Detection of Bowel Cancer: FIT for Purpose?

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Scottish Bowel Screening Programme Statistics.
For invitations - 1 November 2012 and 31 October 2014.
Publication date – 04 August 2015.

Key points:

• For the two-year period: the number of participants exceeded one million for the first time.

• Uptake was 57.6%, an increase of 1.5%. Uptake for females was 60.3% and for males was 54.7%.

• Just over 2% received a positive test result. Of those, 6.9% had a bowel cancer.

• 61.7% of screen detected cancers were diagnosed at the earliest two stages.

• Uptake was lower in areas of higher deprivation.

The earlier a cancer is detected the greater the chances are of successful treatment.
Publication date – 17 November 2015.

Fallen by 11% over last decade: is that good news?
The number of new cases of cancer is predicted to rise by 33% between 2008-2012 and 2023-2027, mainly as a result of the population growing older.

<table>
<thead>
<tr>
<th></th>
<th>Actual 2008-12</th>
<th>Projected 2023-27</th>
<th>Percentage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>8,905</td>
<td>11,366</td>
<td>27.6</td>
</tr>
<tr>
<td>Brain</td>
<td>2,145</td>
<td>2,590</td>
<td>20.8</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>22,421</td>
<td>28,579</td>
<td>27.5</td>
</tr>
<tr>
<td>Cervix</td>
<td>1,594</td>
<td>2,225</td>
<td>39.6</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td><strong>19,833</strong></td>
<td><strong>28,298</strong></td>
<td><strong>42.7</strong></td>
</tr>
<tr>
<td>Uterus</td>
<td>3,235</td>
<td>5,016</td>
<td>55.1</td>
</tr>
<tr>
<td>Kidney</td>
<td>4,672</td>
<td>8,030</td>
<td>71.9</td>
</tr>
<tr>
<td>Lung</td>
<td>25,475</td>
<td>30,648</td>
<td>20.3</td>
</tr>
</tbody>
</table>
Screening for Colorectal Cancer - for Individuals WITHOUT Symptoms.

- Colonoscopy.
- Flexible sigmoidoscopy.
- CT colonography.
- DNA analysis of faeces and/or blood.
- Faecal and blood tests – bewildering variety.

- Tests for the presence of hemoglobin in faeces – markers of bleeding into gut.
Structure of haemoglobin

haem + globin

Each erythrocyte (RBC) contains ~270 million haemoglobin molecules
Guaiac-based FOBT - gFOBT

A number of gFOBT available - based on pseudoperoxidase activity of haem reacting with peroxide in the developer
1990s - Large Randomised Controlled Trials Using gFOBT

16% reduction in mortality
gFOBT Adopted Widely for Screening.

Some Advantages **BUT** Many Disadvantages:

- Multiple samples required.
- **False positive results (positive test result but normal colonoscopy) and false negative results (shown by interval cancers – especially in women).**
- Potential for interference from meat and certain vegetables.
- Detect bleeding from stomach, small and large intestine.
- Not easy to interpret colours – reader variation. Cannot be “automated”.
- Now considered “obsolete” by many experts and opinion leaders.
Each erythrocyte (RBC) contains ~270 million haemoglobin molecules
Faecal Immunochemical Tests (FIT) for Haemoglobin.

- Detect human haemoglobin with antibodies to globin.
- One sample only – generally easier to collect - with user friendly, hygienic specimen collection devices.
- No dietary interferences.
- More specific for lower GI lesions.
- Generally more analytically sensitive than gFOBT.
- Can be automated and give an estimate of faecal haemoglobin.
- Now advocated in many publications and recommended in most modern guidelines – for population screening – THE best non-invasive investigation.

THE FIT (R)EVOLUTION IS HERE!
Haemoglobin Concentration is Related to Disease Severity

Haemoglobin

Normal  →  Low risk adenoma  →  High risk adenoma  →  Cancer

Faecal Haemoglobin

Design of the FIT as a First-Line Test Evaluation.

- Invitation period July 2010 – January 2011
- NHS Ayrshire & Arran and NHS Tayside
- 70,000 sequential invitations
- One sample
- Cut off 400 ng Hb/ml buffer (80 µg Hb/g faeces)
- Comparisons done with NHS Forth Valley and NHS Fife

Outcomes – Clinical Comparison (PPV = true/total positives).
Uptake in FIT as a First-Line Test NHS Boards and Comparable NHS Boards.

Effect of FIT as a First-Line Test evaluation on uptake

- FFLT NHS Boards
- Comparable NHS Boards

Uptake

<table>
<thead>
<tr>
<th>Period</th>
<th>FFLT NHS Boards</th>
<th>Comparable NHS Boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/7/08-31/12/08</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>1/7/09-31/12/09</td>
<td>56%</td>
<td>54%</td>
</tr>
<tr>
<td>1/7/10-31/12/10 (FFLT)</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>1/7/11-31/12/11</td>
<td>52%</td>
<td>54%</td>
</tr>
</tbody>
</table>
Outcome – Increased Uptake in More Deprived Groups.

Scottish Index of Multiple Deprivation Quintile

Evaluation Outcomes.

• Introduction of FIT as a first-line test in Scotland supported by:
  
  • clinical outcomes at least as good as current screening strategies using gFOBT as the initial test and
  
  • increased uptake, easy of use – few calls to Helpline, and practicability of the FIT analysis.

• Cost-Benefit Analysis and Business Case for FIT prepared.
  
  • Change now approved by Scottish Government.
- in good company.

**Faecal Immunochemical Test (FIT)**

Issues with FIT – Cut-off f-Hb Used Determines Outcomes.

Faecal Haemoglobin

Normal → Low risk adenoma → High risk adenoma → Cancer

Outcomes (%) with FIT at Different Cut-off Concentrations.

<table>
<thead>
<tr>
<th>µg Hb/g faeces</th>
<th>Positivity</th>
<th>Detection Rate for AN</th>
<th>PPV</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT 10</td>
<td>8.1</td>
<td>3.2</td>
<td>42</td>
<td>95.5</td>
</tr>
<tr>
<td>FIT 15</td>
<td>5.7</td>
<td>2.7</td>
<td>49</td>
<td>97.2</td>
</tr>
<tr>
<td>FIT 20</td>
<td>4.8</td>
<td>2.5</td>
<td>53</td>
<td>97.8</td>
</tr>
<tr>
<td>FIT 25</td>
<td>4.1</td>
<td>2.3</td>
<td>57</td>
<td>98.2</td>
</tr>
<tr>
<td>FIT 30</td>
<td>4.0</td>
<td>2.3</td>
<td>60</td>
<td>98.4</td>
</tr>
<tr>
<td>FIT 35</td>
<td>3.6</td>
<td>2.2</td>
<td>63</td>
<td>98.7</td>
</tr>
<tr>
<td>FIT 40</td>
<td>3.5</td>
<td>2.1</td>
<td>62</td>
<td>98.8</td>
</tr>
</tbody>
</table>

Issue - f-Hb Varies by Age and Sex - Three Countries - 50-69 years.

Issue – f-Hb Varies with Deprivation - 50-74 years.

Scottish Index of Multiple Deprivation quintile

**Issue - Interval Cancers with High Cut-off f-Hb.**

- **Defined as a “colorectal cancer diagnosed after a negative screening test result and before the date of the next recommended examination”**.

- **Interval cancer rate with FFLT was similar to gFOBT at 50.8%**.
  - 48.4% in men, **53.3% in women**.

- **Those with faecal Hb concentration 60.0-79.9 µg/g more likely to have an IC compared with those with lower f-Hb.**

FIT are IT for Screening - But - Future Challenges.

• Use **ONE** only OR different f-Hb cut-off concentrations for men and women and/or for young and old?

• Report “risk” – from f-Hb alone?

• **Use more sophisticated data analysis - add age and sex - or add other factors such as deprivation - to create a “score”**?

• **Treat people as individuals? Keep records of individual’s faecal haemoglobin concentration and consider changes over time?**

Some difficult to implement - more research needed.
How Is Colorectal Disease Found – Particularly Neoplasia?

- Investigating symptoms (primary care)
- Colonoscopy
- Screening for colorectal cancer
  - Initial faecal test (FIT for choice)
- Surveillance following previous disease
  - according to guidelines
Colorectal Pathway Referrals – Primary Care – NHS Tayside.

The Colonoscopy “Crisis”

![Bar chart showing GP referrals and total cancers from 2007 to 2011-2012.](chart_image)
Assessment of the Symptomatic – Patients Presenting with Lower Abdominal Symptoms in Primary Care.


FITS 10 µg Hb/g faeces: CRC sensitivity - 100% NPV for SCD - 88.1%

Mowat C, et al. Gut – Online. 570 patients. 3 of 28 CRC missed – all women

FITS+ 10 µg Hb/g faeces: CRC sensitivity - 89.3% NPV for SCD - 94.4%


FITS2 10 µg Hb/g faeces: CRC sensitivity - 100% NPV for SCD - 96.2%
The Future of Assessing Patients Presenting in Primary Care?

• No test is perfect - but FIT can be used to rule in cancer in symptomatic patients and, perhaps more importantly, rule out significant colorectal disease.

• No. of referrals for urgent colonoscopy could be cut by up to half.

• Some – smaller adenomas and cases of IBD - would be missed.

Investigating symptoms (primary care)

Screening for colorectal cancer

Initial FIT result

Colonoscopy

Surveillance following previous disease
- according to guidelines
Current work on f-Hb in Diagnosis in Scotland.

- Use different f-Hb cut-off for men and women and/or young and old?

- Assess “risk” – from f-Hb alone – or with age and sex – or plus other factors?

The FAST Score – Faecal Hb, Age and Sex Test

Chief Scientist Office - £300K.
Study to investigate bowel cancer ‘risk score’.
Study aimed at ultimately assisting GP.
Overall Conclusions – FIT are FIT for Purpose!

• Screening using FIT has many advantages over gFOBT but needs better use of quantitative f-Hb estimates to ensure equality across age and sex.

• FIT provide a very good test to rule in CRC and rule out significant colorectal disease in patients with lower abdominal symptoms. Use of FIT in primary care could direct scarce endoscopy resources to those who would benefit most.

• Research is needed how best to apply the quality numerical estimates of f-Hb that can be made with FIT – in screening AND in diagnosis – and other settings.

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