From FOBt to FIT: making it work for patients and populations

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Introduction

Colorectal cancer (CRC) is the UK’s third most common cancer with 41,804 cases and 16,384 deaths in 2016. Improving survival depends on diagnosis at an early stage which can most effectively be achieved within the general population by increasing uptake and coverage of the National Bowel Cancer Screening Programme (NBCSP).

For patients presenting to primary care symptom-based referral criteria have been broadened in an attempt to detect early stage disease, while National Institute for Health and Care Excellence (NICE) NG12 guidance introduced testing for the presence (or absence) of occult blood using guaiac based tests. These changes have led to more urgent 2-week-wait (2WW) cancer referrals however colonoscopies in this group do not detect CRC or other serious bowel pathology. In 2017, NICE recommended replacing the guaiac based test with the newer faecal immunochemical test (FIT) which is more specific for blood, however the demand for colonoscopy from 2WW referral remains a challenge. A 1-day conference at the Royal College of Physicians considered how to utilise FIT most effectively as a means of addressing these issues in the symptomatic population.

Clinical biochemical considerations and NICE guidance

In the first session, Sally Benton provided context from the lab highlighting pre-analytical challenges such as the heterogeneity of faeces, the potential significance of haemoglobin variants and the instability of haemoglobin in faeces. She also discussed analytical challenges around assay standardisation as there are four different FIT manufacturers (although only 3 are approved by NICE) and so without standardisation it is difficult to directly compare results from different studies (see Fig 1). A further problem is that labs are unable to get sufficient reference material for standardisation. However, the International Federation of Clinical Chemistry and Laboratory Medicine hope to have standardised FIT testing imminently. Another issue is the different limits of quantification while the key question is ‘Should we be reporting down to the limit of detection and if not, what is the optimum diagnostic threshold?’

This was followed by an overview of the current NICE guidelines about the use of FIT in symptomatic patients. A major issue for DG30 related to the limited evidence base (only 10 studies on less than 7,000 patients) which could not be related directly to referral criteria as defined by NG12. In addition, most of the studies focused on the negative predictive value (NPV) of FIT to ‘rule out’ cancer in patients already referred for endoscopy. However, to ensure alignment with previous guidance, the final recommendation within DG30 focuses on the positive predictive value (PPV) of FIT as a ‘rule-in’ test. Within his presentation, Dr Logan explained how for most (low prevalent) conditions seen in primary care (and certainly for CRC) small changes to the prevalence can have a significant impact on the PPV. Therefore, by also lowering the referral threshold for suspected CRC within DG30, the PPV of FIT may be much lower than previously estimated (see Fig 2).

This set the context for the next session which looked at how the NPV could potentially be used as a ‘rule out’ test in high risk patients.
From FOBt to FIT pathway. Lastly, results were reported from Eastbourne where they looked at 1,000 2WW referrals with NG12 symptoms. They used stool, collected during digital rectal examination, for FIT testing, with the result used to triage patients to the most appropriate imaging test. This study used HM-JACKarc™ with a cut off at 10 μg/g and reported seven FIT negative cancers (<1% of the total study population, see Table 1). It was highlighted that in several of the studies, patients subsequently found to have CRC (but with an initial negative FIT test), had iron deficiency anaemia at presentation. It was suggested that the biological explanation for this may be due to degradation of haemoglobin from caecal tumours during colonic transit. This also highlighted the importance of a full blood count as part of safety netting in primary care.

Three on-going research trials are also assessing the NPV of FIT and there are plans to combine their data which would contain more than 20,000 patients. The quantitative FIT study in London is looking at all 2WW referrals using FIT (OC-Sensor™) and other aspects such as general practitioner (GP) acceptability. They have detected 76 cancers from 2,801 cases with nine FIT negative cancers at a cut-off of 10 μg/g. Mr Abulafi from RM Partners highlighted how NICE had aimed to reduce the detection of CRC threshold to around 3% and that they had achieved this aim but with the trade-off of many more 2WW referrals. He reported on the largest study which has recruited 11,000 2WW patients and reports 11 FIT negative cancers at a cut-off of 10 μg/g and four at 2 μg/g. Modelling showed a reduction in colonoscopy of 30–50% would be achieved while missing very few cancers. This may help to free up colonoscopy capacity to provide for the bowel cancer screening programme and opportunistic screening through DG30. Data from York, presented by Dr Turvill, highlighted even further the trade-off between trying not to miss any cancer (by using the lowest possible cut-off) versus optimising the use of colonoscopy by using a higher cut-off.

Implementing FIT in primary care / PPV

The afternoon session looked at FIT in primary care based on its PPV with experience shared from three sites. The investigators in Nottingham having previously reported on their pilot work with FIT on the 2WW pathway have now introduced FIT for all 2WW patient pathways. Looking at the service evaluations, Nottingham has used FIT (OC-Sensor™) to triage patients to their first test since 2016. Patients with rectal bleeding are excluded and thresholds assessed at the limit of detection, 10 μg/g (as per NICE DG30) and 150 μg/g. A FIT < 4 μg/g equated to a 0.2% risk of CRC while one between 4 and 10 μg/g equated to a 4.8% risk of CRC and these patients normally had computed tomography colonography (CTC) or colonoscopy as the first investigation. In Leicester, CTC is the primary imaging modality for all patients with change in bowel habit and a FIT (OC-Sensor™) > 4 μg/g. Patients with rectal bleeding, weight loss, iron deficiency anaemia and abdominal or rectal mass are not included in their

Implementing FIT in symptomatic populations: practice, learning and safety netting as a ‘rule out’ test

Six ‘FIT pioneer’ sites shared data from formal research studies and service evaluations where FIT is already being used in 2WW patient pathways. Looking at the service evaluations, Nottingham has used FIT (OC-Sensor™) to triage patients to their first test since 2016. Patients with rectal bleeding are excluded and thresholds assessed at the limit of detection, 10 μg/g (as per NICE DG30) and 150 μg/g. A FIT < 4 μg/g equated to a 0.2% risk of CRC while one between 4 and 10 μg/g equated to a 4.8% risk of CRC and these patients normally had computed tomography colonography (CTC) or colonoscopy as the first investigation. In Leicester, CTC is the primary imaging modality for all patients with change in bowel habit and a FIT (OC-Sensor™) > 4 μg/g. Patients with rectal bleeding, weight loss, iron deficiency anaemia and abdominal or rectal mass are not included in their

Table 1. Demonstrates the number of faecal immunochemical test positive and negative cancers at different thresholds as well as the negative predictive value by faecal immunochemical test pioneer centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>n</th>
<th>FIT test</th>
<th>Threshold, μg Hb / g faeces</th>
<th>FIT positive, n (%)</th>
<th>FIT negative, n (%)</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastbourne</td>
<td>928</td>
<td>HM-Jack™</td>
<td>10</td>
<td>41 (4.4)</td>
<td>7 (0.75)</td>
<td>99.05</td>
</tr>
<tr>
<td>North London (qFIT pilot)</td>
<td>2,801</td>
<td>OC-Sensor™</td>
<td>10</td>
<td>76 (2.7)</td>
<td>9 (0.32)</td>
<td>99.4</td>
</tr>
<tr>
<td>York 1</td>
<td>515</td>
<td>HM-Jack™</td>
<td>≥2 (limit of detection)</td>
<td>26 (5.0)</td>
<td>2 (0.39)</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥12</td>
<td>24 (4.7)</td>
<td>4 (0.78)</td>
<td>99.1</td>
</tr>
<tr>
<td>York 2</td>
<td>869</td>
<td>HM-Jack™</td>
<td>≥2 (limit of detection)</td>
<td>12 (1.4)</td>
<td>1 (0.12)</td>
<td>99.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (1.3)</td>
<td>2 (0.23)</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (1.3)</td>
<td>2 (0.23)</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94 (2.3)</td>
<td>11 (0.27)</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>101 (2.5)</td>
<td>4 (0.01)</td>
<td>99.9</td>
</tr>
</tbody>
</table>

FIT = faecal immunochemical test; NICE = National Institute for Health and Care Excellence; NPV = negative predictive value; qFIT = quantitative faecal immunochemical test.
providing an oversight of the work being done by the ‘FIT pioneer’ sites. She concluded that there is emerging evidence that FIT is effective at ruling out CRC but important knowledge gaps remain (Table 2). She anticipated that as the pioneer group report their findings these gaps will be filled and allow NHS England guidance to be updated later this year.

**Conclusion**

FIT is a highly accurate quantitative test for detecting ‘occult’ haemoglobin in faeces. Its implementation in the NBCSP will improve uptake particularly in those populations most at risk of CRC. Maximising its value in the symptomatic population however will depend on how it is implemented within secondary and primary care. By collating data and sharing learning from the FIT pioneer sites, NHS England and its partners will be able to issue further guidance to support best practice at the earliest opportunity.

**Acknowledgements**


**References**


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11 Chapman C, Bunce J, Oliver S et al. Service evaluation of faecal immunochemical testing and anaemia for risk stratification in the 2-week-wait pathway for colorectal cancer. BJS Open 2019.


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