Appendix A

Focused Search for the Exceptional review of impact of faecal immunochemical tests research on NICE guidance (NICE guideline NG12 and NICE diagnostics guidance DG30)

Search criteria:

The search approach was broad-based, using search criteria for diagnostic accuracy studies, comparative trials (of triage with FIT), and systematic reviews on FIT for colon cancer published from 2016, according to the review questions and criteria used in NICE diagnostic guidance DG30. We removed any limitations applied for settings and type of population.

However, as in NICE diagnostic guidance DG30 and NICE guidance NG12, we limited the diagnostic accuracy studies to those that used colonoscopy as the reference standard.

Review questions (RQ)

Diagnostic accuracy questions

RQ1. Which investigations of symptoms of suspected colorectal cancer should be done with clinical responsibility retained by primary care? [Review question of NG12 (2005)]

RQ2. What is the accuracy of different quantitative FIT assays, where the target condition is CRC determined by colonoscopy (the reference standard is colonoscopy)? [Review question of DG30 (2016)]

RQ3. What is the predictive accuracy of FIT tests for colorectal cancer? (Where the reference standard is long-term follow up) [NEW review question, clarifying the inclusion criteria of cohort studies in the review question of DG30]

Comparative effectiveness for FIT as triage

RQ4. What is the clinical effectiveness of FIT compared with gFOBT or no triage, for achieving appropriate referral for further investigation within the two-week suspected cancer referral target? [Review question of DG30 (2016)]

Prediction models using FIT

RQ5. What is the diagnostic accuracy of prediction models incorporating FIT test results in detecting colorectal cancer? (The reference standard is colonoscopy, or long term follow up of) [NEW review question]

RQ6. What is the clinical effectiveness of prediction models incorporating FIT tests compared to those without FIT tests, or FIT tests alone? [NEW review question]

Search results

2440 records were found in the broad search.

First sift: Inclusion and exclusion criteria

The initial sifts did not apply any additional study design limitation on diagnostic study designs and allowed for controlled clinical trials for RCTs comparing for questions on clinical effectiveness of FIT as a triage tool. As in the earlier guidelines, diagnostic accuracy studies were only included if colonoscopy were used in reference standard.

This resulted in more than 600 abstracts included as potentially relevant. Some modifications were made to the original inclusion and exclusion criteria based on study design, and relevance of reviews, to further restrict the results to the most relevant and lowest risk of bias study designs.

Second sift: Additional inclusion and exclusion criteria based on study design

1. For **diagnostic accuracy studies**, the following criteria were applied:

- Only cross-sectional studies, where the interval between colonoscopy and FIT test is within as stipulated relatively short period (for example within 1 year) were included. [Applicable for RQ1 & RQ2]
- If a longitudinal follow up (cohort design) was used, and/or a different method of follow up was used for the positive FIT versus negative FIT (for example, colonoscopy versus other investigations), all participants who had the FIT should be followed up for at least two years, regardless of the results of FIT test. [Applicable for RQ3]
- Case control studies, where participants were selected based on known outcome, or health status
- Studies where only the positive or negative FIT results patients were followed up/had colonoscopy (partial follow up).
- Data obtained retrospectively, such as database studies and audits which match patient records of FIT vs development of colorectal cancer (such as colonoscopy results or cancer treatment), unless there is evidence that the database accessed could follow up all patients could be followed up for a sufficient period, such as national databases. [Studies using databases were included if these were used for development or validation of predictive scoring systems – the predictive model review questions, RQ 5 and RQ6].

2. For studies on **using FIT as a triage,** the following criteria were applied:

- Non-randomised controlled trials such as before and after studies, parallel cohort studies or audits were excluded.
- Studies where only the positive or negative FIT results patients were had colonoscopy/actively followed up (partial follow up). For example: studies on interval cancers, where only the negative FIT tests were followed up, or “triage” studies in the NHS which only followed up on the positive cases and reported number of cancers found.

- Modelling studies, which modelled the impact of FIT as a triaging tool. This includes cost-effectiveness modelling studies based on non-RCTs or literature review
- Studies which combined the FIT with another additional test, and the impact of the two tests were indistinguishable

3. For studies on **predictive models using FIT,** the following study designs were excluded:

   - Modelling of the effectiveness of models.
   - Analysis of the relative risks or odds of different characteristics, without a scoring system or model proposed

4. Other inclusion/exclusion criteria applied:

   - Systematic reviews were excluded if the search dates were older than 2016
   - Studies with variations of FIT collection methods (such as two samples) were included

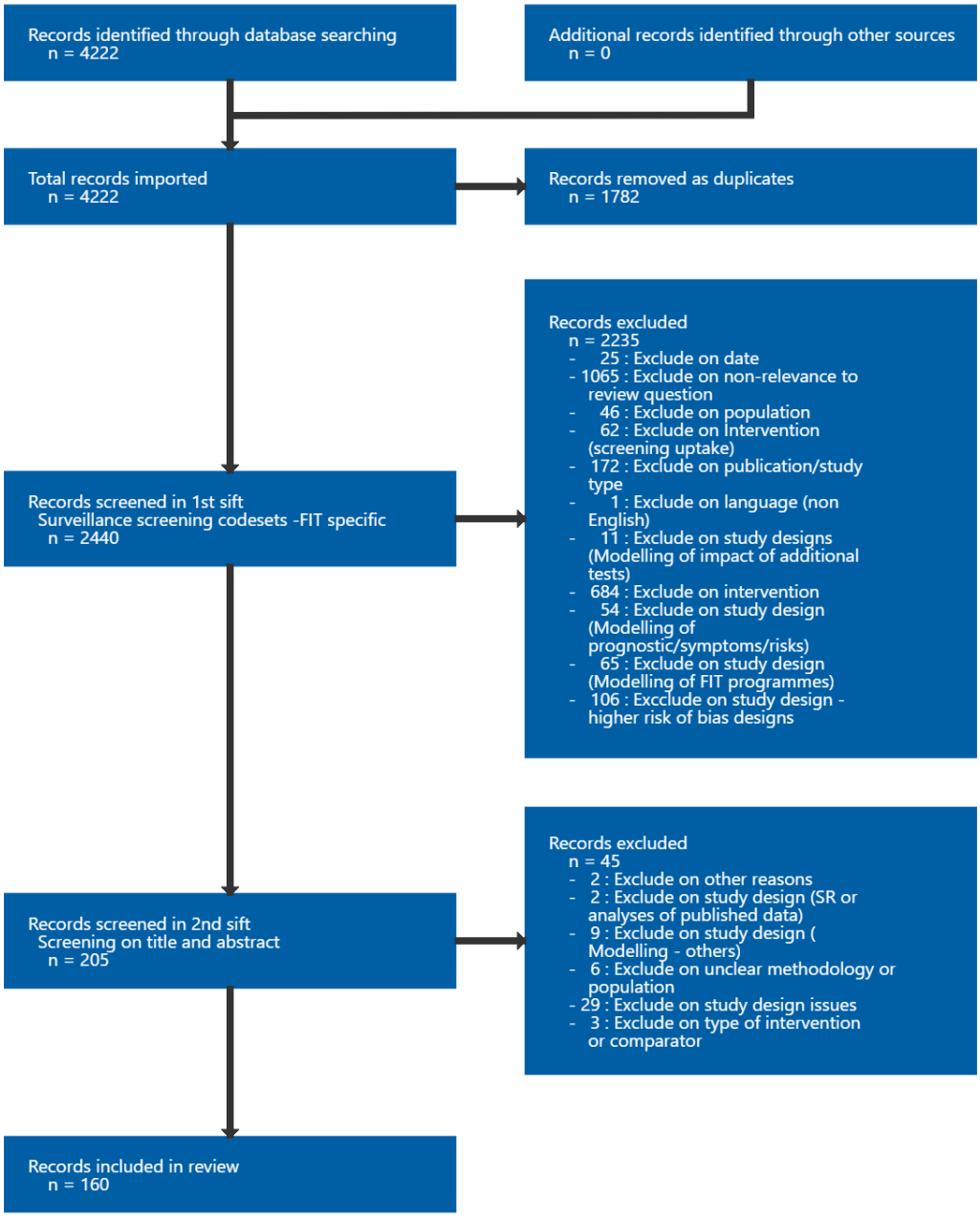
Third Sift – Additional exclusion criteria based on relevance

1. Studies not conducted within the UK, Europe, USA, Canada, New Zealand or Australia were excluded.

2. Studies conducted in screening or asymptomatic patients were excluded. This includes specific populations who maybe at higher risk, but asymptomatic when FIT was applied (for example, screening of CKD patients, or patients with family history).

Inclusion and exclusion of focused search results

PRISMA diagram of the first and second sift



Further exclusions were applied on the 160 short-listed abstracts based on whether participants recruited were symptomatic, and the country of the study in the third sift. Only the results of the 3rd sift were summarised in the Exceptional review.

Results of the third sift on population and location of study

Table 1: Coding of the 160 “included” abstracts in the third sift

Classification of abstract	Number of abstracts
Classification by type of study	
Diagnostic accuracy	75
Predictive accuracy	8
RCT of FIT triage - screening/asymptomatic	19
Prediction model	35
SR of prediction model	2
SR of diagnostic accuracy	25
Notes: 4 abstracts were assigned more than one category	
Classification by symptoms	
Symptomatic	62
Asymptomatic/Screening*	100
Notes: No classification by symptoms could be assigned to the 2 SR of prediction models. 4 SR of diagnostic accuracy included both symptomatic patient and screening studies	
Classification by location (for non-systematic reviews)	
Include – Location - UK, Europe, US, Canada, Australia, and New Zealand	94
Include - Other locations*	39

An abstract may be coded with more than one code if it met several criteria. Each abstract included was coded on symptoms. Non-systematic reviews (SR) were coded for location.

*Abstracts in asymptomatic/screening populations and locations other than UK, Europe, US, Canada, Australia and New Zealand were subsequently excluded.

Studies included after the third sift

Table 2: Diagnostic and predictive accuracy studies of FIT

Study	Comments
1. Auge, Josep Maria, Fraser, Callum G, Rodriguez, Cristina et al. (2016) Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. Clinical chemistry and laboratory medicine 54(1): 125-32	Spain
2. Ayling, Ruth M; Wong, A; Cotter, Finbarr (2021) Use of ColonFlag score for prioritisation of endoscopy in colorectal cancer. BMJ open gastroenterology 8(1)	UK *ColonFlag* *Also excluded for prediction model*
3. Bailey, Sarah E R, Abel, Gary A, Atkins, Alex et al. (2021) Diagnostic performance of a faecal immunochemical test for patients with low-risk symptoms of colorectal cancer in primary care: an evaluation in the South West of England. British journal of cancer 124(7): 1231-1236	UK
4. Chandrapalan, Subashini, Hee, Siew Wan, Widlak, Monika M et al. (2021) Performance of the faecal immunochemical test for the detection of colorectal neoplasms and the role of proton pump inhibitors in their diagnostic accuracy. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 23(7): 1649-1657	UK
5. Chapman, C, Bunce, J, Oliver, S et al. (2019) Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. BJS open 3(3): 395-402	UK
6. Chapman, Caroline J, Banerjea, Ayan, Humes, David J et al. (2021) Choice of faecal immunochemical test matters: comparison of OC-Sensor and HM-JACKarc, in the assessment of patients at high risk of colorectal cancer. Clinical chemistry and laboratory medicine 59(4): 721-728	UK
7. Cruz, A., Carvalho, C.M., Cunha, A. et al. (2021) Faecal diagnostic biomarkers for colorectal cancer. Cancers 13(21): 5568	Spain
8. D'Souza, N, Delisle, T Georgiou, Chen, M et al. (2021) Faecal immunochemical testing in symptomatic patients to prioritize investigation: diagnostic accuracy from NICE FIT Study. The British journal of surgery 108(7): 804-810	UK *NICE-FIT study*
9. D'Souza, Nigel, Georgiou Delisle, Theo, Chen, Michelle et al. (2021) Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study. Gut 70(6): 1130-1138	UK *NICE-FIT study*
10. D'Souza, Nigel, Monahan, Kevin, Benton, Sally C et al. (2021) Finding the needle in the haystack: the diagnostic accuracy of the	UK *NICE-FIT study*

Study	Comments
faecal immunochemical test for colorectal cancer in younger symptomatic patients. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 23(10): 2539-2549	
11. D'Souza, N, Hicks, G, Benton, S C et al. (2020) The diagnostic accuracy of the faecal immunochemical test for colorectal cancer in risk-stratified symptomatic patients. Annals of the Royal College of Surgeons of England 102(3): 174-179	UK
12. Digby, Jayne, Cleary, Shirley, Gray, Lynne et al. (2020) Faecal haemoglobin can define risk of colorectal neoplasia at surveillance colonoscopy in patients at increased risk of colorectal cancer. United European gastroenterology journal 8(5): 559-566	UK
13. Farrugia, A., Widlak, M., Evans, C. et al. (2020) Faecal immunochemical testing (FIT) in symptomatic patients: What are we missing?. Frontline Gastroenterology 11(1): 28-33	UK
14. Godber, Ian M, Todd, Louise M, Fraser, Callum G et al. (2016) Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. Clinical chemistry and laboratory medicine 54(4): 595-602	UK
15. Herrero, Jesus-Miguel, Vega, Pablo, Salve, Maria et al. (2018) Symptom or faecal immunochemical test-based referral criteria for colorectal cancer detection in symptomatic patients: a diagnostic tests study. BMC gastroenterology 18(1): 155	UK *COLONPREDICT study* *Also included for prediction model*
16. Hicks, Georgina, D'Souza, Nigel, Georgiou Delisle, Theo et al. (2021) Using the faecal immunochemical test in patients with rectal bleeding: evidence from the NICE FIT study. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 23(7): 1630-1638	UK *NICE-FIT study*
17. Hogberg, Cecilia, Karling, Pontus, Rutegard, Jorgen et al. (2020) Patient-reported and doctor-reported symptoms when faecal immunochemical tests are requested in primary care in the diagnosis of colorectal cancer and inflammatory bowel disease: a prospective study. BMC family practice 21(1): 129	Swenden
18. ISRCTN49676259 (2017) FIT— Can a Dipstick Test Rule Out Bowel Cancer?. https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN49676259	UK *NICE-FIT study*
19. Khan, A.A.; Klimovskij, M.; Harshen, R. (2020) Accuracy of faecal immunochemical testing in patients with symptomatic colorectal cancer. BJS Open 4(6): 1180-1188	UK
20. Laszlo, Helga E, Seward, Edward, Ayling, Ruth M et al. (2021) Faecal immunochemical test for patients with 'high-risk' bowel symptoms: a large prospective cohort study and updated literature review. British journal of cancer	Norway
21. Lue, A., Hijos, G., Sostres, C. et al. (2020) The combination of quantitative faecal occult blood test and faecal calprotectin is a	Spain

Study	Comments
cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology. Therapeutic Advances in Gastroenterology 13	
22. MacDonald, S., MacDonald, L., Godwin, J. et al. (2021) The diagnostic accuracy of the faecal immunohistochemical test in identifying significant bowel disease in a symptomatic population. Colorectal Disease	UK
23. Maclean, William, Mackenzie, Paul, Limb, Chris et al. (2021) Diagnostic accuracy of point of care faecal immunochemical testing using a portable high-speed quantitative analyser for diagnosis in 2-week wait patients. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 23(9): 2376-2386	UK
24. Navarro, M., Hijos, G., Sostres, C. et al. (2020) Reducing the Cut-Off Value of the Fecal Immunochemical Test for Symptomatic Patients Does Not Improve Diagnostic Performance. Frontiers in Medicine 7: 410	Spain
25. Rutka, Mariann, Bor, Renata, Balint, Anita et al. (2016) Diagnostic Accuracy of Five Different Fecal Markers for the Detection of Precancerous and Cancerous Lesions of the Colorectum. Mediators of inflammation 2016: 2492081	Hungary
26. Schwettmann, L.; Lied, A.; Eriksen, R. (2022) Evaluation of the Sentinel-FOB gold faecal immunochemical test for the presence of haemoglobin using the automated Roche Cobas 8000 system. Practical Laboratory Medicine 29: e00263	Norway
27. Tsapournas, Georgios, Hellstrom, Per M, Cao, Yang et al. (2020) Diagnostic accuracy of a quantitative faecal immunochemical test vs. symptoms suspected for colorectal cancer in patients referred for colonoscopy. Scandinavian journal of gastroenterology 55(2): 184-192	Sweden
28. Turvill, James L, Turnock, Daniel, Cottingham, Dan et al. (2021) The Fast Track FIT study: diagnostic accuracy of faecal immunochemical test for haemoglobin in patients with suspected colorectal cancer. The British journal of general practice : the journal of the Royal College of General Practitioners 71(709): e643-e651	UK *Fast Track FIT study*
29. Turvill, James, Mellen, Samantha, Jeffery, Laura et al. (2018) Diagnostic accuracy of one or two faecal haemoglobin and calprotectin measurements in patients with suspected colorectal cancer. Scandinavian journal of gastroenterology 53(12): 1526-1534	UK
30. Widlak, M M, Neal, M, Daulton, E et al. (2018) Risk stratification of symptomatic patients suspected of colorectal cancer using faecal and urinary markers. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 20(12): o335-o342	UK
31. Widlak, M M, Thomas, C L, Thomas, M G et al. (2017) Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and	UK

Study	Comments
adenoma in symptomatic patients. Alimentary pharmacology & therapeutics 45(2): 354-363	
32. Mowat, Craig, Digby, Jayne, Strachan, Judith A et al. (2021) Faecal haemoglobin concentration thresholds for reassurance and urgent investigation for colorectal cancer based on a faecal immunochemical test in symptomatic patients in primary care. Annals of clinical biochemistry 58(3): 211-219	UK
33. Nicholson, B.D., James, T., East, J.E. et al. (2019) Experience of adopting faecal immunochemical testing to meet the NICE colorectal cancer referral criteria for low-risk symptomatic primary care patients in Oxfordshire, UK. Frontline Gastroenterology 10(4): 347-355	UK
34. Pin-Vieito, Noel, Garcia Nimo, Laura, Bujanda, Luis et al. (2021) Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study. United European gastroenterology journal 9(2): 256-267	Spain

Table 3: Predictive models using FIT

Study	Comments
1. Ayling, Ruth M; Lewis, Stephen J; Cotter, Finbarr (2019) Potential roles of artificial intelligence learning and faecal immunochemical testing for prioritisation of colonoscopy in anaemia. British journal of haematology 185(2): 311-316	*COLONFLAG* *Also included for diagnostic accuracy*
2. Ayling, Ruth M; Wong, A; Cotter, Finbarr (2021) Use of ColonFlag score for prioritisation of endoscopy in colorectal cancer. BMJ open gastroenterology 8(1)	*COLONFLAG*
3. Bujanda, L., Sarasqueta, C., Vega, P. et al. (2018) Effect of aspirin on the diagnostic accuracy of the faecal immunochemical test for colorectal advanced neoplasia. United European Gastroenterology Journal 6(1): 123-130	*COLONPREDICT*
4. Cubiella, Joaquin (2020) Not so FAST. Commentary on the article "Appraisal of the faecal haemoglobin, age and sex test (FAST) score in assessment of patients with lower bowel symptoms: an observational study". BMC gastroenterology 20(1): 231	*FAST*
5. Cubiella, Joaquin, Digby, Jayne, Rodriguez-Alonso, Lorena et al. (2017) The fecal hemoglobin concentration, age and sex test score: Development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients. International journal of cancer 140(10): 2201-2211	*FAST*
6. Cubiella, Joaquin, Vega, Pablo, Salve, Maria et al. (2016) Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC medicine 14(1): 128	*COLONPREDICT*
7. Digby, Jayne, Strachan, Judith A, Mowat, Craig et al. (2019) Appraisal of the faecal haemoglobin, age and sex test (FAST) score in assessment of patients with lower bowel symptoms: an observational study. BMC gastroenterology 19(1): 213	*FAST score*
8. Elias, S.G., Kok, L., de Wit, N.J. et al. (2016) Is there an added value of faecal calprotectin and haemoglobin in the diagnostic work-up for primary care patients suspected of significant colorectal disease? A cross-sectional diagnostic study. BMC Medicine 14(1): 141	*Dutch model*
9. Fernandez-Banares, Fernando, Cleries, Ramon, Boadas, Jaume et al. (2019) Prediction of advanced colonic neoplasm in symptomatic patients: a scoring system to prioritize colonoscopy (COLONOFIT study). BMC cancer 19(1): 734	*COLONOFIT*
10. Herrero, Jesus-Miguel, Vega, Pablo, Salve, Maria et al. (2018) Symptom or faecal immunochemical test based referral criteria for colorectal cancer detection in symptomatic patients: a diagnostic tests study. BMC gastroenterology 18(1): 155	*COLONPREDICT & FAST* *Also included for diagnostic accuracy*

Table 4: Systematic reviews of diagnostic accuracy of symptomatic patients and prediction models

Study	Code [Reason]
1. Chandrapalan, Subashini, Bosch, Sofie, Cubiella, Joaquin et al. (2021) Systematic review with meta-analysis: volatile organic compound analysis to improve faecal immunochemical testing in the detection of colorectal cancer. Alimentary pharmacology & therapeutics 54(1): 14-23	SR of symptomatic patients (diagnostic accuracy)
2. Jung, Y.S.; Im, E.; Park, C.H. (2021) Impact of antiplatelet agents and anticoagulants on the performance of fecal immunochemical tests: a systematic review and meta-analysis. Surgical Endoscopy	SR of symptomatic patients (diagnostic accuracy)
3. Katsoula, Anastasia, Paschos, Paschalis, Haidich, Anna-Bettina et al. (2017) Diagnostic Accuracy of Fecal Immunochemical Test in Patients at Increased Risk for Colorectal Cancer: A Meta-analysis. JAMA internal medicine 177(8): 1110-1118	SR of symptomatic patients (diagnostic accuracy)
4. Lee, Mindy Winghin; Pourmorady, Jonathan S; Laine, Loren (2020) Use of Fecal Occult Blood Testing as a Diagnostic Tool for Clinical Indications: A Systematic Review and Meta-Analysis. The American journal of gastroenterology 115(5): 662-670	SR of symptomatic patients (diagnostic accuracy)
5. Lu, M., Luo, X., Li, N. et al. (2019) Diagnostic accuracy of fecal occult blood tests for detecting proximal versus distal colorectal neoplasia: A systematic review and meta-analysis. Clinical Epidemiology 11: 943-954	SR of symptomatic patients (diagnostic accuracy)
6. Nasir Kansestani, Atefeh, Zare, Mohammad Erfan, Tong, Qingchao et al. (2022) Comparison of faecal protein biomarkers' diagnostic accuracy for colorectal advanced neoplasms: a systematic review and meta-analysis. Scientific reports 12(1): 2623	SR of symptomatic patients (diagnostic accuracy)
7. Niedermaier, Tobias; Balavarca, Yesilda; Brenner, Hermann (2020) Stage-Specific Sensitivity of Fecal Immunochemical Tests for Detecting Colorectal Cancer: Systematic Review and Meta-Analysis. The American journal of gastroenterology 115(1): 56-69	SR of symptomatic patients (diagnostic accuracy)
8. Pin Vieito, Noel; Zarraquinos, Sara; Cubiella, Joaquin (2019) High-risk symptoms and quantitative faecal immunochemical test accuracy: Systematic review and meta-analysis. World journal of gastroenterology 25(19): 2383-2401	SR of symptomatic patients (diagnostic accuracy)
9. Pin-Vieito, N., Tejido-Sandoval, C., De Vicente-Bielza, N. et al. (2021) Faecal immunochemical tests safely enhance rational use of resources during the assessment of suspected symptomatic colorectal cancer in primary care: Systematic review and meta-analysis. Gut	SR of symptomatic patients (diagnostic accuracy)

Study	Code [Reason]
10. Saw, K.S., Liu, C., Xu, W. et al. (2022) Faecal immunochemical test to triage patients with possible colorectal cancer symptoms: meta-analysis. The British journal of surgery 109(2): 182-190	SR of symptomatic patients (diagnostic accuracy)
11. Stonestreet, J, Chandrapalan, S, Woolley, D et al. (2019) Systematic review and meta-analysis : diagnostic accuracy of faecal immunochemical testing for haemoglobin (FIT) in detecting colorectal cancer for both symptomatic and screening population. Acta gastro-enterologica Belgica 82(2): 291-299	SR of symptomatic patients (diagnostic accuracy)
12. Medina-Lara, Antonieta, Grigore, Bogdan, Lewis, Ruth et al. (2020) Cancer diagnostic tools to aid decision-making in primary care: mixed-methods systematic reviews and cost-effectiveness analysis. Health technology assessment (Winchester, England) 24(66): 1-332	SR of prediction model
13. van de Veerdonk, Wessel, Hoeck, Sarah, Peeters, Marc et al. (2019) Towards risk-stratified colorectal cancer screening. Adding risk factors to the fecal immunochemical test: Evidence, evolution and expectations. Preventive medicine 126: 105746	SR of prediction model

Relevant ongoing/unpublished studies funded by the NIHR (National Institute of Health and Care Research)

Project title	**Start - end date**	**Short summary of project**
COLOFIT - Optimal use of Faecal Immunochemical Testing for patients with symptoms of possible colorectal cancer.	Nov 21 – May 23	A study with five work programmes to develop and test an algorithm incorporating FIT and other factors for the diagnosis of CRC (symptomatic patients).
RECEDE Study: REducing Colonoscopies in patients without significant bowEl DiseasE	May 20 – Oct 23	Comparing using Urine VOCs plus FIT vs FIT alone
Impact of COVID-19 on colorectal cancer screening in England	Ended Jul 21	Modelling the impact of pausing CRC screening during the pandemic
Quantitative faecal immunochemical tests (FIT) to guide referral in primary care for people with a change in bowel habit or abdominal pain	Ended Jan 21	Quantitative faecal immunochemical tests to guide referral in primary care for people with a change in bowel habit or abdominal pain [Systematic review for DAP50]