Faecal Immunochemical Testing in Colorectal Cancer Pathways
In June 2015, NICE published the NG12 guidelines and advocated the introduction of tests for “occult blood in faeces” for certain patients presenting in primary care with lower abdominal symptoms but with a low risk of colorectal cancer.

This sparked much controversy regarding the different types of tests available for occult blood detection, since many hospital laboratories had discontinued the provision of guaiac-based tests and did not want to go back to this old technology with its very poor analytical and clinical sensitivity and specificity.

Whilst newer quantitative Faecal Immunochemical Test (FIT) methods have been widely introduced for bowel screening, publications on the use of this methodology in assessment of patients with lower abdominal symptoms have been increasing since 2012. Unfortunately, these had not been part of the data review for the June 2015 NG12 publication. In consequence, NICE have now reviewed the evidence for FIT in this clinical setting and are due to publish new guidelines entitled: “Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care”.

This assessment is focused on peer-reviewed publications on quantitative FIT methods in this particular clinical setting. These publications are concerned with studies on symptomatic patients being planned or considered for colonoscopy on whom a FIT had been performed.

The quantitative FIT results were compared against the clinical findings. These publications identified that the FIT result could be used as a “rule out” test for significant colorectal disease (SCD), that is, colorectal cancer (CRC) plus higher risk adenoma (HRA: sometimes precursors of cancer) and inflammatory bowel disease (IBD: Crohn’s and ulcerative colitis), since they have a very high negative predictive value (NPV) for SCD. In fact, using a cut-off of <10 µg/g Hb/ faeces, the NPV was almost 100% for cancer and >90% for SCD.

The NICE Diagnostics Assessment Committee has published a number of documents online, including the draft diagnostic guidance: www.nice.org.uk/guidance/inddev/gid-dg10005/documents

Differentiating patients with serious bowel disease from those with benign functional disorders, such as Irritable Bowel Syndrome (IBS), and minor colorectal disease such as haemorrhoids, hyperplastic polyps and simple diverticular disease, can be very challenging since the symptoms are very common and overlap in these conditions.

The ability to use a simple, easy to use, inexpensive diagnostic test will provide additional assistance in determining the appropriate patient pathway for further investigation.

Ahead of this publication, several hospitals and CCGs have already committed to the provision of FIT as a means of triaging all patients presenting in primary (and secondary) care with lower abdominal symptoms.
Getting FIT for the Future!
FIT for Clinicians - Symptomatic Patients and Screening Programmes

Why use FIT?

Evidence Base

NHS England spent approximately £178.4 million during 2014 on performing colonoscopies (based on NHS tariff price), yet with approximately 40% of those no pathologies were found. Identifying and prioritising those patients more likely to require urgent intervention could save significant costs, reduce waiting times and improve care.

Publications support the Faecal Immunochemical Test (FIT) for Haemoglobin (Hb) as a rule out test (NPV of FIT at 10µg Hb/g faeces is 100% for Cancer, 94.6% High-Risk Adenoma (HRA), 93.5% Low-Risk Adenoma (LRA) and Inflammatory Bowel Disease 94%1), and demonstrate that with an increased severity of disease a higher faecal Haemoglobin (F-Hb) concentration is detected. Thus FIT enables management of the patient pathway and most effective use of resources based on appropriate evidence.

- Personalised Medicine
  All patients are different and present with a range of symptoms and risk factors. The additional information provided by FIT testing can help determine the optimum management of each individual.

- Resource Management
  Waiting times for endoscopy resources are increasing. Performing an initial FIT test to categorise the patient could, with confidence, predict those for whom colonoscopy is not appropriate. This would remove 40% of patients from waiting lists, significantly improving the turn-around time for those remaining, and ensuring their treatment is optimised and actioned sooner.

- Screening in the Asymptomatic Population
  Using FIT technology, such as the HM-JACKarc automated system, within a screening programme, enables the adjustment of positive cut off concentration. This helps to control the number of referrals for colonoscopy within the limits of available resources. In addition, the specificity of FIT eliminates false positives caused by dietary factors, ensuring positive results are a true indicator of pathology.

Reference

1. Low faecal haemoglobin concentration potentially rules out significant colorectal disease PJ McDonald, et al. Accepted Articledoi:10.1111/codi.12087

FIT for Patients - Informed choice

Concerned about their condition, patients want quick answers, with minimal intervention. With FIT testing they can have access to more information about the symptoms they exhibit and the possible causes for them.

Unfortunately IBS and other benign bowel disorders can exhibit similar symptoms to more serious conditions, such as colorectal cancers. As a consequence the longer it takes to resolve these concerns the more anxious patients become.

- Easier, More Convenient Sample Collection
  Compared to the traditional card format triple guaiac-based faecal occult blood test, sampling for the HM-JACKarc FIT test is quick and hygienic. Only one faecal sample is required and is collected using a small picker device that is then re-sealed in it’s plastic vial ready for testing.

- Rapid Response
  For most, having a rapid non-invasive faecal test to get a faster diagnosis would be the preferred choice. Using a FIT result, about 40% of patients would be informed that no further follow up is necessary and hence relieved straight away. The remaining 60% would have the option of a prioritised process for colonoscopy and get their treatment solutions started sooner.

- Risk Management
  Invasive procedures are not without risk, and this is true of colonoscopy. 1 in 1,000 patients may suffer a perforated bowel during this procedure, with additional risk of morbidity. So, with a non-invasive alternative now available shouldn’t that be the first choice?
  Additionally, delay in identifying any abnormal bowel pathology, also carries a higher risk of mortality. Hence, the ability to identify those at greater risk and then fast track these patients for appropriate colonoscopy and treatment is highly desirable. Treated early before it becomes invasive, bowel cancer has a 93% 5 year survival rate.
Focus on FIT

Evaluating a Faecal Immunochemical Test System for Symptomatic Patient Assessments

by Dr Ian Godber, Consultant Clinical Scientist, Clinical Lead (Biochemistry), Monklands Hospital, NHS Lanarkshire

Dr Ian Godber’s team at NHS Lanarkshire has evaluated the HM-JACKarc automated FIT analytical system for assessment of patients referred from primary care to endoscopy because of lower GI symptoms. As a result of this successful study, the process of rolling out a FIT service to their local General Practitioners (GP) is now well under way.

Matthew Davis, Alpha Laboratories Senior Product Manager, met recently with Ian to find out more from one of the first hospitals in the UK to offer a quantitative Faecal Immunochemical Test for haemoglobin (FIT) service.

Matthew: How did you engage with all the necessary departments to progress the pilot project?

Ian: There was sufficient data in publications on FIT to suggest that the ability to “rule in” patients who potentially had cancer and fast track them through endoscopy was good. In addition, the potential to “rule out” patients with no significant pathology was interesting from a cost saving and improved efficiency perspective. The proposal was taken to the Chief of Medicine for NHS Lanarkshire, at the Wishaw General Hospital site, Mr Hakim Ben Younes, who is also a GI surgeon, and he was keen to proceed. There was sufficient evidence to put the concept forward as a proposal to the Gastroenterologists, in order to relieve the pressure on the endoscopy service. This was a key factor in gaining approval to proceed with the project.

Matthew: Where did the original enquiry for the FIT service come from?

Ian: In 2013, we were approached by Alpha Labs, who asked if we would be interested in undertaking a pilot project. The current evidence in the literature at the time was limited but positive and showed favourable results, so we decided this project was worth progressing.

Matthew: What prompted your laboratory to consider providing the FIT service?

Ian: We initiated investigations on Faecal Immunochemical Tests for haemoglobin (FIT) due to the withdrawal of traditional guaiac-based gFOBT, following Professor Callum Fraser’s audit (ACB Scotland 2005). This highlighted that gFOBT should not be used to investigate symptomatic patients because of false positives and false negatives inherent when using this test.

Our Gastroenterologists and GI surgeons agreed with the cessation of gFOBT but the knock-on effect has been an increased demand for lower GI tract endoscopy. In consequence, we needed to find a way to relieve this additional pressure on the endoscopy service.

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The directorate structure of NHS Lanarkshire aided discussion. The divisional management to which I report is the same for both Diagnostics and Cancer Services, with similar structure and goals. This helped to simplify communication and coordination on this project.

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Matthew: What were the outcomes from the pilot project?

Ian: With support from Gastroenterologists and GI Surgeons, the project was driven forward to a successful conclusion, which resulted in a publication: Clin Chem Lab Med. 2016 Apr;54(4):595-602. doi: 10.1515/clinchem-2015-0617. The conclusions in the paper were essentially that the high negative predictive value of this test, at a cut off of 10µg Hb/g faeces, allows you to triage patients without missing any cancers, where the clinical sensitivity for colorectal cancer was 100%. In this study, all cancers had a f-Hb concentration greater than 150 µg Hb/g faeces.

There still remain a number of questions, mainly around other bowel pathologies that also generate a positive FIT result, and how these patients are managed. It may be that patients with very high f-Hb concentrations, say 150µg Hb/g faeces are sent straight to endoscopy, whereas those who are below that, but above 10 µg Hb/g faeces, are followed up clinically.

We think that there is potential to develop a clinical pathway that involves an initial screen with FIT, with patients then being seen in a clinic if the result is positive. The patient characteristics such as age, as well as the symptoms, may lead the clinician down a different track, favouring referral to Gastroenterology, with the possibility of a calprotectin test being more appropriate. However, the higher the f-Hb concentration initially the more important it is to initiate an urgent colonoscopy.
But, what about the negative FIT results? They may still need to be considered further and, depending on the clinical symptoms, there is possibly a case for following up these patients in 6 to 12 months time with another FIT test.

Matthew: How did you manage to secure funding for a new test?

Ian: At present, the funding still isn’t guaranteed and there is an on-going discussion as to where resources will come from. The NHS Board has indicated that the funding required could be moved from the endoscopy budget through into the laboratory budget. However, this becomes a bit of a grey area in that the test is actually being offered to patients seen in primary care, but the results are going back to secondary care, so it becomes part of the referral process for lower GI endoscopy.

Matthew: How did you work with the community GPs to implement the new test service?

Ian: We’ve engaged with a limited number of GP practices to start with and, over the next few months, we are starting to review how we actually provide this service and then fine-tune it. We’ve gone out and met with these practices and educated them, discussing how we are going to accept referrals for patients that present with lower GI symptoms.

We explain that they would normally have been referred for a lower GI endoscopy but now they will first be provided with patient FIT collection kits, pre-paid envelopes and patient instructions for collection of faecal samples.

So, the idea is that all referrals are done through an electronic mechanism for referral. At the time of referral in primary care, the patient is given an easy to use, hygienic, HM-JACKarc specimen collection device and asked to collect their sample and return it, with the laboratory request form, which identifies them, in the pre-paid envelope provided. They’re told to do that immediately, with their next bowel motion, and send it off as soon as possible. All the devices go back to a central hub, here in Monklands Hospital in Airdrie.

We can’t be seen as a delaying factor in triage. The endoscopy team receives the electronic referral, and they know to expect the f-Hb concentration result, therefore there’s a time window which is currently being fine-tuned for us to return a FIT result. Based on the FIT result, they may choose to fast track that patient straight to colonoscopy.

There is then the potential to avoid expensive, unpleasant and potentially risky colonoscopies where they may not be necessary. Pretty much every GP we’ve spoken with, to date, thinks this is a useful addition to the health service. Remember at present, they don’t have gFOBT, and currently the only option for patients with lower GI symptoms is to offer a referral for colonoscopy. Sometimes the patients’ symptoms have resolved by the time they receive an appointment. Others are put on a long waiting list. Both the patient and the GP can now feel that something is being done at an earlier stage. Patient feedback will be surveyed once this approach is rolled out to a higher number of GP practices. However, there is the potential for this not to work! There are over 100 general practices in NHS Lanarkshire and, when FIT kits were sent out during the pilot project, there was only a 50-60% return rate, so we really want to ensure we have full engagement with the GPs and patients before rolling it out any further. We would like to engage more with general practices first, to ensure they are fully briefed to gain maximum participation from the patients, before rolling it out to all of NHS Lanarkshire.

Matthew: What were the outcomes from the new test implementation?

Ian: The lessons to be learnt are to engage with all parties concerned, maybe forming a group to discuss the patient pathway and implementation involving the laboratories, GPs, GI surgeons and Gastroenterologists, as well as the endoscopy services.

Impacting Abdominal Pain Patient Pathways Through Diagnostics
The sampling aspect was new because the FIT test uses a faecal sampling device that’s placed in a buffer tube. Faecal material in pots is not acceptable for FIT since there’s so much evidence that faecal haemoglobin degrades. We sent out FIT kits with patient instruction leaflets (Figure 1) directly to GP practices and the samples are returned using the normal laboratory transport arrangements. Patients are remarkably happy to do the test as advised and are absolutely fine using the FIT sampling device. We’ve had no negative feedback or issues at all.

Figure 1. Faecal Immunochemical Test (FIT) Sampling Device and Patient Instruction Leaflet.

We promoted the FIT service through a series of joint key newsletters and emails from gastroenterology and the laboratories to the GPs. This supported GP education and engagement so that they became more receptive to the idea. Involvement from gastro is essential and at Tayside the process was virtually led by them. This is really important as the service can’t just be set up from a lab perspective and the joint approach is well received by the GPs.

Triaging with FIT

Tayside has been offering the FIT service for about 16 months now. It took about six months before we got full engagement from the GPs, because this was such a new process. Adding FIT onto our existing colorectal referral bundle through the electronic requesting system helps make it more straightforward. The FIT result is going back to the GP and to further support the process, we signpost them to the Tayside gastroenterology page which details what to do next and what the options are, dependent on the FIT result.

The Fits result is very high, the gastroenterologists may have had a routine referral, now, if the FIT result is with that referral or they can look it up. The FIT result is being used as part of the decision making process as to what to do next. Do they go straight for colonoscopy or are they seen in a clinic? Sometimes if a referral is sent without a FIT, the gastroenterologist will request one, using the two way interactive electronic referral system.

A crucial part of this process is to have the clinical input from the GPs as the FIT result can’t be used in isolation. It has to be taken in conjunction with clinical signs and symptoms. If there is high clinical suspicion of a colorectal cancer or other serious condition, but the FIT result is negative, then of course that should not stop a referral. It’s really important that this message is clear and FIT is used in combination to get the bigger picture.

With the increased awareness and roll out of FIT, there is anecdotal feedback that the GPs really like the ability to offer this test. Some patients are reluctant to be referred to gastro because they are worried that they will end up having a colonoscopy. Now, the GP can offer this test first, before that decision is made. If the FIT result is positive then they know there are good grounds for proceeding to colonoscopy. If it is negative, then the chances are there is nothing seriously wrong and the patient is given that reassurance.

We also have evidence that the referral status of people is changing. Previously where someone may have had a routine referral, now, if the FIT result is very high, the gastroenterologists may change that referral to urgent.

So, individual patients are getting a colonoscopy and diagnosis of a cancer much faster.

We’re also starting to see a reduction in actual referrals into gastroenterology for the first time that anyone can remember. So, that shows that the GPs are gaining confidence that if there is a negative FIT the chances are that their patient doesn’t have anything seriously wrong. The benefit is that by the reducing the number of people being referred unnecessarily, those that really do need it, are being seen much faster.

Engaging the GPs

Once we had obtained funding, the next step was to engage with the GPs. We went to them with a ‘package’ early on to make it as easy as possible. It’s important that the service fits local referral practice. At first there were some concerns from the GPs, because they were being asked to request another test and didn’t want to delay an urgent referral. The GPs had input into the patient instruction leaflets and guidance on how to get samples back.

Data from our initial investigation was published in GUT in 2016. GPs asked patients that they were already referring to gastroenterology to submit a faecal sample, so that we could analyse their faecal haemoglobin with FIT. This didn’t affect the patients’ subsequent management and progression along the standard gastro pathway. We then, in retrospect, assessed clinical outcomes against the FIT result for each patient. This analysis showed that a negative FIT result correlated with a very low chance of having any significant bowel disease such as cancer or IBD.

Using this data we were able to demonstrate that provision of FIT was viable, since we believed the number of unnecessary colonoscopies performed could be cut quite significantly. This was obviously very attractive, not only financially, but also in the potential for reducing the waiting times and pressures for the increasingly challenged personnel.

Engaging the GPs

Gastroenterologists are increasingly challenged to provide an appropriate colonoscopy service to the population with increasing numbers of referrals and longer waiting times. In Tayside, we had seen the number of colonoscopies going year by year. However, the number of cancers being identified wasn’t changing, despite an increasing number of people being subjected to an invasive and potentially risky procedure.

NHS Tayside has a long standing history of bowel screening and, more recently, of analysing faecal haemoglobin in samples from symptomatic patients. Based on concerns about increasing colonoscopy lists, we became involved in discussions with our gastroenterology team exploring whether we could introduce quantitative faecal immunochemical testing (FIT) into our existing colorectal referral pathways. Could we triage people using a FIT result to refine whether they really needed a colonoscopy?

Focus on FIT

Introducing the FIT Service at NHS Tayside

Judith Strachan, Consultant Clinical Scientist, Ninewells Hospital & Medical School, NHS Tayside
Reducing Colonoscopy Lists

We are now getting real reductions in waiting times for colonoscopy in Tayside, with patients advancing through the system much faster.

Without the FIT implementation I’m sure referrals would have continued to grow, but they have now plateaued and fallen for the first time in years.

FIT Service Success Factors

Referral pathways differ across the UK, so it’s important for any labs planning to set up a FIT service to fully understand their local procedures. It’s essential to engage with the gastro service. There may not always be a seamless communication system. I think you’ve got to adapt to whatever exists or take the opportunity to influence it. Labs have to understand the role of the GPs and you really need to know what your gastroenterologists want out of the testing. How are they going to use the test result, what turnaround time is appropriate and how many samples will there be? It’s important to look at how many referrals there are to gastro and how many colonoscopies are being done. Without that information you can’t really start to plan how the lab is going to offer the service.

I think the key success factor for the Tayside implementation has been the team work between gastro and the labs. Flexibility and good communication on both sides has worked really well. We’ve also learned a lot from the GPs over time and adapted to providing more kits, as we initially underestimated that. Feedback to the GPs has been really crucial and we liaise every two or three months through a newsletter. We feedback regularly about what we’re actually funding, how many tests we’ve performed, how many referrals there have been etc.

Support from the supplier of the test is also crucial because you need their offering to work with the local system, provision of instruction leaflets and help with the whole package. You need a logistics solution to get the tubes from the lab to the GP and back again in a time frame that suits the service. Labs shouldn’t underestimate the time taken to set this up. The next step for Tayside is really in refining the service, particularly regarding the detailing of the reports. We want to provide further guidance on what results mean to give GPs more confidence to make decisions. We are happy that our process is robust and just need to focus on further education of GP practices that haven’t yet engaged. We’re really interested to look at the population we have results from, to see if they are the demographic that is slow to engage with the GP.

We’d also like to investigate sequential samples. If a patient has a negative FIT but still has symptoms, is it worth doing further tests? So there are lots of possibilities that we’ve not really explored yet.

The team is hoping to publish the work to date by mid-2017. There’s an inevitable lag time in obtaining details of the clinical outcomes of these patients a lot of resource required to check on referral and clinical outcomes and this should not be underestimated.

Reference

A Tale of Two Settings
by Professor Callum G. Fraser,
Centre for Research into Cancer Prevention and Screening, University of Dundee, Ninewells Hospital and Medical School, Dundee

Faecal Immunochemical Tests (FIT) are now used for asymptomatic population-based bowel (cancer) screening and also for the assessment of patients presenting with lower abdominal symptoms, particularly in primary care.

FIT provide one investigation that is of significant value in these two very different clinical settings. These applications have different target populations, aims, faecal haemoglobin cut-offs, interpretation of results, potential harms, additional benefits, potential improvements and possible strategies for the future.

It is important that these different aspects of FIT are appreciated as this test rolls out across the UK and the major advantages of increasing screening uptake and helping to decide which patients presenting in primary care would benefit most from colonoscopy are gained.

The adjacent table clarifies the attributes.

<table>
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<tr>
<th>Characteristic</th>
<th>Target Population</th>
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<tr>
<td>Purpose</td>
<td>Aim</td>
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<td>Interpretation of Results</td>
<td>Faecal Haemoglobin Cut-off Used</td>
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<td>Potential Harms</td>
<td>Additional Benefits</td>
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<td>Potential Improvements</td>
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## Distinguishing FIT in Screening from FIT in Assessment of the Symptomatic

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<thead>
<tr>
<th>FIT in Screening</th>
<th>FIT in the Symptomatic</th>
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<tr>
<td>Asymptomatic individuals eligible to participate in structured screening programmes, which differ from nation to nation in the UK, being 60-74 years in England, Wales and Northern Ireland, and 50-74 years in Scotland along with those older individuals who choose to “opt-in”.</td>
<td>Patients of any age who present in primary care with lower abdominal symptoms such as rectal bleeding, a change in bowel habit to constipation or diarrhoea, unexplained weight loss, anaemia, abdominal pain, and abdominal or rectal mass. In addition, some patients seen at certain secondary care clinics such as gastroenterology, will benefit.</td>
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<td>To select those participants in screening programmes who have no symptoms, but are at highest risk of colorectal neoplasia – cancer and higher-risk (advanced) adenoma.</td>
<td>To identify those patients who are most unlikely to have significant colorectal disease and would not benefit from referral for colonoscopy, saving resources and shortening waiting times, as well as identifying those who have significant colorectal disease and would benefit.</td>
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<tr>
<td>Rule in neoplasia.</td>
<td>Rule out significant colorectal disease (cancer + higher-risk adenoma + Inflammatory Bowel Disease). Rule in significant colorectal disease.</td>
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<td>High – especially in colonoscopy constrained countries. Selected to give the screening programme performance characteristics desired, such as the positivity rate with which the available colonoscopy resource could cope.</td>
<td>Low – 10 µg Hb/g faeces is widely recommended. Selected to ensure that patients with “negative” results, most unlikely to have significant colorectal disease, do not necessarily get early referral for colonoscopy. And, if “positive”, stimulates early referral to secondary care for further investigation.</td>
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<td>A “positive” result means that a risk of significant colorectal disease is present and further investigation is warranted. A “negative” result means the participant should be invited again at the set screening interval, currently two years in the UK.</td>
<td>If the result is “negative”, there is considerable reassurance that significant colorectal disease is not present. A “detectable” faecal haemoglobin means that the patient warrants further investigation.</td>
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<td>Not all colorectal neoplasia is detected – interval cancer proportions are high when high faecal haemoglobin cut-offs are applied. Thus, a “negative” result does not mean that colorectal neoplasia is absent and participants receive information on lifestyle and symptoms. There is a “reassurance” effect of a “negative” result. Moreover, a “positive” result does not mean that colorectal neoplasia is present, but the participant will undergo an invasive and potentially harmful investigation.</td>
<td>FIT in assessment of the symptomatic is not perfect and some colorectal disease will be missed if a “negative” result is used as guidance for no referral. Most cancers are detected, but a slightly greater proportion of higher-risk adenoma and inflammatory bowel diseases are not detected. Thus, patients with “negative” results could be given reassurance, but possible alternatives such as watching and waiting, referral to secondary care clinics, or a repeat FIT might be warranted, particularly if symptoms persist.</td>
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<td>Not only cancer detected but also some higher-risk adenoma, sometimes precursors of cancer, and Inflammatory Bowel Disease.</td>
<td>Not only possibility of significant colorectal disease being “excluded”, but cancer, higher-risk adenoma, sometimes precursors of cancer, and Inflammatory Bowel Disease detected.</td>
</tr>
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<td>As FIT screening progresses and as the available colonoscopy resource expands, implementation of lower cut-offs over time would increase detection of cancer and even more higher-risk adenoma.</td>
<td>Investigation of more analytically sensitive methods for detection of faecal haemoglobin, since many patients have undetectable faecal haemoglobin with current methodology. Use of FIT result in combination with other variables such as blood haemoglobin.</td>
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A FIT Sample

New Faecal Immunochemical Test Systems could Improve Sample Integrity for Faecal Haemoglobin

One of the challenges in clinical diagnostics is the logistics of getting a quality sample from the patient to the laboratory for analysis.

When considering the detection of faecal haemoglobin (f-Hb), this is partly dependent on the technology to be employed. In the days of guaiac-based faecal testing, samples were sent in traditional blue-capped “stool pots”. This was clearly wrong, since haemoglobin in native faeces is very unstable (Brown and Fraser). It degrades rapidly at physiological and ambient temperatures. In passed faeces, which contains digestive enzymes, bacteria and fungi, it will degrade even more quickly.

The moiety being examined in gFOBT is the haem component of the haemoglobin molecule. Young et al. demonstrated that, with gFOBT, the degradation was more pronounced in the samples that were not dried, as when collected into a traditional faecal pot, versus a thin dried smeared sample (taken directly onto the gFOBT card).

The conclusion was that sampling directly onto the card should be made as soon as possible following defecation. In addition, analysis of gFOBT should be delayed for a few days so that potential interference from plant peroxidases, leading to false positive results, can be minimised.

With the move to a more sensitive technology based on an immunoassay specific for human haemoglobin, it is vital to stabilise the haemoglobin present in the specimen collection device, prior to analysis, to protect it from degradation and maintain integrity.

Brown and Fraser performed a similar study to Young et al. However, they used both qualitative and quantitative FIT methods to analyse five haemoglobin spiked faecal samples, with daily sampling for up to 14 days. The conclusion was that false negative results for faecal haemoglobin could occur if sampling fresh into the tubes or onto the cards of FIT collection devices is delayed.

With NICE, through a Diagnostics Assessment Committee, now focussing on the benefits of the application of FIT as a means to triage patients with lower gastrointestinal (GI) symptoms, it is important that any loss of f-Hb is protected.

Using a low level cut-off of 10µg of Hb/g faeces, the negative predictive value (NPV) for cancer is very high (100% in the hallmark study by McDonald et al.). Similarly high NPVs of 94%, are seen for higher risk adenomas (HRA) and Inflammatory Bowel Disease (IBD). Further studies in the UK have also shown a high degree of NPV when using FIT with cut-offs at this f-Hb concentration.

The introduction of new quantitative FIT methods has vastly improved the method of faecal sample collection. This is an important aspect of the process since the clinical outcomes are dependent on the ability of the method to detect faecal haemoglobin at very low versus undetectable concentrations.

The HM-JACKarc specimen collection device contains a proprietary buffer which can stabilise f-Hb in samples for up to 14 days at ambient temperature (up to 25 °C) or up to 120 days in the fridge (4°C). This was confirmed in a study by Carroll et al. investigating the performance characteristics of four FIT methods.

With any method, sample integrity is key to the quality of result. Typically laboratories would be concerned that a layperson would be unable to provide a consistent sample. However, the collection device of the HM-JACKarc is unique, in that it has two hexagonal dimples on one side of the collection probe. This ensures that as the probe is pushed back into the collection device after sampling of the faeces, any excess faecal matter is removed and a consistent amount of sample is passed into the constant volume of buffer. This is irrespective of the consistency of the faecal sample which can vary from liquid to hard pellets.

Use of the HM-JACKarc specimen collection devices ensures stability of f-Hb and low variation in the ratio of faecal mass collected to volume of buffer. Suchhygienic devices are simple for patients to use and encourage taking up the test in those who have concerns about handling faeces.

For more information on the HM-JACKarc quantitative FIT method please visit www.alphalabs.co.uk/FIT

References

Which FIT’s Best?

Guildford Medical Device Evaluation Centre (GMEC)
Evaluation of Quantitative Faecal Immunochemical Tests for Haemoglobin

The excellent clinical outcome data demonstrated in many publications, require faecal haemoglobin cut-offs for referral for further investigation, at the low end of the analytical range of the available FIT systems.

The choice of laboratory method is therefore important to the objective evaluation of patients, not only for haemoglobin stability in the specimen collection device, but also for its low bias and small imprecision at the lower limit of the analytical working range.

Four FIT analytical systems were evaluated by the Guildford Medical Device Evaluation Centre (GMEC) in 2013.

The resulting report is available online: http://194.97.148.137/assets/downloads/pdf/activities/fit_reports/gmec_fit_evaluation_report.pdf

Extracts of data from that report are represented here.

In this study, the HM-JACKarc system, supplied by Alpha Laboratories, was described as one of the more precise methods (Table 1). Its analytical working range correlated well to the expected values of spiked faecal samples. The ability to detect haemoglobin at both the lower and higher limits of the analytical range was confirmed (Figure 1). HM-JACKarc demonstrated a high sensitivity with a lower limit of detection of just 0.6 µg Hb/g faeces, making it ideal for symptomatic testing (Table 2). In addition, sample stability was proven at 20°C throughout the 30 day period of the study (Table 3).

Table 1. HM-JACKarc Precision

<table>
<thead>
<tr>
<th>Buffer Samples</th>
<th>GMEC data mean</th>
<th>sr</th>
<th>Manufacturer data</th>
<th>Consistent/ not consistent with claim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMEC data mean</td>
<td>sr</td>
<td>Manufacturer data</td>
<td>Consistent/ not consistent with claim</td>
</tr>
<tr>
<td>HM-JACKarc (µg Hb/g faeces)</td>
<td>13.5</td>
<td>0.9</td>
<td>11.3</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>58.8</td>
<td>1.3</td>
<td>56.1</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>319.4</td>
<td>5.4</td>
<td>279.5</td>
<td>7.9</td>
</tr>
</tbody>
</table>

KEY:
- sr – GMEC measured estimate of repeatability
- σr – manufacturers’ claimed repeatability
- NSD – Not statistically different from manufacturers’ claim

Table 2. HM-JACKarc Sensitivity

<table>
<thead>
<tr>
<th>Mean concentration of 20 un-spiked collection tubes (µg Hb/g faeces)</th>
<th>Standard deviation</th>
<th>Lower limit of detection (µg Hb/g faeces)</th>
<th>Quoted lower limit of detection (µg Hb/g faeces)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM-JACKarc</td>
<td>0.3</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>NS-PLUS C15</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>OC-SENSOR DIANA</td>
<td>2.1</td>
<td>0.9</td>
<td>3.8</td>
</tr>
<tr>
<td>FOB Gold/BioMajesty</td>
<td>0.5</td>
<td>0.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 3. HM-JACKarc Sample Stability

<table>
<thead>
<tr>
<th>Temperature</th>
<th>HM-JACKarc Measured Stability of Diluted Hb and Faecal Samples Spiked with Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20°C, 4°C, 20°C</td>
<td>All concs</td>
</tr>
<tr>
<td>Concentration (µg Hb/g faeces)</td>
<td>All concs</td>
</tr>
<tr>
<td>Hb in buffer</td>
<td>STS</td>
</tr>
<tr>
<td>Hb in faeces</td>
<td>STS</td>
</tr>
</tbody>
</table>

KEY:
- STS – Stable throughout study (30 days)
- i.e. the concentration of Hb did not fall below 50% of the initial concentration during the study.
- Cons – haemoglobin concentrations.

Four concentrations of Hb were tested ranging from the detection limit to a strong positive FIT result.
A FIT System for Any Laboratory

The HM-JACKarc is a high throughput, fully automated, compact bench top analyser that provides quantitative faecal haemoglobin (f-Hb) concentration results on a simple to use platform.

It has a wide dynamic range from 7ng/ml to 400 ng/ml (ng/ml = µg Hb/g faeces), making it ideal for use in clinical settings for both asymptomatic screening and assessment of the symptomatic.

The latex reagent is specific for human haemoglobin and is measured by spherical turbidimetry. Quantitative Faecal Immunochemical Tests (FIT) offer significant advantage over traditional guaiac based tests and qualitative FIT methods, both of which have subjective end points with varying cut off levels.

The HM-JACKarc system is easy to set up and can be loaded with up to 80 samples at any one time. It can stand alone or be linked to the LIS, allowing flexible options for connectivity and full audit trail of results, QC and reagent lot numbers.

Advanced Sample Collection System
- Easy to use sample device collects a consistent sample size across different faecal matter
- Internal septum removes excess sample
- <2mg of sample in 2ml of buffer (ng/ml = µg Hb/g faeces)
- Tamper seal and window to confirm sample applied
- Unique bar code number for the tube (lot no./expiry date/tube no.)
- Collection buffer stabilises the faecal sample haemoglobin
  - 120 days at 4°C (refrigerated)
  - 14 days at 25°C (ambient temp)

Fully Automated Instrument
- Compact and lightweight bench top unit with touchscreen interface
- Uses Integrated Sphere Latex Turbidimetry to measure faecal haemoglobin concentration
- Sensitivity: 7 ng/mL
- Cut-off concentrations can be selected depending on requirements – Screening or Symptomatic Testing
- No prozone effect up to 200,000 ng/mL
- High speed performance: 200 samples/hour
  - Time to first result 5.6 minutes
  - Additional results every 18 seconds

Factory set Master curve with local 2 point recalibration
- Calibrates system to local conditions and reagent combinations
- Calibration weekly
- System can store 2 calibration curves
- Calibration of different lots of latex
- Same lots with different calibrators

Latex Reagent
- Provides a large concentration of capture antibodies
- Wide dynamic range
- 7ng/ml to 400 ng/ml (ng/ml = µg Hb/g faeces)
- High Hook capacity > 200,000ng/ml
- Ensures no samples give a falsely lower result
- Drives reaction kinetics to end stage equilibrium quickly

To find out more visit www.alphalabs.co.uk/FIT
Watch the HM-JACKarc in action at www.alphalabs.co.uk/hmj-video or contact us for support in setting up your FIT Service

Automated FIT Testing: Easy as 1-2-3!

1. Add samples
2. Press START
3. Read results