Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and cost-effectiveness analysis

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Scientific summary

Faecal immunochemical tests for suspected colorectal cancer

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Scientific summary

Background

The primary indication for this assessment is the use of tests for the presence of occult blood in the faeces as a triage step in the investigation of people presenting in primary care settings with lower abdominal symptoms, in whom investigation for possible colorectal cancer (CRC) is being considered.

Quantitative faecal immunochemical tests (FITs) use antibodies that specifically recognise the globin of human haemoglobin (Hb) to determine the amount of Hb that is present in a faecal sample. Four FIT assays for Hb [OC-Sensor (Eiken Chemical Co./MAST Diagnostics, Tokyo, Japan), HM-JACKarc (Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan), FOB Gold (Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy), RIDASCREEN Hb, R-Biopharm, Darmstadt, Germany)] and one FIT assay for human Hb–haptoglobin (Hp) complex (RIDASCREEN Hb/Hp complex, R-Biopharm) are currently available for use in the UK NHS in England and Wales. Quantitative FIT assays the estimation of quantities of blood that are not detectable by normal visual inspection.

Faecal immunochemical testing has been approved for the Scottish Bowel Screening Programme and has recently been approved for use in the NHS Bowel Cancer Screening Programme in England. This assessment considers the clinical effectiveness and cost-effectiveness of FIT assays, used at various thresholds, in symptomatic populations.

Objectives

To assess the clinical effectiveness and cost-effectiveness of testing for the presence of occult blood in faeces, using quantitative faecal immunochemical testing, as a triage test, for people presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC.

Methods

Assessment of clinical effectiveness

Thirteen databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched to March 2016. Search results were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Study quality was assessed using QUADAS-2 and PROBAST (Prediction model study Risk Of Bias Assessment Tool). The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC curves for meta-analyses involving four or more studies. For meta-analyses with fewer than four studies, we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression. Analyses were conducted separately for each FIT assay, threshold and target condition {CRC, advanced neoplasia [CRC or high-risk adenoma (HRA)] or significant bowel disease (CRC or HRA or inflammatory bowel disease)} for which data were available.

Assessment of cost-effectiveness

A de novo health economic model was developed to explore the cost-effectiveness of using faecal immunochemical testing for Hb as a triage step in the investigation of symptomatic people presenting in primary care who are at low risk of CRC. The cost-effectiveness of faecal immunochemical testing was

compared with guaiac faecal occult blood tests (gFOBTs) and no triage (referral straight to colonoscopy). The model consists of three parts: a decision model reflecting the diagnosis of colorectal cancer; a Markov state-transition model to estimate long-term costs and the effects [life-years (LYs) and quality-adjusted life-years (QALYs)] associated with the treatment and progression of CRC; and a Markov state-transition model to estimate the LYs and QALYs associated with those who do not have CRC. The following strategies were included in the main economic analysis:

- triage using OC-Sensor at a threshold of 10 µg Hb/g faeces
- triage using HM-JACKarc at a threshold of 10 µg Hb/g faeces
- triage using guaiac faecal occult blood testing
- no triage (referral straight to colonoscopy).

The model was largely based on that used in the National Institute for Health and Care Excellence (NICE) guideline [National Collaborating Centre for Cancer. *Suspected Cancer*: *Recognition and Referral*. NG12. London: NCC-C; 2015. URL: www.nice.org.uk/guidance/ng12/evidence/full-guidance-74333341 (accessed 13 January 2016)], but with diagnostic accuracy data coming from the systematic review that was used to inform the assessment of effectiveness. When available, data were obtained from the most recent published sources, although expert opinion was required to inform some parameters. Any differences in costs between the tests in patients without CRC were assumed to occur only in the first year. Any differences in life expectancy between tests for patients without CRC were assumed to be due only to difference in mortality due to colonoscopy/computed tomography colonography (CTC). A negative FIT or gFOBT results in a watchful waiting strategy, in which a colonoscopy/CTC will be performed when symptoms persist, which is assumed to occur with all patients with CRC. All of the unit cost data on faecal immunochemical testing were obtained from manufacturers where supplied.

The uncertainty about the model input parameters and the potential impact on the model results were explored by scenario, one-way deterministic and probabilistic sensitivity analyses.

Results

Assessment of clinical effectiveness

Ten studies (25 publications and two unpublished manuscripts) were included in the systematic review. The main potential sources of bias in the included studies related to patient spectrum and patient flow (numbers of patients who did not return a FIT sample or who were subsequently excluded). All of the included studies had concerns about the applicability of the population, as no study reported data for a population that exactly matched that defined in the scope for this assessment.

When faecal immunochemical testing was based on a single faecal sample and a threshold of 10 µg Hb/g faeces, sensitivity estimates indicated that a negative result using either OC-Sensor and HM-JACKarc may be considered adequate to rule out CRC; the summary estimate of sensitivity for OC-Sensor was 92.1% (95% CI 86.9% to 95.3%), based on four studies, and the only study of HM-JACKarc to assess the 10 µg Hb/g faeces threshold reported a sensitivity of 100% (95% CI 71.5% to 100%). The corresponding specificity estimates were 85.8% (95% CI 78.3% to 91.0%) and 76.6% (95% CI 72.6% to 80.3%), respectively. (Confidential information has been removed.)

Where a lower diagnostic threshold was considered, that is, the target condition included HRA as well as CRC, the rule-out performance of all FIT methods was reduced. For faecal immunochemical testing based on a single faecal sample and a threshold of 10 µg Hb/g faeces, the sensitivity estimates indicated that neither a negative OC-Sensor nor a negative HM-JACKarc FIT would be likely to be considered to have adequate rule-out performance; the summary estimate of sensitivity for OC-Sensor was 62.9% (95% CI 55.9% to 69.4%), based on three studies, and the estimate of sensitivity for HM-JACKarc was 70.0%

(95% CI 50.6% to 85.3%), based on one study. The corresponding specificity estimates were 84.6% (95% CI 82.8% to 86.2%) and 77.8% (95% CI 73.8% to 81.4%), respectively.

Triage using faecal immunochemical testing at thresholds of around 10 µg Hb/g faeces has the potential to correctly rule out CRC and avoid colonoscopy in approximately 75% of symptomatic patients. In addition, the relatively high proportion of FIT false positives (FPs) that are observed when the target condition is CRC may be mitigated by the detection of other bowel pathologies in these patients. Based on data from the studies included in our systematic review, between 22.5% and 93% of patients with a positive FIT and no CRC will have other significant bowel pathologies.

No studies were identified which assessed the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients.

No studies were identified which directly compared the performance of different FIT assays, or which compared one or more FIT assays with a gFOBT method.

Assessment of cost-effectiveness

The results of the base-case analysis suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the no-triage strategy (referral straight to colonoscopy) is the most expensive. Overall, faecal immunochemical testing was cost-effective when compared with no triage. This was either because the latter was dominated (less effective and more costly) or because faecal immunochemical testing was slightly less effective, but cheaper, than no triage. In this case the cost savings could be said to 'outweigh' the slight loss in QALYs. When the comparator was guaiac faecal occult blood testing, the cost-effectiveness results showed that faecal immunochemical testing was more effective and more costly than guaiac faecal occult blood testing, but the incremental cost-effectiveness ratios (ICERs) obtained were below the common threshold ICER of £30,000 and thus faecal immunochemical testing remained cost-effective.

The results of the different scenario analyses did not differ substantively from the base-case results. The scenarios for which the accuracy estimates for guaiac faecal occult blood testing were based on studies that were considered more representative of the population of this diagnostic assessment were more favourable than the base-case with regard to faecal immunochemical testing. In only two scenarios would faecal immunochemical testing not be considered cost-effective because the ICER exceeded the £30,000 threshold. The highest ICER was obtained when OC-Sensor was compared with guaiac faecal occult blood testing when a threshold of any detectable Hb was assumed for faecal immunochemical testing (£65,192). This was expected, as reducing the threshold for FIT results in the test being less effective in avoiding colonoscopies, that is, this threshold is associated with the highest number of FPs. When HM-JACKarc was compared with guaiac faecal occult blood testing in the scenario with high mortality due to colonoscopy the ICER was £45,271.

Conclusions

Implications for service provision

There is evidence to suggest that triage using faecal immunochemical testing, when used at a threshold of 10 µg Hb/g faeces for OC-Sensor or HM-JACKarc, may be sufficient to rule out CRC in symptomatic patients. In addition, the relatively high proportion of FIT FPs observed when the target condition is CRC may be mitigated by the potential to diagnose other bowel pathologies in these patients. There was insufficient evidence to adequately assess the diagnostic performance of FOB Gold, RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients. Similarly, there was no direct evidence about the comparative performance of different FIT assays, or faecal immunochemical testing versus guaiac faecal occult blood testing.

The base-case cost-effectiveness results suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the no-triage strategy (referral to colonoscopy) is the most expensive. Overall, faecal immunochemical testing was cost-effective when compared against no triage or guaiac faecal occult blood testing. The results of the different scenario analyses did not differ substantially from the base-case results. However, the scenarios for which the accuracy estimates for guaiac faecal occult blood testing were based on studies that were considered more representative of the population of this diagnostic assessment were more favourable than the base-case scenario with regard to faecal immunochemical testing. The results of our analysis suggest that faecal immunochemical testing could provide a cost-effective (cost-saving) triage option for patients whose symptoms are not considered high risk for CRC.

Suggested research priorities

New studies are needed to fully evaluate the performance of faecal immunochemical testing in the setting (primary care) and population (symptomatic patients who are at low risk of CRC, as defined in NG12) specified in the scope for this assessment. Further research (diagnostic cohort studies or multivariable prediction modelling studies) is needed to fully explore possible variation in the performance of faecal immunochemical testing in relevant subgroups (e.g. age and sex) and explore the possible advantages of using faecal immunochemical testing as part of a risk score. Studies that can fully explore the potential benefits of faecal immunochemical testing in symptomatic patients, including those relating to diagnoses other than CRC, are also likely to be informative. This issue may be particularly important in younger patients, where the prevalence of CRC is lowest and other diagnoses are more likely.

Study registration

This study is registered as PROSPERO CRD42016037723.

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