Testing for colorectal cancer: a focus on FIT technology

Quantitative faecal immunochemical testing looks set to reassure patients and clinicians concerned about colorectal cancer. Reducing referrals, colonoscopy investigations and overall waiting times, FIT enables GPs to manage patients confidently in primary care.

Approximately 41,000 people are diagnosed with colorectal cancer (CRC) in the UK each year.[1] The prognosis is better in those with early-stage cancerous lesions or advanced adenomas (the pre-cancerous stages), with over 90% of cases being treated successfully following early detection. Diagnosing CRC is a complex process, typically starting with patients reporting to their GP with symptoms, subsequent referral for a gastroenterology consultation, a colonoscopy investigation and biopsy confirmation from histopathology.

To address reports that relative cancer survival rates are lower in the UK compared with other European countries, rapid diagnostic and treatment pathways were proposed as part of the 2000 National Health Service (NHS) Cancer Plan. This included an urgent 14-day referral pathway (known as the 'two-week wait') for an out-patient gastrointestinal (GI) consultation for patients presenting to their GP with 'Red Flag' symptoms.[2,3] This pathway continues in secondary care where patients are investigated, and treatment commences within 62 days of the out-patient GI consultation.[4]

To refer patients with suspected CRC selectively in a primary care setting is immensely challenging. Patients present to their GP with a range of symptoms including weight loss, abdominal pain, unusual bowel motions, rectal bleeding and anaemia. Although these are often considered to be key risk factors for CRC, such symptoms are also indicative of more common conditions, resulting in a low positive predictive value.[5]

The National Institute for Health and Care Excellence (NICE) costing statement reported 209,625 primary care referrals in 2013–14 under the 14-day pathway for lower GI investigation.[6] This demand on colonoscopy resources is increasing by 10% annually.[6] At the same time, the ability of NHS trusts to achieve the 62-day urgent referral target fell by 5% to only 74% in 2013–14.[4,7,8]

Eiken OC Sensor iO.

At a local level, NHS Tayside, for example, receives approximately 4000 out-patient GI referrals annually; 1% of the general population. Of these, GPs mark 35–40% of referrals as 'urgent' or 'urgent, suspected cancer'.[9] Following an out-patient GI consultation, 75% of patients (both urgent and routine referrals) are forwarded for urgent investigation. Mowat *et al*. found that the overall yield following colonoscopy remains low at only 2% CRC and 5% inflammatory bowel disease (IBD).[9] On concluding this research, the team stated that "New means of assessing patients in primary care are urgently needed to help GPs determine which patients are in need of rapid investigation and in turn ease pressure on secondary care services".

Despite these resource-intensive efforts, only half of CRC cases are detected through the urgent cancer referral pathway. The remaining patients not presenting with 'red flag' symptoms are not eligible for urgent referral.[5,10]

Colonoscopy services in the UK are under enormous pressure. Waiting times for routine GP referrals vary widely across the UK, with some patients often waiting months. This is putting patients at risk by delaying diagnosis, and thus commencement of treatment. With an increasingly aged population, the reported increase in obesity and other detrimental lifestyle factors, it is evident that the demand on colonoscopy resources is not going away.

In June 2015, NICE published a revision of 'NICE Guidance 12: Urgent cancer referral' (NG12), amending the 'red flag' criteria for the two-week wait in a likely bid to increase the detection rate for CRC. The revisions to NG12 have been received by clinical and laboratory

specialists as a widening of the goal posts, putting already stretched resources at increased risk because more patients will be eligible for urgent referral.

For the first time, NG12 includes the option to test for occult blood in faeces. This presents an immediate issue for pathology services because most laboratories stopped offering the traditional guaiac faecal occult blood tests (gFOBT) some time ago. While intended to cover specific patient cohorts, the guidelines stop short of suggesting appropriate technologies and how to establish this new service. Clinical commissioning groups (CCGs) need to understand how to interpret the occult blood result, its impact on the patient care pathway, and the provision of secondary care services.

As a generalisation, the amount of detectable haemoglobin in a stool sample (and therefore the level of bleeding) increases as a lesion develops through the various tumour stages. Men generally bleed more than women, potentially disadvantaging women if using insensitive FOBT products or those with inappropriately fixed cut-off levels. The quantitative data available so far suggests that most detected cancers bleed significantly. The problem is that there are always a few patients who bleed intermittently, if at all. In a bid to overcome these issues, research has shown that by adapting the cut-off of a quantitative faecal immunochemical test (FIT), a single sample and a lower cut-off can match the diagnostic yield of a two-day sampling algorithm.[11]

Guaiac faecal occult blood test

At the mention of 'FOBT', most people automatically think of the traditional guaiac tests. Nowadays, most laboratories have discontinued the use of gFOBT products because the results offer little clinical value. Traditional gFOBT involved application by the patient of three consecutive stool samples to a guaiac-impregnated card. This proved unpleasant and unpopular, and, in a bid to improve compliance, GPs resorted to forwarding native stools, in all manner of containers, to be processed in the laboratory. The laboratory would apply reagent to the card and observe a blue/green colour change.

Haemoglobin is an unstable protein when left in a stool sample, meaning that by the time a sample arrives in the laboratory, 24–48 hours after deposition, stools with low levels of haemoglobin would likely be degraded; increasing the risk of a false negative and reducing the sensitivity of the gFOBT. Additionally, gFOBT are not specific for haemoglobin.

Unique sample collection device, complete with an integrated sample filter.

In order to avoid the likelihood of false positives, dietary restrictions on red meat and foods high in vitamin C are recommended by manufacturers. The interpretation of the colour change can also be subjective, especially at the lower limits of detection, even in highly experienced hands. Furthermore, gFOBTs are impossible to automate for integration into the modern laboratory.

Although perceived as cheap, guaiac products are approximately 100 times less sensitive than the modern quantitative FITs now available.

Faecal immunochemical tests

The FIT is based on the agglutination of antihuman haemoglobin-specific antibodies to the haemoglobin present in a stool sample. There are many FIT products available on the market and can be differentiated as manual qualitative tests or automated quantitative platforms. As a result of the increased sensitivity, specificity and improved sample processing procedures associated with the immunochemical reaction, FIT is rapidly replacing the use of gFOBT products.

Qualitative tests are typically presented in a lateral-flow format. The sample is applied to the lateral-flow device, allowed to react for an incubation period, and the presence of a test and control line is then recorded. Owing to the use of specific antibodies, qualitative tests overcome the need for dietary restrictions and show improved sensitivity over gFOBT. Although often marketed as point-of-care tests (POCTs), care should be taken as all qualitative tests are not the same. Published comprehensive comparisons of the market-leading qualitative tests clearly demonstrate the differences in performance, accuracy, limit of detection and clinical outcome.[12,13] The qualitative FIT is less subjective than gFOBT, but the interpretation of faint or partially formed bands in the test zone is still open to error. Additionally, the cut-off is fixed by the manufacturer, meaning that users cannot adapt the performance to complement the locally available colonoscopy resource.

Quantitative tests overcome the limitations of both gFOBT and qualitative FIT by using a precisely engineered device to collect a measured amount of stool sample in a known volume of buffer. Samples are then processed on an automated platform which reports a numerical value against a cut-off determined by local criteria, as opposed to criteria defined by the manufacturer. Quantitative FIT is now accepted as the method of choice for CRC screening programmes around the world.[9] The World Endoscopy Organisation (WEO) has established an Expert Working Party to coordinate and share research into the application of quantitative FIT.

OC-Sensor, the No 1 FIT solution

OC-Sensor, manufactured by the Eiken Chemical Company and distributed by Mast Group, is a leading platform, with a pedigree dating back to 1989, and is the only quantitative FIT that has US Food and Drug Administration (FDA) 510K approval. As a result of continued innovation and dedication to quality research, OC-Sensor has been adopted for laboratory use and CRC screening programmes in over 42 countries. OC-Sensor offers two dedicated and successful platforms (OC-Sensor iO and OC-Sensor PLEDIA) for the processing of FIT samples.

The OC-Sensor iO is a small-footprint analyser for laboratories with even the most limited bench space available. With a throughput of 88 samples per hour, ready-to-use reagents, fully automatic calibration curve generation, primary tube sampling and minimal maintenance requirements, the OC-Sensor iO is a reliable platform on which to establish a FIT service.

OC-Sensor PLEDIA is the successor to the OC Diana platform. With a throughput of 320 samples per hour, ready-to-use reagents, fully automated calibration curves and onboard statistical analysis package, the PLEDIA continues to be the leading choice both for national screening programmes and large laboratories.

The OC-Sensor technology is simple to use and provides a range of benefits to enhance user experience and streamline sample processing:

- Primary tube sampling removes the need for laboratory processing. It's as simple as loading the sample into the analyser and pressing 'start'.

- The analyser is able to read all barcode types, allowing the laboratory to employ existing specimen tracking protocols.
- The OC-Sensor sample bottle contains an integrated filter. This prevents particulate matter and faecal fats from getting into the sample chamber and therefore being picked up by the analyser. The filter also aids Lean processing in the laboratory as samples do not need to settle or be centrifuged before analysis, or resealed after processing.
- OC-Sensor was the first to develop ready-to-use liquid reagents, including stable haemoglobin controls and calibrators. This removes the need to rehydrate and aliquot lyophilised pellets, improving reproducibility and removing the hands-on time and potential for error.
- Calibration curves are stable, only required when changing the lot of the latex reagent. With a ready-to-use calibrator kit, fully automated serial dilution and curve generation, the process can be completed in less than a minute. The procedure could not be simpler.
- OC-Sensor has a wide analytical range. Samples are analysed against the calibration curve and numerical results reported. OC-Sensor has an automatic dilution feature for samples and employs an algorithm to alert the user to issues including prozone.
- OC-Sensor instruments run a stringent washing procedure which, in addition to the sample filter, removes carryover and contamination, reducing laboratory maintenance to almost nothing.

Eiken OC Sensor Pledia.

The solution

In a blinded study in two Spanish health centres, OC-Sensor FIT showed higher sensitivity for CRC detection than that in NICE criteria (87.6%, 61.9%; $P<0.001$) and SIGN criteria (82.5%; $P=0.4$). The specificity of FIT was also higher than NICE and SIGN criteria (77.4%, 65.2%, 42.7%; $P<0.001$).[14] However, the incorporation of FIT into the referral pathway for patients suspected of CRC could have a number of positive impacts for managing patients and on available resources in secondary care.

The real impact of FIT is its very high negative predictive value (NPV). McDonald *et al.*[15] reported an NPV of 100% for CRC, while Mowat *et al.*[9] reported the NPV for CRC, higher-risk adenoma and IBD as 100%, 97.8% and 98.4%, respectively. These data suggest that FIT could be an effective 'rule out' test for all organic disease, and should give the clinician and patient confidence that a colonoscopy is unlikely to be of benefit.

Detecting low levels of haemoglobin is essential to the clinical application of FIT. Patients must collect the samples directly and return them to the laboratory as soon as possible in order to reduce the risk of a false-negative result that would have an impact on decisions in their care pathway. To facilitate this, a method disseminating and receiving sample bottles via the GP should be established.

Patients have clearly shown that OC-Sensor is preferable to gFOBT and other FIT products.[16–19] As the impact of a negative result is established, it is likely that patients will benefit from reduced anxiety caused by long periods of waiting and the need to undergo an unpleasant invasive procedure.

Currently, GPs refer 60–65% of patients for an out-patient GI consultation under the normal referral pathways (ie those that do not meet the 'red flag' criteria for urgent referral).[9] If the new guidelines are followed, the perceived widening of the goal posts apparent with the 2015 amendments to NG12 are not likely to increase the total number of people referred for colonoscopy (as GPs could continue to refer symptomatic patients as they do now), but could well increase the proportion of these patients referred under the two-week wait, increasing pressures at secondary care.

Laboratories that have already adopted FIT for use in symptomatic patients have opted for the lowest cut-off (10 µg/g). At this cut-off, Mowat *et al.*[9] reported a FIT positivity rate of only 25.2% when offered to all patients referred for an out-patient GI appointment. As a result, FIT should be considered alongside other clinical parameters to improve the decision-making process either for referral from primary care or a decision to offer colonoscopy subsequent to the GI out-patient appointment. A benefit of quantitative FIT is that once data become available locally, the laboratory can adapt the cut-off to suit current resources.

The key to the successful implementation of a FIT service is cooperation and understanding between key stakeholders, including GPs, clinical specialists in secondary care, and, of course, the laboratory. Only in this way can FIT be implemented appropriately and not simply offered to everyone who reports with vague symptoms, which would lead to an overall increase in referrals. Over time, quantitative FIT could reduce significantly the number of referrals for out-patient GI consultations.

So, what is the incentive for implementing FIT in the laboratory now? If used to triage all patients referred to secondary care (normal and 'two-week wait' pathways), it is likely that some streamlining will be evident. Patients who otherwise meet the 'red flag' criteria but have negative FIT results could be transferred to the normal colonoscopy pathway. Those who do not have 'red flag' symptoms could be upgraded to an urgent referral on the basis of a positive FIT test. The result would be an improved service to patients by promoting those most at need (based on the FIT result).

Eventually, this re-organisation could lead to a reduction in overall waiting times for patients and enable a significant proportion of patients to be monitored in primary care, preventing unnecessary referrals. Above all, quantitative FIT will greatly reduce unnecessary colonoscopies, saving the NHS time and money.

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