach		Collins (2012a)	Abdominal pain	All patients	0.2 (0.2-0.2) 437/246998	both	30	84
Oesophageal /stomach		Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/91627	both	30	84
Oesophageal		Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	0 (0-0.8) 0/577	both	40	>90
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Oesophageal /stomach		Collins (2012a)	Abdominal pain	Women	0.1 (0.1-0.1) 139/144266	women	30	84
Oesophageal /stomach		Collins (2012a)	Abdominal pain	Men	0.3 (0.3-0.3) 298/102732	men	30	84
META-ANALYSES (3) Stomach								
Oesophagus/ stomach	2 combining gastro-oesophageal and 1 reporting on stomach cancer separately	Meta-analysis	Abdominal pain	N = 3389979/3 studies	0.34 (0.16-0.71)	both	2 studies 30-84, 1 study 40- >90	
The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under oesophageal, avoid double counting it):								
Oesophageal		Collins	Abdominal	All patients	0.2 (0.2-0.2)	both	30	84

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
/stomach		(2012)	pain		437/246998			
Oesophageal /stomach		Hippisley-Cox (2011)	Abdominal pain	All patients	0.3 (0.3-0.4) 309/91627	both	30	84
Stomach		Møllmann (1981)	Upper abdominal pain > 2 weeks	All patients	1 (0.4-2.4) 6/577	both	40	>90

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Appetite loss

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in one of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by this study are however likely to have gone some way in addressing this issue. Cost-effectiveness evidence.

Evidence statement

Appetite loss (5 studies, N = 4961516) presenting in a primary care setting is associated with an overall positive predictive value of 4.65% for cancer. The studies were associated with 0-1 bias/applicability concern (see also Table 126).

Table 126: Non-site specific symptoms of concern: Calculation of overall positive predictive value of appetite loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.18 (0.07-0.4)
Colorectal	Hippisley-Cox (2012)	30	84	0.9 (0.6-1.2)
Lung	Hamilton*	40	no upper limit	1.285

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
	(2005)			
Oesophagus/stomach	Hippisley-Cox (2011)	30	84	1.1 (0.8-1.5) 35/3391
Pancreatic	Hippisley-Cox (2012)	30	84	0.8 (0.5-1.2)
Sum				4.65

** Used an average.*

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Table 127: Non-site specific symptoms of concern: Positive predictive values for appetite loss

Cancer site	Comment / relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/ renal		Collins (2013)	Appetite loss	Women	0.1 (0.04-0.3)	Women	30	84
Bladder/ renal		Hippisley-Cox (2012)	Appetite loss	All patients	0.18 (0.07-0.4)	both	30	84
Colorectal		Hippisley-Cox (2012a)	Loss of appetite	All patients	0.9 (0.6-1.2)	both	30	84
Colorectal		Collins (2012)	Loss of appetite	All patients	0.8 (0.6-1.1)	both	30	84
Colorectal		Collins (2012)	Loss of appetite	Men 30-84 years	1 (0.6-1.5)	men	30	84
Colorectal		Collins (2012)	Loss of appetite	Women 30-84 years	0.6 (0.4-1)	women	30	84
Lung		Hamilton (2005)	Appetite loss	All included patients	0.87 (0.6-1.3)	both	40	No upper limit
Lung		Hamilton (2005)	Appetite loss (reported twice)	All included patients	1.7 (NR)	both	40	No upper limit
Lung		Hamilton (2005)	Appetite loss	Patients 40-69 years	1.1 (NR)	both	40	69
Lung		Hamilton (2005)	Appetite loss	All smokers	1.8 (NR)	both	40	No upper limit
Lung		Hamilton (2005)	Appetite loss (reported	All smokers	2.7 (NR)	both	40	No upper limit

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Cancer site	Comment / relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
			twice)					
Oesophagus/ stomach		Collins (2012a)	Appetite loss	All patients	0.6 (0.5-0.9) 37/5838	both	30	84
Oesophagus/ stomach		Collins (2012a)	Appetite loss	Women	0.4 (0.2-0.7) 12/3317	women	30	84
Oesophagus/ stomach		Collins (2012a)	Appetite loss	Men	1 (0.7-1.5) 25/2521	men	30	84
Oesophagus/ stomach		Hippisley-Cox (2011)	Appetite loss	All patients	1.1 (0.8-1.5) 35/3391	both	30	84
Pancreatic		Collins (2013a)	Appetite loss	All patients	0.39 (0.26-0.59)	both	30	84
Pancreatic		Collins (2013a)	Appetite loss	Women	0.32 (0.17-0.59)	women	30	84
Pancreatic		Collins (2013a)	Appetite loss	Men	0.49 (0.27-0.86)	women	30	84
Pancreatic		Hippisley-Cox (2012b)	Appetite loss	All patients	0.8 (0.5-1.2)	both	30	84

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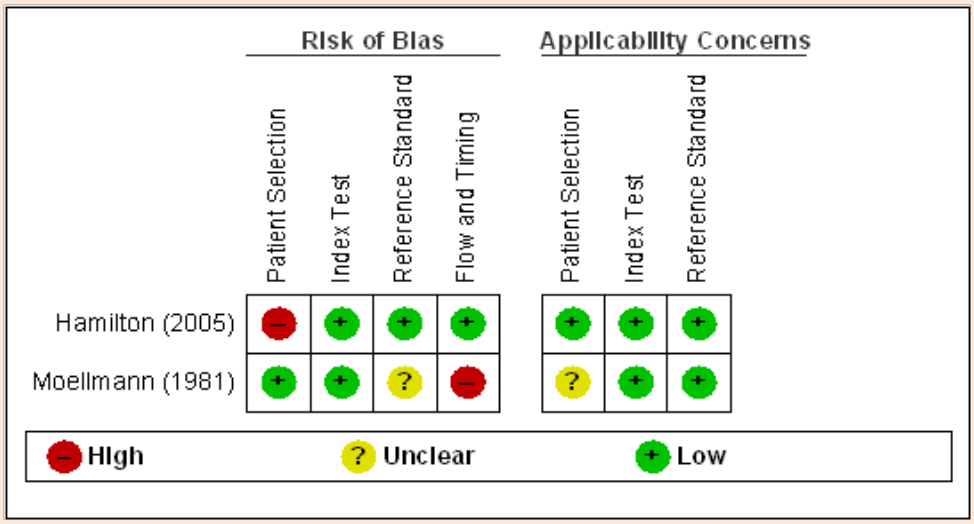
Appetite loss and weight loss

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not based on a consecutive or random series of patients in one of the studies, while the other study was conducted in a population that is not necessarily directly relevant to the current question. Studies employing non-consecutive/random sampling are at high risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.



Evidence statement

Appetite loss with weight loss (2 studies, N = 2962) presenting in a primary care setting is associated with an overall positive predictive value of 4.3% for cancer. The studies were associated with 1-3 bias/applicability concerns (see also Table 128).

Table 128: Non-site specific symptoms of concern: Calculation of overall positive predictive value of appetite loss with weight loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Lung	Hamilton (2005)	40	no upper limit	2.3 (1.2-4.4)
Oesophagus	Møllmann (1981)	40	>90	0 (0-8.9) 0/50
Stomach	Møllmann (1981)	40	>90	2 (0.1-12) 1/50
Sum				4.3

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Table 129: Non-site specific symptoms of concern: Positive predictive values for weight loss + appetite loss

Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Lung	Rec: Offered FBC and xray	Hamilton (2005)	Weight loss + appetite loss	All included patients	2.3 (1.2-4.4)	both	40	no upper limit
Lung	Rec: Offered FBC and xray	Hamilton (2005)	Weight loss + appetite loss	All smokers	5 (NR)	both	40	no upper limit
Oesophagus		Møllmann (1981)	Weight loss and/or anorexia	All patients	0 (0-8.9) 0/50	both	40	>90
Stomach	Rec: UGI endoscopy	Møllmann (1981)	Weight loss and/or anorexia	All patients	2 (0.1-12) 1/50	both	40	>90

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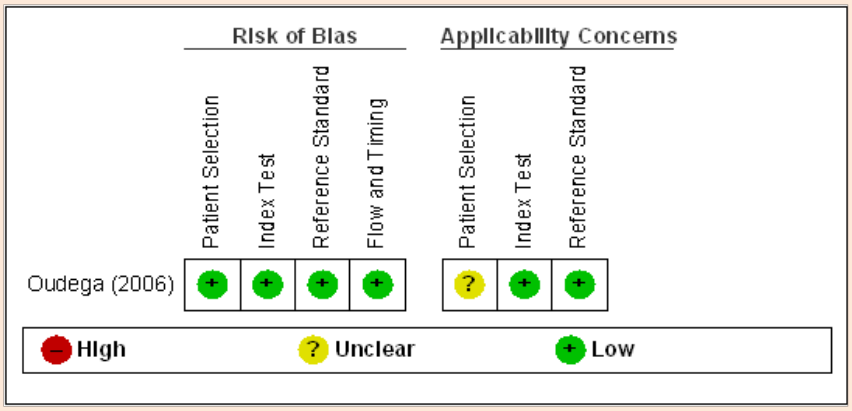
Deep Vein Thrombosis

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised in the figure below. The main validity issue to note is that the study was conducted in the Netherlands and the findings are only applicable to the extent that the study population and setting are comparable to a UK GP population as defined for the current purposes.



Evidence statement

Deep vein thrombosis (1 study, N = 430) presenting in a primary care setting is associated with an overall positive predictive value of 3.49% for cancer. The study was associated with 1 applicability concern (see also Table 130).

Table 130: Non-site specific symptoms of concern: Calculation of overall positive predictive value of deep vein thrombosis for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Colorectal	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.7 (0.2-2.2) 3/430
Urogenital	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		1.16 (0.4-2.9) 5/430
Breast	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.93 (0.3-2.53) 4/430
Lung	Oudega (2006)	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years		0.7 (0.2-2.2) 3/430
Sum				3.49

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Table 131: Non-site specific symptoms of concern: Positive predictive values for deep vein thrombosis

Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Colorectal		Oudega (2006)	Deep vein thrombosis	All included patients	0.7 (0.2-2.2) 3/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years	
Urogenital		Oudega (2006)	Deep vein thrombosis	All included patients	1.16 (0.4-2.9) 5/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years	
Breast		Oudega (2006)	Deep vein thrombosis	All included patients	0.93 (0.3-2.53) 4/430	women	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years	
Lung		Oudega (2006)	Deep vein thrombosis	All included patients	0.7 (0.2-2.2) 3/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years	
Other		Oudega (2006)	Deep vein thrombosis	All included patients	0.93 (0.3-2.53) 4/430	both	No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years	

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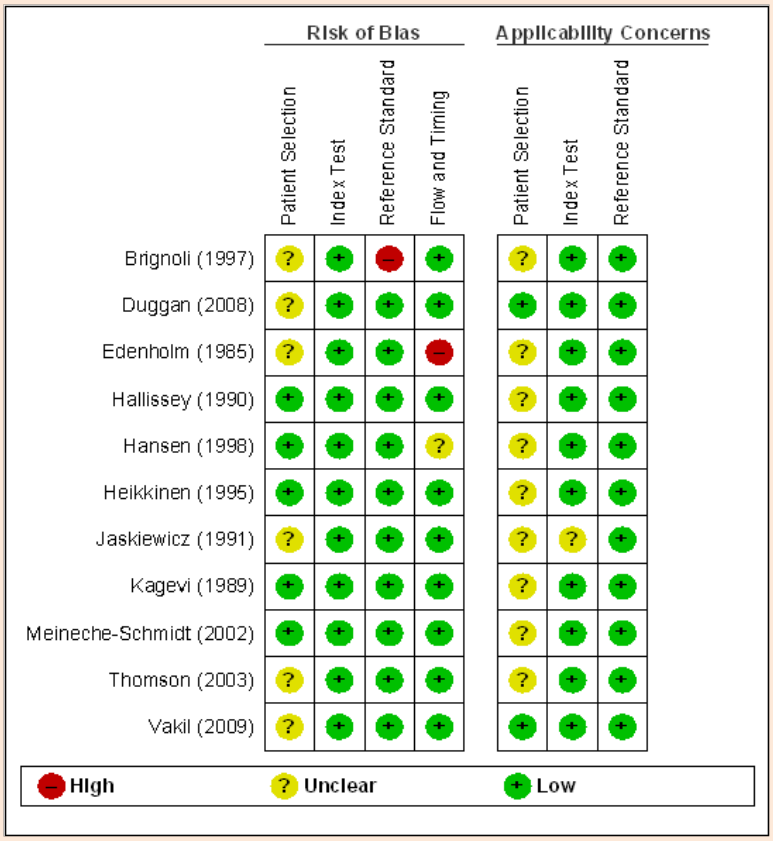
Dyspepsia

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and the vast majority of the studies were conducted in populations that are not clearly directly relevant to the current question. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.



Evidence statement

Dyspepsia (11 studies, N = 18464) presenting in a primary care setting is associated with an overall positive predictive value of 2.02% for cancer. The study was associated with 1-3 bias/applicability concerns (see also Table 132).

Table 132: Non-site specific symptoms of concern: Calculation of overall positive predictive value of dyspepsia for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Liver	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.25) 1/2585
Pancreatic	Hallissey (1990)	40	no upper limit	0.23 (0.09-0.53) 6/2585

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Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Uterine	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.25) 1/2585
Leukaemia	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.3) 1/2585
Gall bladder	Hallissey (1990)	40	no upper limit	0.04 (0.002-0.3) 1/2585
Prostate	Hallissey (1990)	40	no upper limit	0.08 (0.01-0.3) 2/2585
Bronchial	Hallissey (1990)	40	no upper limit	0.3 (0.1-0.6) 8/2585
Oesophagus/stomach	Meta-analysis	varied	varied	0.65 (0.33-1.3)
Colorectal	Meta-analysis	varied	varied	0.6 (0.27-1.35)
Sum				2.02

1

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Table 133: Non-site specific symptoms of concern: Positive predictive values for dyspepsia

Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Liver		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585	both	40	no upper limit
Pancreatic		Hallissey (1990)	Dyspepsia	All patients	0.23 (0.09-0.53) 6/2585	both	40	no upper limit
Uterine		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.25) 1/2585	both	40	no upper limit
Leukaemia		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585	both	40	no upper limit
Gall bladder		Hallissey (1990)	Dyspepsia	All patients	0.04 (0.002-0.3) 1/2585	both	40	no upper limit
Prostate		Hallissey (1990)	Dyspepsia	All patients	0.08 (0.01-0.3) 2/2585	both	40	no upper limit
Bronchial		Hallissey (1990)	Dyspepsia	All patients	0.3 (0.1-0.6) 8/2585	both	40	no upper limit
Other		Hallissey (1990)	Dyspepsia	All patients	0.3 (0.1-0.6) 8/2585	both	40	no upper limit
Other		Meineche-Schmidt (2002)	Dyspepsia	All patients	0.4 (0.16-0.92) 6/1491	both	18	65+
META-ANALYSES (1) Oesophageal								
Oesophagus/ stomach	2 combining gastro-oesophageal and 9 reporting on	Meta-analysis	Dyspepsia	N = 11403/11 studies	0.25 (0.13-0.5)	both	2 studies > 15, 2 studies > 18, 1 study > 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18- >65, 1 study NR but mean (SD) = 41-42 (15-16) Individual study details provided below	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
	oesophageal cancer separately							
The 11 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under stomach, avoid double counting it):								
Oesophageal		Brignoli (1997)	Dyspepsia	All patients	0 (0-0.58) 0/828	both	Mean (SD) age = 41-42 (15-16) years	
Oesophageal		Duggan (2008)	Dyspepsia	All patients	0.27 (0.05-1.1) 2/753	both	18	70
Oesophageal		Edenholm (1985)	Persisten epigastric pain/ulcer-like dyspepsia	All patients who received an UGI endoscopy	0.61 (0.03-3.8) 1/165	both	17	80
Oesophageal		Hallissey (1990)	Dyspepsia	All patients	0.58 (0.33-0.98) 15/2585	both	40	No upper limit
Oesophageal/ stomach		Hansen (1998)	Dyspepsia	All patients	1 (0.4-2.2) 6/612	both	Mean age (SD) = 47 (16.8)	
Oesophageal		Heikkinen (1995)	Dyspepsia	All patients	0.5 (0.09-2) 2/400	both	77% were > 44 years.	
Oesophageal		Jaskiewicz (1991)	Dyspepsia	All included patients	0 (0-0.8) 0/585	both	19	87
Oesophageal		Kagevi (1989)	Dyspepsia	All included patients	0 (0-2.7) 0/172	both	16	No upper limit
Oesophageal/ stomach		Meineche-Schmidt	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1491	both	18	65+

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
		(2002)						
Oesophageal		Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040	both	18	84
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741	both	18	70
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.18 (0.03-0.71) 2/1127	both	45	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 50 years old	0.24 (0.04-1) 2/829	both	50	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 55 years old	0.18 (0.01-1.16) 1/554	both	55	70
Oesophageal		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 60 years old	0.3 (0.02-2) 1/323	both	60	70
Oesophageal/ stomach		Hansen (1998)	Ulcer-like dyspepsia	All patients	0.6 (0.03-3.9) 1/161	both	Mean age (SD) = 47 (16.8)	
Oesophageal/ stomach		Hansen (1998)	Dysmotility -like dyspepsia	All patients	0 (0-2.9) 0/163	both	Mean age (SD) = 47 (16.8)	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Oesophageal/ stomach		Hansen (1998)	Reflux-like dyspepsia	All patients	1.16 (0.2-4.6) 2/173	both	Mean age (SD) = 47 (16.8)	
Oesophageal/ stomach		Hansen (1998)	Unclassifiable dyspepsia	All patients	0.9 (0.05-5.8) 1/107	both	Mean age (SD) = 47 (16.8)	
META-ANALYSES (2) Stomach								
Oesophagus/ stomach	2 combining gastro-oesophageal and 9 reporting on stomach cancer separately	Meta-analysis	Dyspepsia	N = 11403/11 studies	0.65 (0.33-1.3)	both	2 studies > 15, 2 studies > 18, 1 study > 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18- >65, 1 study NR but mean (SD) = 41-42 (15-16) Individual study details provided below.	
The 11 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under oesophageal, avoid double counting it):								
Stomach		Brignoli (1997)	Dyspepsia	All patients	0.4 (0.09-1.14) 3/828	both	Mean (SD) age = 41-42 (15-16) years	
Stomach		Duggan (2008)	Dyspepsia	All patients	0.27 (0.05-1.1) 2/753	both	18	70
Stomach		Edenholm (1985)	Persisten epigastric pain/ulcer-like dyspepsia	All patients who received an UGI endoscopy	1.2 (0.21-4.77) 2/165	both	17	80
Stomach		Hallissey (1990)	Dyspepsia	All patients	2.28 (1.76-3) 59/2585	both	40	No upper limit
Oesophageal/		Hansen	Dyspepsia	All patients	1 (0.4-2.2)	both	Mean age (SD) = 47 (16.8)	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
stomach		(1998)			6/612			
Stomach		Heikkinen (1995)	Dyspepsia	All patients	1.75 (0.8-3.7) 7/400	both	77% were > 44 years.	
Stomach		Jaskiewicz (1991)	Dyspepsia	All included patients	2.7 (1.6-4.5) 16/585	both	19	87
Stomach		Kagevi (1989)	Dyspepsia	All included patients	1.16 (0.2-4.6) 2/172	both	16	No upper limit
Oesophageal/ stomach		Meineche-Schmidt (2002)	Dyspepsia	All patients	0.54 (0.25-1.1) 8/1491	both	18	65+
Stomach		Thomson (2003)	Dyspepsia	All patients	0.1 (0.01-0.6) 1/1040	both	18	84
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	All included patients	0.1 (0.03-0.35) 3/2741	both	18	70
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Stomach		Jaskiewicz (1991)	Dyspepsia	Males	3.4 (1.8-6) 12/355	Males	19	87
Stomach		Jaskiewicz (1991)	Dyspepsia	Females	1.7 (0.6-4.7) 4/230	Females	19	87
Oesophageal/ stomach		Hansen (1998)	Ulcer-like dyspepsia	All patients	0.6 (0.03-3.9) 1/161	Both	Mean age (SD) = 47 (16.8)	
Oesophageal/ stomach		Hansen (1998)	Dysmotility-like dyspepsia	All patients	0 (0-2.9) 0/163	Both	Mean age (SD) = 47 (16.8)	

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Oesophageal/ stomach		Hansen (1998)	Reflux-like dyspepsia	All patients	1.16 (0.2-4.6) 2/173	Both	Mean age (SD) = 47 (16.8)	
Oesophageal/ stomach		Hansen (1998)	Unclassifiable dyspepsia	All patients	0.9 (0.05-5.8) 1/107	Both	Mean age (SD) = 47 (16.8)	
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 45 years old	0.27 (0.07-0.84) 3/1127	both	45	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 50 years old	0.36 (0.09-1.15) 3/829	both	50	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 55 years old	0 (0-0.86) 0/554	both	55	70
Stomach		Vakil (2009)	Dyspepsia without alarm symptoms	Patients ≥ 60 years old	0 (0-1.47) 0/323	both	60	70
META-ANALYSES (3) Colorectal								
Colorectal	1 study from 15, 1 study from 18-65+ and	Meta-analysis	Dyspepsia	3 studies, N = 4476	0.6 (0.27-1.35)	both	15-18	65+

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
	1 study from 40.							
The 3 studies below are those included in the meta-analysis reported in the cell above:								
Colorectal		Hallissey (1990)	Dyspepsia	All patients	0.5 (0.3-0.9) 14/2585	both	40	No upper limit
Colorectal		Heikkinen (1995)	Dyspepsia	All patients	0/400	both	77% were > 44 years.	
Colorectal		Meineche -Schmidt (2002)	Dyspepsia	All patients	1.14 (0.7-1.9)	both	18	65+

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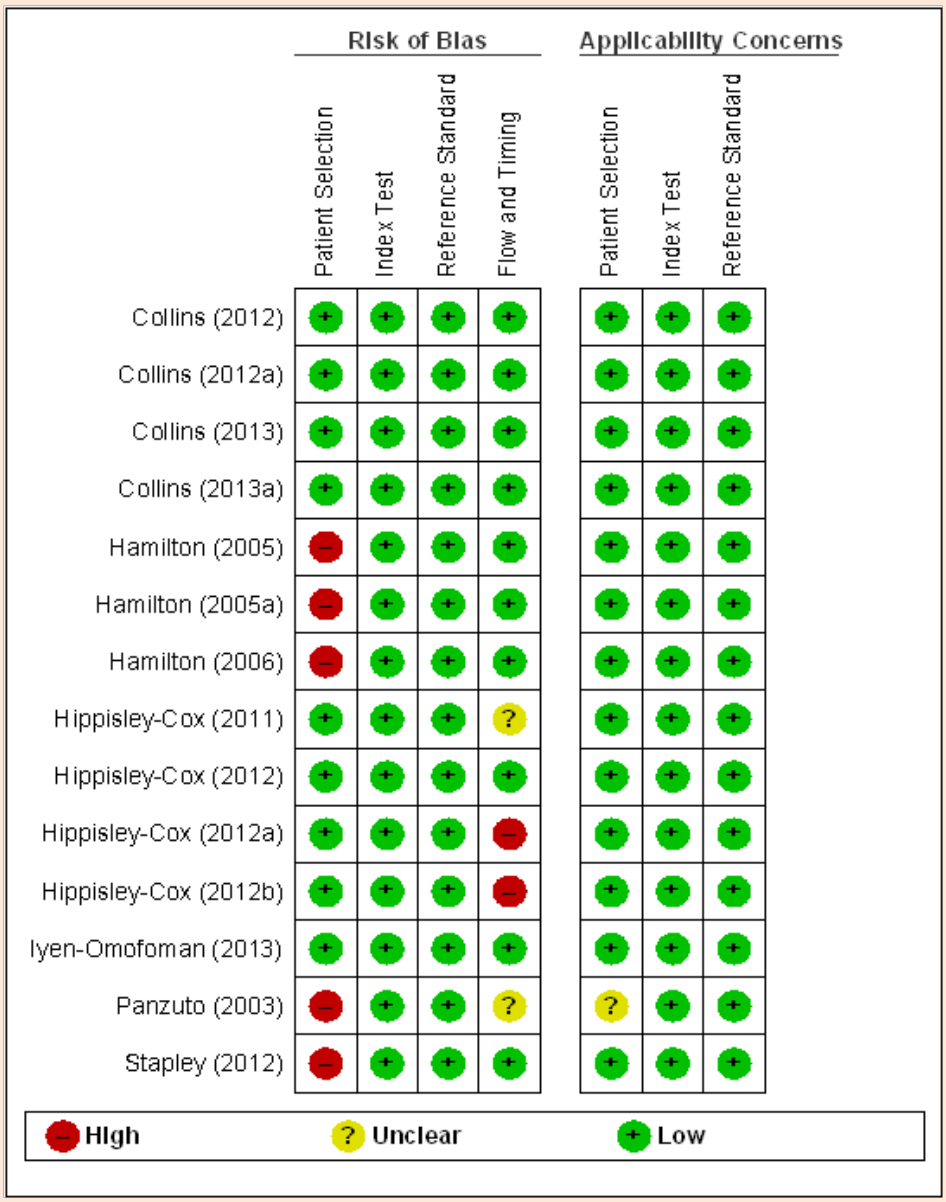
Weight loss

Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by these studies are however likely to have gone some way in addressing this issue. One study was conducted in a setting that is unlikely to be directly applicable to UK-based primary care and, as a consequence, also seems to present inflated PPVs that may be more reflective of secondary care. Finally, some of the studies were compromised by missing data, the influence of which on the results is difficult to determine.



Evidence statement

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Weight loss (8 studies, N = 3768550) presenting in a primary care setting is associated with an overall positive predictive value of 7.06% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 134).

Table 134: Non-site specific symptoms of concern: Calculation of overall positive predictive value of weight loss for cancer

Cancer site	Study	Lower age limit	Upper age limit	PPV (95% CI), prevalence
Bladder/renal	Hippisley-Cox (2012)	30	84	0.41 (0.3-0.6)
Colorectal	Meta-analysis	18	87	3 (0.32-22.89)
Lung	Hamilton (2005)	40	No upper limit	1.1 (0.8-1.6)
Oesophagus/stomach	Hippisley-Cox (2011)	30	84	1.2 (1-1.4) 107/9170
Pancreatic	Hippisley-Cox (2012)	30	84	0.6 (0.5-0.8)
Prostate	Hamilton (2006)	40	No upper limit	0.75 (0.38-1.4)
Sum				7.06

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Table 135: Non-site specific symptoms of concern: Positive predictive values for weight loss

Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Bladder/ renal		Collins (2013a)	Weight loss	Women	0.1 (0.1-0.2)	Women	30	84
Bladder /renal		Hippisley-Cox (2012b)	Weight loss	All patients	0.41 (0.3-0.6)	both	30	84
Lung		Hamilton (2005a)	Weight loss	All included patients	1.1 (0.8-1.6)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss (reported twice)	All included patients	1.2 (0.7-2.3)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss	All smokers	2.1 (NR)	both	40	no upper limit
Lung		Hamilton (2005a)	Weight loss (reported twice)	All smokers	1.7 (NR)	both	40	no upper limit
Lung		Iyen-Omofoman (2013)	Weight loss	Validation cohort	0.34 (0.23-0.5)	both	40	no upper limit
Oesophagus/ stomach		Collins (2012a)	Weight loss	All patients	0.8 (0.7-0.9) 218/28403	both	30	84
Oesophagus/ stomach		Collins (2012a)	Weight loss	Women	0.6 (0.4-0.7) 86/15465	Women	30	84
Oesophagus/ stomach		Collins (2012a)	Weight loss	Men	1 (0.9-1.2) 132/12938	Men	30	84

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Oesophagus/ stomach		Hippisley-Cox (2011)	Weight loss	All patients	1.2 (1-1.4) 107/9170	both	30	84
Pancreatic		Collins (2013)	Weight loss	All patients	0.28 (0.22-0.35)	both	30	84
Pancreatic		Collins (2013)	Weight loss	Women	0.16 (0.11-0.24)	women	30	84
Pancreatic		Collins (2013)	Weight loss	Men	0.42 (0.32-0.54)	men	30	84
Pancreatic		Hippisley-Cox (2012a)	Weight loss	All patients	0.6 (0.5-0.8)	both	30	84
Pancreatic		Stapley (2012)	Weight loss	All patients	0.44 (0.36-0.55)	both	40	no upper limit
Pancreatic		Stapley (2012)	Weight loss	Patients ≥ 60 years	0.8 (0.7-1)	both	60	no upper limit
Prostate		Hamilton (2006)	Loss of weight	All included patients	0.75 (0.38-1.4)	men	40	no upper limit
Prostate		Hamilton (2006)	Loss of weight (reported twice)	All included patients	2.1 (NR)	men	40	no upper limit
Colorectal		Hamilton (2005)	Loss of weight (reported once)	All patients	1.2 (0.9-1.6) Cases: 94/349 Controls: 92/1744	both	40	no upper limit
Colorectal		Hamilton (2005)	Loss of weight (reported twice)	All patients	1.4 (0.8-2.6)	both	40	no upper limit

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
Colorectal		Hamilton (2005)	Loss of weight	Patients 40-69 years	0.74 (NR)	both	40	69
Colorectal		Hamilton (2005)	Loss of weight	Patients ≥ 70 years	2.5 (NR)	both	70	no upper limit
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged < 60 years	0.1 (0.05-0.2)	Males	40	59
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged 60-69 years	0.3 (0.2-0.4)	Males	60	69
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged 70-79 years	0.7 (0.5-0.8)	Males	70	79
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Men aged ≥ 80 years	0.5 (0.3-0.8)	Males	80	no upper limit
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men < 60 years	0.2 (0.1-0.3)	Males	40	59
Colorectal		Hamilton	Weight	Men 60-69	0.7 (0.4-0.9)	Males	60	69

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
		(2005)	loss ≥ 10% (read off graph)	years				
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men 70-79 years	1.5 (1.2-1.8)	Males	70	79
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Men ≥ 80 years	0.8 (0.6-1.4)	Males	80	no upper limit
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women < 60 years	0.05 (0.05-0.05)	Females	40	59
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women 60-69 years	0.2 (0.1-0.3)	Females	60	69
Colorectal		Hamilton (2005)	Weight loss 5-10% (read off graph)	Women 70-79 years	0.4 (0.3-0.6)	Females	70	79
Colorectal		Hamilton (2005)	Weight loss 5-	Women ≥ 80 years	0.4 (0.3-0.6)	Females	80	no upper limit

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
			10% (read off graph)					
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women < 60 years	0.06 (0.06-0.08)	Females	40	59
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women 60-69 years	0.5 (0.3-0.7)	Females	60	69
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women 70-79 years	0.8 (0.6-1.1)	Females	70	79
Colorectal		Hamilton (2005)	Weight loss ≥ 10% (read off graph)	Women ≥ 80 years	0.8 (0.6-1.1)	Females	80	no upper limit
META-ANALYSES (1) Colorectal								
Colorectal		Meta-analysis	Weight loss	N = 42338 patients/3 studies	3 (0.32-22.89)	both	2 studies 30-84, 1 study 18-87 Individual study details below	
The 3 studies below are those included in the meta-analysis reported in the cell above:								
Colorectal		Collins (2012)	Weight loss	All patients (N =	0.8 (0.7-0.9)	both	30	84

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Cancer site	Comment/ relevant recs	Study	Symptom	Patient group	Positive predictive value% (95% CI), prevalence	Sex	Age inclusion, lower limit	Age inclusion, upper limit
				28289)				
Colorectal		Hippisley-Cox (2012)	Weight loss	All patients (N = 14007)	0.8 (0.7-0.9)	both	30	84
Colorectal		Panzuto (2003)	Weight loss	All patients (N = 42)	35.7 (22-52)	both	18	87
The following results are any extra analyses reported by the studies included in the above meta-analysis:								
Colorectal		Collins (2012)	Weight loss	Males	1 (0.8-1.1)	Males	30	84
Colorectal		Collins (2012)	Weight loss	Females	0.6 (0.5-0.7)	Females	30	84

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Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**For people with unexplained weight loss, which is a symptom of several cancers including colorectal, gastro-oesophageal, lung, prostate, pancreatic and urological cancer:** • **carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and** • **offer urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). [new 2015]** **For people with unexplained appetite loss, which is a symptom of several cancers including lung, oesophageal, stomach, colorectal, pancreatic, bladder and renal cancer:** • **carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and** • **offer urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). [new 2015]** **For people with deep vein thrombosis, which is associated with several cancers including uro-genital, breast, colorectal and lung cancer:** • **carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and** • **consider urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). [new 2015]**
Relative value placed on the outcomes considered	The GDG considered the positive predictive value to be the most important outcome when identifying which signs and symptoms predict cancer.
Quality of the evidence	The quality of the evidence as assessed by QUADAS-II varied for the positive predictive values for the different symptoms but was generally of moderate-high quality, although for deep vein thrombosis it consisted of only one study.
Trade-off between clinical benefits and harms	The GDG considered that a potential benefit of recommending which symptoms should prompt urgent investigation or referral would be to identify those people with cancer more rapidly. However, the GDG recognised the importance of recommending the “right” symptoms, in order to minimise the number of people without cancer who get inappropriately referred or assessed whilst maximising the number of people with cancer who get appropriately referred or assessed. In order to strike an appropriate balance between these considerations, the GDG had previously agreed to recommend referral for those symptoms with a positive predictive value for a

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	site-specific cancer of 3% or above in adults. The GDG were confident that at this threshold the advantages of a suspected cancer pathway referral in those adults with cancer outweighed the disadvantages to those adults without. For this reason and in order to be internally consistent, the GDG decided to retain the 3% threshold for making recommendations for those symptoms that were predictive of cancer in general. The GDG noted that in adults the positive predictive values for unexplained weight loss, unexplained appetite loss and deep vein thrombosis exceeded the 3% threshold and, based on the evidence, decided to make recommendations for urgent investigation/referral for these symptoms. The GDG also decided to include a list of potential cancers giving rise to the symptoms in the recommendations, listed in descending order of positive predictive value, in order to inform prioritisation of the investigation/referral. However, the GDG also recognised that the included list of potential cancer sites is a function of which cancers have been studied and that the symptoms may be due to cancers for which no evidence is (as yet) available, and therefore reflected this in the recommendations. The GDG noted that the cumulative positive predictive values for abdominal pain and dyspepsia were between 2% and 3%, but also that both symptoms are intra-abdominal, which is an area that has already been heavily studied. The GDG therefore considered that further studies are unlikely to materially change the positive predictive values for these symptoms and consequently, the GDG decided not to make any recommendations for abdominal pain and dyspepsia.
Trade-off between net health benefits and resource use	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG estimated that the overall cost of referring/investigating these people is unlikely to change, but that the patient experience should be improved by reducing multiple attendances for investigation.

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20 Recommendations for specific symptoms and signs

The GDG considered evidence and made recommendations by cancer site. This was logical, in that the recommendations would suggest the appropriate specialist or primary care test. This approach was also dictated by the fact that almost all primary care research on cancer symptoms is structured by cancer site. Taking a cancer by cancer approach also made it less likely that something important would be missed.

Structuring our guidance solely on a cancer site basis would not always be the most helpful approach for day to day use. The clinician would need to look through several cancers within the guideline each time a patient presented with symptoms; with a danger that something could be missed.

It is people with symptoms, signs and abnormal test results that the primary care clinician sees. There is merit in structuring the key information to clinicians in that manner: showing which particular cancers are associated with a given set of symptoms and the range of recommendations that apply to those symptoms, signs or abnormal test results. Therefore, the GDG decided to include a section in the guidance ordered according to symptom.

An approach based upon the symptoms and signs of presentation may also be a useful resource from which patients can gain information and reassurance about their own care.

The ordering of symptoms, signs and abnormal test results is initially alphabetical. Within a specific symptom or group of symptoms, we gave priority to recommendations with the most urgent action. For the sake of simplicity, where there were multiple recommendations for a symptom and a particular cancer site, these were kept together.

Some recommendations are very similar (or even identical) for two or more cancers. These were retained in full as it was important to reflect that each cancer had been considered in its own right. Conversely, some recommendations for the same symptom or group of symptoms differ – particularly in age thresholds. This reflects the same reasoning and the underlying evidence underpinning the recommendations for each cancer.

It must be emphasised that these are recommendations only. Clinicians should use their clinical judgement to determine which, if any, recommendations are appropriate for the particular patient.

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Abdominal distension

Specific features	Possible cancer	Recommendation
None	Ovarian	Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month: • persistent abdominal distension (women often refer to this as 'bloating') • feeling full (early satiety) and/or loss of appetite • pelvic or abdominal pain • increased urinary urgency and/or frequency. **[2011]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**

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1 Abdominal or pelvic mass or organomegaly

Specific features	Possible cancer	Recommendation
None	Leukaemia	Refer children and young people for immediate specialist assessment for leukaemia if they have unexplained petechiae or hepatosplenomegaly. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**
None	Neuroblastoma or Wilm's Tumour	Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for neuroblastoma or Wilm's tumour in children with a palpable abdominal mass or unexplained enlarged abdominal organ. **[new 2015]**
None	Ovarian	Refer the woman urgently[pp] if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). **[2011]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**
None	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people with a rectal or abdominal mass. **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**
None	Stomach	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with an upper abdominal mass consistent with stomach cancer. **[new 2015]**
None	Gall Bladder	Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for gall bladder cancer in people with an upper abdominal mass consistent with an enlarged gall bladder. **[new 2015]**
None	Liver	Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for liver cancer in people with an upper abdominal mass consistent with an enlarged liver. **[new 2015]**

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2 Abdominal or pelvic pain

Specific features	Possible cancer	Recommendation

pp An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

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Specific features	Possible cancer	Recommendation
With weight loss	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 40 with unexplained weight loss and abdominal pain. **[new 2015]**
With rectal bleeding	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or** • weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who: • have abdominal pain **or** • have weight loss **or** • are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**
With weight loss	Oesophageal	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people: • with dysphagia **or** • aged 55 and over with weight loss and any of upper abdominal pain or reflux or dyspepsia. **[new 2015]**
With raised platelet count	Oesophageal	Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people aged 55 or over with: • weight loss and nausea/vomiting **or** • reflux/dyspepsia and nausea/vomiting **or** • upper abdominal pain and raised platelet count. **[new 2015]**
None	Ovarian	Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month: • persistent abdominal distension (women often refer to this as 'bloating') • feeling full (early satiety) and/or loss of appetite • pelvic or abdominal pain • increased urinary urgency and/or frequency. **[2011]**
None	Ovarian	Carry out appropriate tests for ovarian cancer in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[qq], because IBS rarely presents for the first time in women of this age. **[2011]**
With weight loss	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms:

Update 2014

qq See the NICE guideline on irritable bowel syndrome in adults

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Specific features	Possible cancer	Recommendation
		• diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**
With weight loss	Stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who: • are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting **or** • are aged 55 and over with upper abdominal pain, reflux or dyspepsia. **[new 2015]**
With weight loss	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with weight loss who: • also have appetite loss **or** • are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more **or** • are aged 55 and over with nausea/vomiting. **[new 2015]**
With raised platelet count	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 and over with upper abdominal pain and raised platelet counts. **[new 2015]**

Update 2015

1 **Absent red reflex**

2 See ‘Examination findings (abnormal)’.

3 **Alcohol-induced lymph node pain**

Specific features	Possible cancer	Recommendation
None	Hodgkin’s lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin’s lymphoma in people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**

4 **Anaemia**

Specific features	Possible cancer	Recommendation
None	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged 60 and over and have unexplained iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
With rectal bleeding	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or**

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Specific features	Possible cancer	Recommendation
		• weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who: • have abdominal pain **or** • have weight loss **or** • are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**

1 **Anal mass**

2 See ‘Examination findings (abnormal)’ or ‘Lump or mass’.

3 **Anorexia**

4 See ‘Appetite loss or early satiety’

5 **Appetite loss or early satiety**

Specific features	Possible cancer	Recommendation
None	Lung, oesophageal, stomach, colorectal, pancreatic, bladder or renal	For people with unexplained appetite loss, which is a symptom of several cancers including lung, oesophageal, stomach, colorectal, pancreatic, bladder and renal cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and • offer urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). **[new 2015]**
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms: • cough • fatigue

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Specific features	Possible cancer	Recommendation
		• shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Ovarian	Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month: • persistent abdominal distension (women often refer to this as 'bloating') • feeling full (early satiety) and/or loss of appetite • pelvic or abdominal pain • increased urinary urgency and/or frequency. **[2011]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**
With weight loss	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with weight loss who: • also have appetite loss **or** • are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more **or** • are aged 55 and over with nausea/vomiting. **[new 2015]**

Update 2014

1 **Axillary lump**

2 See ‘Lump or mass’.

3 **Back pain**

Specific features	Possible cancer	Recommendation
With weight loss	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss

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Specific features	Possible cancer	Recommendation
		and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**
None	Myeloma	Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture. **[new 2015]**

1 **Bleeding - unexplained**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**

Update 2015

2 **Bleeding - haematemesis**

3 See ‘Haematemesis’

4 **Bleeding – haematuria**

5 See ‘Haematuria’

6 **Bleeding – haemoptysis**

7 See ‘Haemoptysis’

8 **Bleeding – post menopausal**

9 See ‘Post menopausal bleeding’

10 **Bleeding – rectal**

11 See ‘Rectal bleeding’

12 **Bleeding – vaginal**

13 See ‘Post menopausal bleeding’

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1 **Bleeding – vulval**

2 See ‘Skin or surface symptoms’

3 **Bone pain**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Bone Sarcoma	Consider an urgent direct access X-ray (within 2 weeks) to assess for bone sarcoma in children and young people with unexplained bone swelling or pain. **[new 2015]**
None	Myeloma	Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture. **[new 2015]**

4 **Bone swelling**

5 See ‘Lump or mass’

6 **Breast lump**

7 See ‘Lump or mass’

8 **Bruising or petechiae**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Refer children and young people for immediate specialist assessment for leukaemia if they have unexplained petechiae or hepatosplenomegaly. **[new 2015]**
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following

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Specific features	Possible cancer	Recommendation
		symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**

1 **Central neurological function**

Specific features	Possible cancer	Recommendation
None	Brain and Central Nervous System	Consider a very urgent referral (for an appointment within 48 hours) for suspected brain or central nervous system cancer in children and young people with newly abnormal cerebellar or other central neurological function. **[new 2015]**
None	Brain and Central Nervous System	Consider an urgent direct access MRI scan of the brain (within 2 weeks) to assess for brain or central nervous system cancer in adults with progressive, sub-acute loss of central neurological function. **[new 2015]**

2 **Cervical lymphadenopathy**

3 See 'Lymphadenopathy'

4 **Change in bowel habit**

Specific features	Possible cancer	Recommendation
None	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 60 and have unexplained changes in their bowel habit. **[new 2015]**
With rectal bleeding	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or** • weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who: • have abdominal pain **or** • have weight loss **or** • are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**

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Specific features	Possible cancer	Recommendation
None	Ovarian	Carry out appropriate tests for ovarian cancer in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[rr], because IBS rarely presents for the first time in women of this age. **[2011]**
None	Ovarian	Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit. **[2011]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**
With weight loss	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**

1 **Chest infection**

Specific features	Possible cancer	Recommendation
None	Lung	Offer an urgent chest X-ray (within 2 weeks) to assess for lung cancer in people with either: • thrombocytosis **or** • persistent or recurrent chest infection. **[new 2015]**

Update 2015

2 **Chest pain**

Specific features	Possible cancer	Recommendation
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms:

rr See the NICE guideline on irritable bowel syndrome in adults

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Specific features	Possible cancer	Recommendation
		• cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**

Update 2015

1 **Clubbing**

2 See ‘Finger clubbing’

3 **Constipation**

4 See ‘Change in bowel habit’.

5 **Cough**

Specific features	Possible cancer	Recommendation
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**

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Specific features	Possible cancer	Recommendation
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**

Update 2015

1 **Cutaneous symptoms**

2 See ‘Skin or surface symptoms’

3 **Deep vein thrombosis**

Specific features	Possible cancer	Recommendation
None	Uro-genital, breast, colorectal or lung	For people with deep vein thrombosis, which is associated with several cancers including uro-genital, breast, colorectal and lung cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and • consider urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). **[new 2015]**

4 **Diabetes**

5 See ‘New onset diabetes’

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1 **Diarrhoea**

2 See ‘Change in bowel habit’.

3 **Dyspepsia (see also ‘Reflux’ and ‘Nausea and vomiting’)**

Specific features	Possible cancer	Recommendation
With weight loss	Oesophageal	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people: • with dysphagia **or** • aged 55 and over with weight loss and any of upper abdominal pain or reflux or dyspepsia. **[new 2015]**
	Stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who: • are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting **or** • are aged 55 and over with upper abdominal pain, reflux or dyspepsia. **[new 2015]**
	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with weight loss who: • also have appetite loss **or** • are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more **or** • are aged 55 and over with nausea/vomiting. **[new 2015]**

4 **Dysphagia**

Specific features	Possible cancer	Recommendation
None	Oesophageal or stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal or stomach cancer in people with dysphagia. **[new 2015]**

Update 2015

5 **Dyspnoea**

6 See ‘Shortness of breath’.

7 **Dysuria**

Specific features	Possible cancer	Recommendation
With weight loss	Bladder	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. **[new 2015]**

8 **Enlarged abdominal organ**

9 See ‘Abdominal or pelvic mass or organomegaly’.

10 **Erectile dysfunction**

Specific features	Possible cancer	Recommendation
None	Prostate	Consider a prostate-specific antigen (PSA) test and digital

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Specific features	Possible cancer	Recommendation
		rectal examination to assess for prostate cancer in men with: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention **or** • erectile dysfunction **or** • visible haematuria. **[new 2015]**

1 Examination findings (abnormal)

Specific features	Possible cancer	Recommendation
Abdominal examination	Ovarian	Refer the woman urgently[ss] if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). **[2011]**
Gynaecological examination	Cervical	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for women if the appearance of their cervix is consistent with cervical cancer. **[new 2015]**
Rectal examination	Prostate	Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their prostate feels malignant on digital rectal examination. **[new 2015]**
	Anal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for anal cancer in people with an unexplained anal mass or unexplained anal ulceration. **[new 2015]**
	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people with a rectal or abdominal mass. **[new 2015]**
Respiratory system examination	Mesothelioma	Offer an urgent chest X-ray (within 2 weeks) to assess for mesothelioma in people aged 40 and over with either: • finger clubbing **or** • chest signs compatible with pleural disease. [new 2015] [R28]
	Lung	Consider an urgent full blood count and chest X-ray (within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following: • finger clubbing **or** • supraclavicular lymphadenopathy or persistent cervical lymphadenopathy **or** • chest signs compatible with lung cancer. **[new 2015]**
Ocular examination	Retinoblastoma	Consider urgent referral (for an appointment within 2 weeks) for ophthalmological assessment for retinoblastoma in children with an absent red reflex. **[new 2015]**

2 Fatigue

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor

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ss An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

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Specific features	Possible cancer	Recommendation
		• persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath

Update 2015

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Specific features	Possible cancer	Recommendation
		• chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**
None	Ovarian	Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit. **[2011]**

1 **Faecal occult blood**

2 See 'Investigations (abnormal)'

3 **Fever**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leuakemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**
None	Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in

Update 2015

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Specific features	Possible cancer	Recommendation
		people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**

1 **Finger clubbing**

2 See 'Examination findings (abnormal)'

3 **Fracture**

Specific features	Possible cancer	Recommendation
None	Myeloma	Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture. **[new 2015]**

4 **Haematemesis**

Specific features	Possible cancer	Recommendation
None	Oesophageal	Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people with haematemesis. **[new 2015]**

5 **Haematuria**

Specific features	Possible cancer	Recommendation
None	Wilm's Tumour	Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for Wilm's tumour in children with unexplained visible haematuria. **[new 2015]**
None	Bladder or renal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder or renal cancer if they are aged 45 and over and have unexplained visible haematuria without urinary tract infection or visible haematuria that persists or recurs after successful treatment of urinary tract infection. **[new 2015]**
With weight loss	Bladder	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. **[new 2015]**
None	Endometrial	Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with unexplained symptoms of vaginal discharge who: • are presenting with these symptoms for the first time **or** • have thrombocytosis **or**

Update 2015

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Specific features	Possible cancer	Recommendation
		• report haematuria. **[new 2015]**
None	Endometrial	Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with visible haematuria and any of the following: • low haemoglobin levels **or** • thrombocytosis **or** • high blood glucose levels. **[new 2015]**
None	Prostate	Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention **or** • erectile dysfunction **or** • visible haematuria. **[new 2015]**

1 **Haemoptysis**

Specific features	Possible cancer	Recommendation
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**

Update 2015

2 **Hepatomegaly**

3 See ‘Abdominal or pelvic mass or organomegaly’.

4 **Hepatosplenomegaly**

5 See ‘Abdominal or pelvic mass or organomegaly’.

6 **Hoarseness**

Specific features	Possible cancer	Recommendation
None	Laryngeal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for laryngeal cancer in people aged 45 and over with persistent unexplained hoarseness. **[new 2015]**

7 **Infection (see also ‘Chest infection’)**

Specific features	Possible cancer	Recommendation

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Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**

Update 2015

1 **Inguinal lymphadenopathy**

2 See ‘Lymphadenopathy’

3 **Investigations (abnormal)**

Specific features	Possible cancer	Recommendation
Blood tests	Myeloma	Offer very urgent protein electrophoresis (within 48 hours) to assess for myeloma in people aged 60 and over with hypercalcaemia or leucopenia and a presentation that is consistent with possible myeloma. **[new 2015]**
Blood tests	Myeloma	Consider very urgent protein electrophoresis (within 48 hours) to assess for myeloma if the plasma viscosity or erythrocyte sedimentation rate and presentation are consistent with possible myeloma. **[new 2015]**
Blood tests	Myeloma	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) if the results of protein electrophoresis suggest myeloma. **[new 2015]**
Blood tests	Bladder	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for bladder cancer if they are aged 60 and over and have unexplained non-visible haematuria and either dysuria or a raised white cell count on a blood test. **[new 2015]**
Blood tests	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged 60 and over and have unexplained iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**

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Specific features	Possible cancer	Recommendation
Faecal test	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if tests show occult blood in their faeces. **[new 2015]**
Blood tests	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or** • weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
Blood tests	Colorectal	Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who: • have abdominal pain **or** • have weight loss **or** • are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
Imaging	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
Blood tests	Lung	Offer an urgent chest X-ray (within 2 weeks) to assess for lung cancer in people with either: • thrombocytosis **or** • persistent or recurrent chest infection. **[new 2015]**
Blood tests	Prostate	Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their PSA levels are above the age-specific reference range. **[new 2015]**
Imaging	Ovarian	If the ultrasound suggests ovarian cancer, refer the woman urgently[tt] for further investigation. **[2011]**
Blood tests	Ovarian	If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis. **[2011]**
Blood tests	Ovarian	For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound: • assess her carefully for other clinical causes of her symptoms and investigate if appropriate

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tt An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

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Specific features	Possible cancer	Recommendation
		• if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent. **[2011]**
Imaging	Bone Sarcoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people if an X-ray suggests the possibility of bone sarcoma. **[new 2015]**
Imaging	Soft Tissue Sarcoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people if they have ultrasound scan findings that are suggestive of soft tissue sarcoma or if ultrasound findings are uncertain and clinical concern persists. **[new 2015]**
Blood tests	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**
Blood tests	Endometrial	Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with unexplained symptoms of vaginal discharge who: • are presenting with these symptoms for the first time **or** • have thrombocytosis **or** • report haematuria. **[new 2015]**
Blood tests	Endometrial	Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with visible haematuria and any of the following: • low haemoglobin levels **or** • thrombocytosis **or** • high blood glucose levels. **[new 2015]**

Update 2014

1 **Iron deficiency anaemia**

2 See ‘Anaemia’

3 **Jaundice**

Specific features	Possible cancer	Recommendation
None	Pancreatic	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for pancreatic cancer if they are aged 40 and over and have jaundice. **[new 2015]**

4 **Lump or mass (see also ‘Abdominal or pelvic mass or organomegaly’)**

Specific features	Possible cancer	Recommendation
None	Breast	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer if they are aged 30 and over and have an unexplained breast lump with or without pain. **[new 2015]**

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Specific features	Possible cancer	Recommendation
None	Breast	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer in people aged 30 and over with an unexplained lump in the axilla. **[new 2015]**
None	Anal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for anal cancer in people with an unexplained anal mass or unexplained anal ulceration. **[new 2015]**
None	Laryngeal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for laryngeal cancer in people aged 45 and over with an unexplained lump in the neck. **[new 2015]**
None	Oral	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a lump on the lip or in the oral cavity that has been assessed by a dental surgeon to be consistent with oral cancer. **[new 2015]**
None	Oral	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with a persistent and unexplained lump in the neck. **[new 2015]**
None	Oral	Consider an urgent referral (for an appointment within 2 weeks) for assessment for oral cancer by the community dental service in people with an unexplained lump on the lip or in the oral cavity that has not been assessed by a dental surgeon. **[new 2015]**
None	Thyroid	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for thyroid cancer in people with an unexplained thyroid lump. **[new 2015]**
None	Vaginal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for vaginal cancer in women with an unexplained palpable mass in or at the entrance to the vagina. **[new 2015]**
None	Bone Sarcoma	Consider an urgent direct access X-ray (within 2 weeks) to assess for bone sarcoma in children and young people with unexplained bone swelling or pain. **[new 2015]**
None	Soft Tissue Sarcoma	Consider an urgent direct access ultrasound scan (within 2 weeks) to assess for soft tissue sarcoma in people with an unexplained lump that is increasing in size. **[new 2015]**

Update 2015

1 **Lymphadenopathy**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to

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Specific features	Possible cancer	Recommendation
		assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**
None	Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**
None	Lung	Consider an urgent full blood count and chest X-ray (within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following: • finger clubbing **or** • supraclavicular lymphadenopathy or persistent cervical lymphadenopathy **or** • chest signs compatible with lung cancer. **[new 2015]**

Update 2015

1 **Mass**

2 See 'Lump or mass'

3 **Nausea or vomiting (see also 'Dyspepsia' and 'Reflux')**

Specific features	Possible cancer	Recommendation
With weight loss	Stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who: • are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting **or** • are aged 55 and over with upper abdominal pain, reflux or dyspepsia. **[new 2015]**
With weight loss	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with weight loss who: • also have appetite loss **or** • are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more **or** • are aged 55 and over with nausea/vomiting. **[new 2015]**

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Specific features	Possible cancer	Recommendation
With reflux	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 and over with reflux and nausea/vomiting. **[new 2015]**
With weight loss	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**
With reflux	Oesophageal	Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people aged 55 or over with: • weight loss and nausea/vomiting **or** • reflux/dyspepsia and nausea/vomiting **or** • upper abdominal pain and raised platelet count. **[new 2015]**

1 **New onset diabetes**

Specific features	Possible cancer	Recommendation
None	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**

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2 **Night sweats**

Specific features	Possible cancer	Recommendation
None	Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**

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1 **Nipple changes**

Specific features	Possible cancer	Recommendation
None	Breast	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for breast cancer if they are aged 50 and over with any of the following symptoms in 1 nipple only: • discharge • retraction • other changes of concern. **[new 2015]**

2 **Oral lesions**

Specific features	Possible cancer	Recommendation
None	Oral	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with unexplained ulceration in the oral cavity lasting for more than 14 days. **[new 2015]**

3 **Pallor**

Specific features	Possible cancer	Recommendation
None	Leukaemia	Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent infection • generalised lymphadenopathy • persistent or unexplained bone pain • unexplained bruising • unexplained bleeding. **[new 2015]**
None	Leukaemia	Consider a very urgent full blood count (within 48 hours) to assess for leukaemia in adults with any of the following symptoms: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae • hepatosplenomegaly. **[new 2015]**

4 **Parental concern**

Specific features	Possible cancer	Recommendation
None	Childhood cancer	Take into account the insight and knowledge of parents and carers when considering making a referral for suspected cancer in a child or young person. Consider referral for children if their parent or carer has persistent concern or

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Specific features	Possible cancer	Recommendation
		anxiety about the child's symptoms, even if the symptoms are most likely to have a benign cause. **[2015]**

Pelvic mass

See 'Abdominal or pelvic mass or organomegaly'.

Pelvic pain

See 'Abdominal or pelvic pain'.

Penile mass

See 'Skin or surface symptoms'.

Petechiae

See 'Bruising or petechiae'.

Pigmented lesion

See 'Skin and surface symptoms'

Post menopausal bleeding

Specific features	Possible cancer	Recommendation
None	Endometrial	Refer women using a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause). **[new 2015]**
None	Endometrial	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer in women aged under 55 with post-menopausal bleeding. **[new 2015]**

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Pruritus

Specific features	Possible cancer	Recommendation
None	Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**

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Pyrexia

See ‘Fever’

Recurrent chest infection

See ‘Chest infection’

Rectal bleeding

Specific features	Possible cancer	Recommendation
None	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 50 and have unexplained rectal bleeding. **[new 2015]**
None	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or** • weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**

Rectal mass

See ‘Examination findings (abnormal)’

Reflux (see also ‘Dyspepsia’ and ‘Nausea and vomiting’)

Specific features	Possible cancer	Recommendation
With weight loss	Oesophageal	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people: • with dysphagia **or** • aged 55 and over with weight loss and any of upper abdominal pain or reflux or dyspepsia. **[new 2015]**
With weight loss	Stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who: • are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting **or** • are aged 55 and over with upper abdominal pain, reflux or dyspepsia. **[new 2015]**
None	Stomach	Consider direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 and over with reflux and nausea/vomiting. **[new 2015]**

Satiety

See ‘Appetite loss or early satiety’.

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Signs

See ‘Examination findings (abnormal)’

Shortness of breath

Specific features	Possible cancer	Recommendation
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Hodgkin’s Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin’s lymphoma in people presenting with unexplained lymphadenopathy. When

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Specific features	Possible cancer	Recommendation
		considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**

1 **Skin lesion**

2 See 'Skin or surface symptoms'

3 **Skin or surface symptoms**

Specific features	Possible cancer	Recommendation
None	Melanoma	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) if dermatoscopy suggests malignant melanoma of the skin. **[new 2015]**
None	Melanoma	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for malignant melanoma if they present with a suspicious pigmented skin lesion that has a weighted 7-point checklist score of 3 or more. Major features of the lesions (scoring 2 points each): • change in size • irregular shape • irregular colour. Minor features of the lesions (scoring 1 point each): • largest diameter 7 mm or more • inflammation • oozing • change in sensation. **[new 2015]**
None	Penile	Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer if they have a penile mass or ulcerated lesion, and sexually transmitted infection has been excluded as a cause or a persistent penile lesion after treatment for a sexually transmitted infection has been completed. **[new 2015]**
None	Penile	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for penile cancer in men with unexplained or persistent symptoms affecting the foreskin or glans. **[new 2015]**
None	Anal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for anal cancer in people with an unexplained anal mass or unexplained anal ulceration. **[new 2015]**
None	Basal Cell Carcinoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a skin lesion that raises the suspicion of a basal cell carcinoma if there is

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Specific features	Possible cancer	Recommendation
		concern that a delay may have an unfavourable impact, because of factors such as lesion site or size. **[new 2015]**
None	Basal Cell Carcinoma	Consider routine referral for people if they have a skin lesion that raises the suspicion of a basal cell carcinoma[uu]. **[new 2015]**
None	Squamous Cell Carcinoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for people with a skin lesion that raises the suspicion of squamous cell carcinoma. **[new 2015]**
None	Vulval	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for vulval cancer in women with an unexplained vulval lump, ulceration or bleeding. **[new 2015]**

Splenomegaly

See 'Abdominal or pelvic mass or organomegaly'.

Supraclavicular lymphadenopathy

See 'Lymphadenopathy'.

Sweats

See 'Night sweats'

Testicular symptoms

Specific features	Possible cancer	Recommendation
None	Testicular	Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for testicular cancer if they have a non-painful enlargement or change in shape or texture of the testis. **[new 2015]**
None	Testicular	Consider a direct access ultrasound scan as part of clinical reassessment for testicular cancer in men with unexplained or persistent testicular symptoms. **[new 2015]**

Thrombocytosis

See 'Investigations (abnormal)'

Ulceration – anal

See 'Skin or surface symptoms'

Ulceration – oral

See 'Oral lesions'

Ulceration – vulval

See 'Skin or surface symptoms'

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uu Typical features of basal cell carcinoma include: an ulcer with a raised rolled edge; prominent fine blood vessels around a lesion; or a nodule on the skin (particularly pearly or waxy nodules).

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1 Urological symptoms (excluding haematuria)

Specific features	Possible cancer	Recommendation
None	Bladder	Consider referral for bladder cancer in people aged 60 and over with recurrent or persistent urinary tract infection that is unexplained. **[new 2015]**
None	Ovarian	Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month: • persistent abdominal distension (women often refer to this as 'bloating') • feeling full (early satiety) and/or loss of appetite • pelvic or abdominal pain • increased urinary urgency and/or frequency. **[2011]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer. **[2011]**
None	Prostate	Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention **or** • erectile dysfunction **or** • visible haematuria. **[new 2015]**

2 Vaginal discharge

Specific features	Possible cancer	Recommendation
None	Endometrial	Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with unexplained symptoms of vaginal discharge who: • are presenting with these symptoms for the first time **or** • have thrombocytosis **or** • report haematuria. **[new 2015]**

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3 Vomiting

4 See ‘Nausea or vomiting’.

5 Vulval bleeding

6 See ‘Skin or surface symptoms’.

7 Vulval lump

8 See ‘Skin or surface symptoms’.

9 Vulval ulceration

10 See ‘Skin or surface symptoms’.

11 Weight loss

Specific features	Possible cancer	Recommendation
None	Colorectal, gastro-	For people with unexplained weight loss, which is a symptom

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Specific features	Possible cancer	Recommendation
	oesophageal, lung, prostate, pancreatic or urological cancer	of several cancers including colorectal, gastro-oesophageal, lung, prostate, pancreatic and urological cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely **and** • offer urgent investigation or a suspected cancer pathway referral (for an appointment within 2 weeks). **[new 2015]**
None	Colorectal	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if they are aged over 40 with unexplained weight loss and abdominal pain. **[new 2015]**
None	Colorectal	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in people aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings: • abdominal pain **or** • change in bowel habit **or** • weight loss **or** • iron-deficiency anaemia (haemoglobin levels 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer testing for occult blood in faeces to assess for colorectal cancer in people without rectal bleeding who: • have abdominal pain **or** • have weight loss **or** • are aged under 60 and have a change in bowel habit or iron-deficiency anaemia (with haemoglobin levels of 12 g/dl or below for men and 11 g/dl or below for women). **[new 2015]**
None	Colorectal	Offer a digital rectal examination to people with unexplained symptoms related to the lower gastrointestinal tract. **[2015]**
None	Lung	Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they: • have chest X-ray findings that suggest lung cancer **or** • are aged over 55 with haemoptysis **or** • are aged 40–55, smoke or have smoked in the past, and have haemoptysis **or** • are aged 40–55, have never smoked and have haemoptysis and at least 1 of the following symptoms: o cough o fatigue o shortness of breath o chest pain o weight loss o appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who smoke or have smoked in the past and have any one of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss

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Specific features	Possible cancer	Recommendation
		• appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count and chest X-ray to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any 2 or more of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Lung or Mesothelioma	Offer a full blood count to assess for lung cancer or mesothelioma in people aged 40 and over who have never smoked and have any of the following unexplained symptoms: • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss. **[new 2015]**
None	Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain. **[new 2015]**
None	Non-Hodgkin's Lymphoma	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for non-Hodgkin's lymphoma in people presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **[new 2015]**
None	Oesophageal	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for oesophageal cancer in people: • with dysphagia **or** • aged 55 and over with weight loss and any of upper abdominal pain or reflux or dyspepsia. **[new 2015]**
None	Oesophageal	Consider direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people aged 55 or over with: • weight loss and nausea/vomiting **or** • reflux/dyspepsia and nausea/vomiting **or** • upper abdominal pain and raised platelet count. **[new 2015]**
None	Stomach	Offer urgent direct access upper gastrointestinal endoscopy (within 2 weeks) to assess for stomach cancer in people with weight loss who: • are aged 40 and over with upper abdominal pain lasting 2 weeks or more and nausea/vomiting **or** • are aged 55 and over with upper abdominal pain, reflux or dyspepsia. **[new 2015]**
None	Stomach	Consider direct access upper gastrointestinal endoscopy to

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Specific features	Possible cancer	Recommendation
		assess for stomach cancer in people with weight loss who: • also have appetite loss **or** • are aged under 55 with dyspepsia or upper abdominal pain lasting 2 weeks or more **or** • are aged 55 and over with nausea/vomiting. **[new 2015]**
None	Pancreatic	Consider an urgent direct access CT scan (within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following symptoms: • diarrhoea • back pain • abdominal pain • nausea/vomiting • constipation • new-onset diabetes. **[new 2015]**
None	Ovarian	Measure serum CA125 in primary care in women with symptoms that suggest ovarian. **[2011]**
None	Ovarian	Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue or changes in bowel habit. **[2011]**

1

2

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