Establishing the optimum threshold value for haemoglobin in faecal immunochemical tests (FITs) for use in the primary care symptomatic population: South West Cancer Alliance FIT programme evaluation

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Lay Summary

Colorectal cancer is the fourth most common cancer in the UK, and the second leading cause of cancer-related deaths. Diagnosing colorectal cancer is difficult, as the symptoms are the same as many non-cancerous conditions.

The NICE guideline NG12 (2015) recommends that patients consulting their GP with 'alarm' symptoms of colorectal cancer are urgently referred for colonoscopy. However, not all patients with colorectal cancer have these alarm symptoms. Many have vague low-risk symptoms that do not warrant a colonoscopy under NG12. In 2017, a new NICE guidance DG30 suggested that faecal immunochemical tests (FITs) are used for patients with these vague symptoms that could suggest colorectal cancer, but do not represent a great enough risk for an urgent referral. FITs measure the amount of haemoglobin (Hb) in a stool sample. A high level of Hb in a stool sample may suggest bleeding in the bowel caused by cancer. However, we don't know how high Hb in the stool should be before the patient is offered a colonoscopy, when the patient has these vague symptoms.

In this study, our primary aims are 1) to determine the optimum cut off point for Hb in FITs in a symptomatic primary care population, and 2) to estimate the diagnostic performance of FITs at detecting cancer in a symptomatic primary care population.

In the South West, FITs have been in use since June 2018. We will collect data on all FITs performed in the region during the 18-month study period. This will include the amount of Hb present in the patients' samples, whether or not they were referred for colonoscopy, patient demographic data, the type of FIT used, and whether or not the patient was diagnosed with colorectal cancer within one year of their FIT. We will also collect data on the number and type of referrals and diagnoses in the region during the study period, and the number of FITs ordered from primary care during that time. We estimate that around 30,000 FITs will be performed during the data collection period.

This study will be complemented by a narrative review providing an overview of FIT use across the globe in primary care symptomatic patients, and a health economics study to evaluate the cost implications of FITs.

Aims and objectives

1.1. To determine the optimum cut off point for FITs for the detection of colorectal cancer in a symptomatic primary care population.

1.2. To determine the diagnostic performance of FITs at detecting cancer in a symptomatic primary care population by estimating the sensitivity, specificity, PPV, and NPV of the test.

Background

Recently, the NICE guidance DG30 'approved' FIT for use in primary care for persons aged 18 years and over with symptoms potentially indicative of colorectal cancer, without rectal bleeding, who do not meet NICE criteria for urgent referral under the suspected cancer pathway.(1) Faecal immunochemical tests (FITs) measure the amount of haemoglobin (Hb) in a stool sample and can be

used to identify possible colorectal cancer. An abnormally high level of Hb suggests bleeding in the lower GI tract, a clinical feature of several pathologies, including colorectal cancer. An abnormal FIT will generally be followed up with further diagnostic testing, usually a colonoscopy. FITs are considered to be superior to the faecal occult blood test (FOBT); the former require only one stool sample, are not sensitive to any dietary factors or medications, and have higher uptake rates than FOB, so appear more acceptable to patients. There is also evidence in some populations that the FIT is a more sensitive test for colorectal cancer than the FOBT.

NICE guidance for FITs (DG30) presents a review of studies of the diagnostic performance of various FIT assays, but much (if not all) of the evidence presented is from screening or secondary care-based studies. The spectrum effect (the variation in measures of test performance by the prevalence and distribution of disease in the test population)(2) means that the diagnostic performance achieved in those studies may not apply to the symptomatic primary care population. The underlying prevalence of colorectal cancer will be higher in the secondary care population (and lower in an asymptomatic population undergoing screening) than it will be in the symptomatic primary care population. It may not be valid to apply the evidence identified in DG30 to primary care FITs. Additionally, commonly used threshold values for Hb in studies of FIT performance are 50 or 100 ng/ml (ng of Hb per ml of suspension), but there is a high level of between-study variation in this and other features. The NICE guidance (DG30) suggests a threshold of 10ng/ml to be deemed 'positive', and thus warranting definitive investigation.

Many studies of FIT performance focus on its potential as a screening tool in asymptomatic patients. To date, only one study has specifically investigated the diagnostic performance and optimum cut off for FIT in a symptomatic primary care population (3); furthermore, it is difficult to draw any conclusions from the current literature due to variation in study settings and samples, recruitment strategies, definitions of symptomatic, thresholds, assays, and other factors. Determining the optimum threshold in a primary care population will enable FITs to be used as triage tests to stratify patients by risk and aid GPs in selecting only those with a high risk of colorectal cancer for colonoscopy (current models of care cannot support the sharp increases in urgent referrals to colonoscopy seen over the last few years).(4) Therefore, with the NICE guidance DG30, we are on the cusp of a giant national experiment. There is an urgent need to develop a policy for use of FIT for symptomatic patients in primary care that is safe in terms of the threshold used for an abnormal value (the balance between sensitivity and specificity; not missing significant numbers of colorectal cancers whilst protecting endoscopic services from overload with healthy patients), and is acceptable to primary care physicians and patients, therefore likely to have a high rate of acceptance when offered.

The two South West Cancer Alliances (Peninsula Cancer Alliance, and Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance) have been funded by NHS England to roll out and evaluate FITs in primary care in their region. The geographical area covers ten CCGs with a total patient population of 4,376,696. FITs will be offered in the area for a period of 18 months; the expected demand for FITs is 52,000 per year. Testing will be carried out by the Exeter Blood Sciences Laboratory at the Royal Devon and Exeter (RD&E) and The Clinical Biochemistry Department in Bristol, which is part of Severn Pathology. The present study will be carried out in collaboration with the South West Cancer Alliance to establish the optimum Hb threshold for FITs in primary care, and to evaluate the diagnostic performance of FITs.

Study design and population

A cohort study comprising patients who have had a FIT within the study period. Patients will be aged 18 years and over, who have a primary care-ordered FIT at a participating laboratory. As DG30 recommends FIT testing for patients with symptoms that indicate colorectal cancer (but do not

qualify for referral), it is to be expected that patients in the study sample will be symptomatic (although this may not always be the case – we may consider a sub-study reviewing GP notes to identify any cases of quasi-screening). Entry to the study will be at the point of the FIT being carried out.

FIT will be offered in primary care to patients who meet the criteria set out in NICE Guidance (NG12) in the Appendix.

Sample size

As this is a 'natural experiment' we cannot determine in advance the number of FITs that will be carried out during the 18-month study period. We expect the final number to be in excess of 30,000. If 2% of those tested have cancer we would expect 95% confidence intervals around an estimated AUC of 0.9 to be 0.883 to 0.917. If only 1% have cancer these will widen to 0.877 to 0.923. If 1 % of those tested have cancer 95% confidence intervals from 0.85 to 0.95 could be achieved with a sample size of 6500.

Data collection

FIT testing packs are distributed to GPs from the two labs, and then given directly to patients by the GPs at the time of consultation. Patients complete the test at home and then return their samples directly to the lab by post. Results will be electronically transmitted to GPs, reported on the same day of processing. GPs will receive both the numerical value of the test result, and a 'positive or negative', based on the 10ng/ml threshold.

The exposure variable will be the patients' FIT result (a continuous numerical value), and the assay type used by the laboratory. Only OC Sensor and HM-JACKarc are being used. This is crucial, as assays differ in their lower thresholds for detecting Hb. There is variation between assays in how the samples are prepared which affect the value that is returned – and so the optimum threshold value for further investigation. Covariates will include patient age and sex. Further patient data may be available for patients in the Peninsula Cancer Alliance; they have a local database of patient data. We are currently exploring access to these data.

The primary outcomes of interest will be diagnoses of colorectal cancer or pre-colorectal cancer (low, intermediate-risk adenomas according to UK guidelines, defined as 1-2 large (≥10 mm) adenomas, or 3-4 small adenomas, or high-risk adenoma), collected from local cancer registries. All cancers diagnosed within the study period will be requested from registries, and matched to patients who had a FIT, to determine which patients receive a diagnosis. We will also collect diagnoses of other serious bowel disease (inflammatory bowel disease) if possible. The time at which these diagnoses are made relative to the FIT will be captured; patient follow-up will span one year to capture all incident cases and to estimate false negative rates associated with different Hb threshold values.

Statistical analysis

The primary aim of this study is to determine the optimum cut off point for FITs in a symptomatic primary care population. A Receiver Operating Characteristic (ROC) curve analysis will be used to address this aim in the entire study population and with subgroup analyses by age and sex. Initially this will include all patient data; the analysis may be stratified by assay type if we collect sufficient data. The power calculation suggests this will be possible. NICE approved assays are OC Sensor, HM-JACKarc, and FOB Gold; only the first two of these are being used in the SW region. We hope to be

able to establish diagnostic performance measures for different thresholds, for the two different assays.

We will estimate the threshold FIT level with a positive predictive value (PPV) of 3%, overall and per assay-type. We will also examine other thresholds and their associated PPVs (as our previously published work suggests that the public would request colonoscopy at risks as low as 1%). Currently available FITs are only able to report Hb values as low as 10ng/ml, which may limit the scope of this aspect of the study.

Our second aim of determining the diagnostic performance of FITs in the symptomatic primary care population will be achieved by estimating the sensitivity, specificity, PPV, and NPVs of the test. This will be achieved with a 2x2 table approach.

Further work

The work described above will be complemented by a qualitative study (possibly carried out in collaboration with the Policy Research Unit). This will investigate (1) GP awareness of the guideline approving use of FIT in primary care; (2) reported use of FIT in primary care, which will be cross-checked with the volume of use in the threshold study; and (3) GP and patient attitudes and perceptions of the FIT test in the diagnostic toolkit. We also propose qualitative research involving open-ended interviews of both practitioners and patients on attitudes and perceptions of diagnosis of bowel cancer and specifically faecal testing in the diagnostic setting. These results will further inform experimental work using vignettes to investigate GP decision making and influences thereon following the availability of FIT.

References

1. NICE. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care [DG30] [Internet]. 2017. Available from: https://www.nice.org.uk/guidance/dg30/chapter/1-Recommendations
2. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. BMJ. 2016;353.
3. Kok L, Elias SG, Witteman BJM, Goedhard JG, Muris JWM, Moons KGM, et al. Diagnostic accuracy of point-of-care fecal calprotectin and immunochemical occult blood tests for diagnosis of organic bowel disease in primary care: The cost-effectiveness of a decision rule for abdominal complaints in primary care (CEDAR) study. Clin Chem. 2012;58(6):989–98.
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Appendix. NG12 colorectal cancer guidelines, as changed after the introduction of DG30

The original NG12, published before DG30, detailed specific symptom groups deemed eligible for testing for occult blood in faeces. This was in the 'old' paragraph 1.3.4. The 'new' 1.3.4 does not detail which symptoms are to be used; rather it leaves it to the GP's judgement.

Colorectal cancer

1.3.1 Refer adults using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if:

- they are aged 40 and over with unexplained weight loss and abdominal pain **or**
- they are aged 50 and over with unexplained rectal bleeding **or**
- they are aged 60 and over with:
  - iron-deficiency anaemia **or**
  - changes in their bowel habit, **or**
- tests show occult blood in their faeces. **[new 2015]**

1.3.2 Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults with a rectal or abdominal mass. **[new 2015]**

1.3.3 Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults aged under 50 with rectal bleeding **and** any of the following unexplained symptoms or findings:

- abdominal pain
- change in bowel habit
- weight loss
- iron-deficiency anaemia. **[new 2015]**

1.3.4 This recommendation has been replaced by our diagnostics guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. The diagnostics guidance recommends tests for occult blood in faeces, for people without rectal bleeding but with unexplained symptoms that do not meet the criteria for a suspected cancer pathway referral in recommendations 1.3.1 to 1.3.3.