FIT Screening
Challenges and Opportunities
‘Screening is about identifying healthy people who may be at increased risk of disease’

Participants

Healthy Subjects

-ve Screen

FURTHER TESTS

Colonoscopy

Patients

-ve Screen

Higher Risk

WHO 1968 - Criteria for Screening

The risk of harm is less than that of benefit
Alive - 5 years after treatment

93% 77% 48% 7%

>50 years old - 1 in 4 have polyps

1 in 10 change to invasive cancer

Colorectal Cancer Pathogenesis

Case for Screening

Screening Colonoscopy – 30 to 45 mins

• Look for cancers – surgery
• Look for polyps – remove (polypectomy)

Polyp

Alive - 5 years after treatment

10 years
FIT
A one sample, simple, easy and clean test
European guidelines for quality assurance in colorectal cancer screening and diagnosis. Chapter 4. Faecal occult blood testing.
Halloran SP, Launoy G, Zappa M
Endoscopy 2012; 44 (S 03):SE65-SE87

In good company!
### Study Cohort 1

<table>
<thead>
<tr>
<th>Invited</th>
<th>gFOBt</th>
<th>FIT</th>
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<tbody>
<tr>
<td></td>
<td>5004</td>
<td>5007</td>
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<table>
<thead>
<tr>
<th>Participation</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|               | 2,351 | 2,979| (49.5%)
|               | 62    | 137 | (95%)

<table>
<thead>
<tr>
<th>Positive test</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|               | 65    | 143 | (2.8%) (4.8%)

<table>
<thead>
<tr>
<th>Follow-up examination</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|                       | 62    | 137 | (95%)

<table>
<thead>
<tr>
<th>Advanced adenomas &amp; cancers</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|                             | 26    | 73  | (1.2%) (2.5%)

<table>
<thead>
<tr>
<th>Detected cancers</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|                  | 6     | 14  | (0.3%) (0.5%)

<table>
<thead>
<tr>
<th>False Positives</th>
<th>gFOBt</th>
<th>FIT</th>
</tr>
</thead>
</table>
|                 | 34    | 64  | (55) (47%)

### Study Cohort 2

<table>
<thead>
<tr>
<th>Invited</th>
<th>gFOBt</th>
<th>FIT</th>
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<td>10,301</td>
<td>10,322</td>
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<th>Participation</th>
<th>gFOBt</th>
<th>FIT</th>
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</thead>
</table>
|               | 4,836 | 6,157| (47%) (60%)
|               | 103   | 280  | (88%) (83%)

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<thead>
<tr>
<th>Positive test</th>
<th>gFOBt</th>
<th>FIT</th>
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|               | 117   | 339 | (2.4%) (5.5%)

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<th>FIT</th>
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|                       | 103   | 280 | (88%) (83%)

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|                             | 57    | 143 | (0.6%) (1.4%)

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<th>gFOBt</th>
<th>FIT</th>
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|                  | 11    | 24  | (0.1%) (0.2%)

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<th>False Positives</th>
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|                 | 46    | 135 | (45%) (48%)
What is the **Faecal Immunochemical Test?**

**Making the Test Reagents**

- **Globin**
  - Protein structure unique to the humans

- **Haem**
  - Contains iron

**Hb**
What is the *Faecal Immunochemical Test*?

*Making the Test Reagents*

1. Antibodies prepared against...

2. ...human haemoglobin (*just the globin*)
What is the **Faecal Immunochemical Test?**

**Test Reagents**

- **Anti-human Hb antibodies**
- **Particles of a ‘latex polymer’** (e.g. polystyrene)
- ‘Latex’ coated with anti-human Hb immunoglobulin
What is the *Faecal Immunochemical Test*?

Latex particles coated with anti-Hb antibodies + Blood in faeces (human haemoglobin) = Latex bound antibody-Hb complexes
What is the **Faecal Immunochemical Test?**

Light source wavelength 660-570nm

Particles cross link and block the passage of light

The reduction in light intensity relates to Hb concentration

Immunoturbidimetric analysis

Light measurement ‘Photometer’
UK FIT Pilot – 150 samples – 600 individual measurements

5 Batches each of 30 samples, 4 analysers, 2 sites over 7 months
April – October 2014

Individual analyser results ngHb/mL

Mean result of 4 analysers ngHb/mL

y = x
Line of best fit
y = 0.997x + 0.1122
Methylated vimentin

Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer
carcinoembryonic antigen (CEA)

Carbohydrate antigen 19-9 (CA 19-9)

Epidermal growth factor receptor (EGFR)
P53 gene
K-ras / KRAS gene
APC gene

Screening Biomarkers
Non-Invasive Investigations

FIT - Faecal Immunochemical Test for haemoglobin

Methylated vimentin

Proteins (M2-PK)

Epidermal growth factor receptor (EGFR)
Screening Biomarkers
Non-Invasive Investigations

FDA Advisers Back Exact Sciences Colon Cancer Test
WASHINGTON March 27, 2014 (AP)

Multi-target Stool DNA & FIT test
- FOBT (FIT)
- Methylated BMP3 & NDRG4
- Mutant KRAS & B-Actin

Multitarget Stool DNA Testing for Colorectal-Cancer Screening
Thomas F. Imperiale, M.D., David F. Ransohoff, M.D., Steven H. Itzkowitz, M.D., Theodore R. Levin, M.D., Philip Lavin, Ph.D., Graham P. Lidgard, Ph.D., David A. Ahlquist, M.D., and Barry M. Berger, M.D.
March 19, 2014 | DOI: 10.1056/NEJMoA1311194
Comparative Sensitivity of Multitarget Stool FIT /DNA Test and a Single (FIT) Cancer Stage

More sensitive than FIT (92% vs 74%)
Less specific (87%-90%) vs FIT (95%-96%)
...more of false positives!

Cancer Stage

Multitarget Test

FIT

Imperiale TF et al. NJMed2014;370:1287-97
Comparative Sensitivity of Multitarget Stool FIT /DNA Test and a Single (FIT)

Advanced adenomas

P value for trend:
Multitarget DNA Test, P<0.001
FIT, P<0.001

Adenoma Size (increased cancer risk)

Imperiale TF et al. NJMed2014;370:1287-97
Comparative Sensitivity of Multitarget Stool FIT /DNA Test and a Single (FIT)

Higher-risk subtypes amongst advanced precancerous lesions

Multitarget Test

FOBt (FIT)

Imperiale TF et al. NJMed2014;370:1287-97
‘Colorectal cancer screening: An updated review of the available options’
Iyad A Issa, Malak Noureddine
World J Gastroenterol 2017 July 28; 23(28): 5086-5096

Blood based markers - **Septin 9**
- Limitations, caveats... *faded enthusiasm*
- Prospective trials... *disappointing results*

Non-invasive stool tests - **Cologuard**
- Cologuard stool DNA test... *prohibitive cost*
- **and... similar performance to FIT!**
‘Colorectal cancer screening: An updated review of the available options’
Iyad A Issa, Malak Noureddine
*World J Gastroenterol* 2017 July 28; 23(28): 5086-5096

‘FIT is... ...still the most appropriate screening test'
England

Biennial Screening for Bowel Cancer

Population Served (millions)

England
5 Hubs

Screening Hub Activities
- Organisation
- Call & recalls (25,000/week)
- Analysis
- Helpline (4,000/week)
- Make Appointments
- Data analysis
England

Biennial Screening for Bowel Cancer

Southern Hub Data

Screening Centres (18)

Colonoscopy Site

Clinic Sites

Clinic Sites

Clinic Sites

Southern Hub (Guildford)

Clinical & Lab ‘Quality’
1. Facilities & premises
2. Staff
3. Audit procedures

14.6 million
Screening Organisation

**Invitation**
- Kit & Return Package

**Pre-Invitation**
- At Screening Due Date

**Start**
- 2 yearly Screening Cycle

**Day 1**
- Kit Returned

**Day 8**
- Kit Read

**+ve Result**
- Patient & GP Letter

**1 day**
- <2 days

**<14 days**
- SSP Clinic Appointment

**<14 days**
- Screening Colonoscopy

**Surveillance Colonoscopy**
- GP Letter

**Appointment**
- Day 29

**Reminder**
- Letter

**No Response**
- GP Letter/E-Comms

**D29**
- M3

**Next Pre-Invitation**
- 2 Years

**Start**
- Freephone Helpline
Easy access to Information

- Emphasis on reaching everyone!

Special arrangements for:
- Prisoners
- Military personnel

Major challenges to reach those with:
- Dementia
- Learning difficulties
- Blindness

Available in 21 Languages

Large Print Version

Sign Language
Programme design &...

...participation rate!

• Subjects... *looking* for a reason *not to do* the test!
  • Make screening easy
  • Provide no excuse to delay.

• ‘Design’ to maximise uptake
  • Don’t make good participation an ‘after-thought’
  • Consulting widely, test, trial and then apply!

• *One size... does not fit all!*
  • Population are not uniform
  • Personalise when possible!
NHS BCSP News

Headline Statistics!
(July 2006 – April 1st 2018)

- 39 million invitations
- 24 million gFOBt analysed
- 440,000 colonoscopies
- 31,000 cancers
- 102,000 advanced adenomas
# FIT measures of Faecal Haemoglobin Concentration

*FIT Concentration relates to disease severity*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean FIT Conc. ug Hb /g faeces</th>
<th>Positives at 20 ug /g Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10 (1-20)</td>
<td>6.9%</td>
</tr>
<tr>
<td>All adenoma</td>
<td>14 (4-23)</td>
<td>9.3%</td>
</tr>
<tr>
<td>Adv. adenoma</td>
<td>81 (37-125)</td>
<td>34.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>170 (89-252)</td>
<td>84.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoscopic Classification</th>
<th>Mean FIT Conc. ug Hb /g faeces</th>
<th>+ve at 20 ug /g Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
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<tr>
<td>LGD</td>
<td>27</td>
<td>14.1%</td>
</tr>
<tr>
<td>HGD</td>
<td>197</td>
<td>50.0%</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>12</td>
<td>9.0%</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>99</td>
<td>36.4%</td>
</tr>
<tr>
<td>Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 adenoma</td>
<td>14</td>
<td>10.1%</td>
</tr>
<tr>
<td>≥ 3 adenoma</td>
<td>65</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

*OC-SENSA MICRO*

Dong Il Park, MD\(^1\), Seungho Ryu, MD\(^2\), Young-Ho Kim, MD\(^3\), Suck-Ho Lee, MD\(^4\), Chang Kyun Lee, MD\(^4\), Chang Soo Eun, MD\(^5\) and Dong Soo Han, MD\(^5\)
The “best” faecal haemoglobin cut-off value for detecting colorectal cancer with three quantitative FIT


<table>
<thead>
<tr>
<th>Faecal Hb (ug/g)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>92.3</td>
<td>87.2</td>
</tr>
<tr>
<td>15</td>
<td>92.3</td>
<td>89.1</td>
</tr>
<tr>
<td>20</td>
<td>92.3</td>
<td>90.1</td>
</tr>
<tr>
<td>23</td>
<td>92.3</td>
<td>90.9</td>
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<tr>
<td>25</td>
<td>84.6</td>
<td>91.3</td>
</tr>
<tr>
<td>30</td>
<td>84.6</td>
<td>92.0</td>
</tr>
<tr>
<td>31</td>
<td>84.6</td>
<td>92.3</td>
</tr>
</tbody>
</table>
Choose a cut-off to meet your clinical requirements

Adjustable sensitivity – greatest asset of FIT!

- Adjust screening threshold to meet...
  - Clinical expectation and aspirations
  - Colonoscopy resource available

The “best” faecal haemoglobin cut-off value for detecting colorectal cancer with three quantitative FIT
FIT Cut-off - Predicts Interval Cancers
Taiwanese Population Screening Cohort

Cumulative Incidence of neoplasm / 1000 person years

20 ug/g
16 – 19
12 – 15
8 – 11
1 – 7
Undetected

Prospective cohort study
• 2001 and 2007
• 45,992 participants
One or two day FIT screening?


Single FIT – OK for screening!

Most efficient strategy

1-day FIT

2-day FIT (>= 1 positive)

2-day FIT (mean of both)

2-day FIT (sum of both)

2-day FIT (both positive)
Economic modelling of gFOBT and FIT


Whatever you invest in screening

- gFOBT – least cost effective
- Low threshold FIT - most cost effective

Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England

Uptake & Deprivation
2015 London Pilot

London

IMD 1 (Posh): (8.3%)
IMD 2: (7.7%)
IMD 3: (10.0%)
IMD 4: (7.4%)
IMD 5 (Poor): (9.8%)

gFOBt in London
FIT
Uptake in Prevalent Episodes
2014/5 Southern, Midlands & NW, London Pilots

1 – 5 invitations but no previous response

- **Both**: 11.6% Increase
- **Southern**: 11.8%
- **London**: Uptake doubled! 9.7% to 19.5%
- **Mid & NW**: 11.3%

FIT gFOBt
Uptake & All Episodes
2014 Southern, Midlands & NW Pilot

0 – 5 previous screening invitations

- **7.1% Increase**
- **7.0%**
- **7.3%**

**290,000 Additional screens each year!**
Polypectomy rate increase to >64% with... 
...more polyps in each category.

Challenge...
FIT Threshold and Positivity

2014 South, Midlands & NW Pilot

Uncertainty & Pilot

- 7.9%
- 1.7%
- 1.56%

Comparison of Positivity:

- gFOBt
- FIT 20
- FIT 40
- FIT 100
- FIT 150
- FIT 180
Relationship between FIT Threshold, % Uptake & Screen Detected Advanced Adenomas
(Biennial screen of 4.4 million in England)

Detected Advanced Adenomas (4.4 m Population)

- 70% Uptake
- 60% Uptake

FIT Threshold ug/g

FIT

gFOBt

England
Relationship between FIT Threshold, % Uptake & Screen Detected Cancers

France
- 30% Uptake
- 30ug/g Threshold

Netherlands
- 71-73% Uptake
- 47ug/g Threshold

Scotland
- 60-65% Uptake
- 80ug/g Threshold

Screen Detected Cancers (4.4 m Population) vs FIT Threshold ug/g
Faecal Immunochemical Test (FIT) & Positivity
Thresholds adopted by National Bowel Cancer Screening Programmes
(1st October 2016)

Predicted FIT positivity - % of participants referred for colonoscopy

<table>
<thead>
<tr>
<th>Country</th>
<th>% Referred</th>
</tr>
</thead>
<tbody>
<tr>
<td>England (April 2018)</td>
<td>12%</td>
</tr>
<tr>
<td>England (April 2018)</td>
<td>12%</td>
</tr>
<tr>
<td>Scotland (Dec. 2017)</td>
<td>7.8%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5.2%</td>
</tr>
<tr>
<td>Southern Ireland</td>
<td>2.9%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>2.1%</td>
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<tr>
<td>Canada (Quebec)</td>
<td>1.7%</td>
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<tr>
<td>France</td>
<td>1.5%</td>
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<tr>
<td>Portugal</td>
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<tr>
<td>Norway (pilot)</td>
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<tr>
<td>Denmark</td>
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<td>Hungary</td>
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<td>Iceland (planned)</td>
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<td>Italy (North &lt;20)</td>
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<td>Korea</td>
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<td>Malta</td>
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<td>Singapore</td>
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<td>Slovenia</td>
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<td>Spain (Catalonia)&lt;20</td>
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<td>Taiwan</td>
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<td>Uruguay</td>
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<td>England (pilot)</td>
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<td>Australia</td>
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<td>Lithuania (pilot)</td>
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<td>Latvia (pilot)</td>
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<td>Belgium (Flanders)</td>
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<td>Switzerland (not ...)</td>
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<td>Netherlands (pilot)</td>
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<tr>
<td>New Zealand (pilot)</td>
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<td>Israel</td>
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<tr>
<td>Austria</td>
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<td>Sweden (pilot)</td>
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</tbody>
</table>

Colonoscopy Capacity Problems

Threshold used in the FIT pilot in England
Faecal Immunochemical Test (FIT) & Positivity
Thresholds adopted by National Bowel Cancer Screening Programmes
(1st October 2016)

Estimate from pilots

No. of cancers missed relative to those detected using a 20ug/g threshold

<table>
<thead>
<tr>
<th>Country/Programme</th>
<th>0</th>
<th>780</th>
<th>1,900</th>
<th>2,900</th>
<th>3,500</th>
<th>3,600</th>
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Colonoscopy Capacity Problems

Challenges...
- Increase colonoscopy capacity
- Increase Positive Predictive Value
- Use FIT more intelligently
Positivity rate of FIT at 10ug/g Temperature dependence

Use ‘recent ambient temperature’ in a FIT risk algorithm?

Warm summers... Lower FIT concentrations

Elapse time - *period sample collection to analysis*

8,950 FIT screens - 8.8% positivity
Mean return time 3 days

Use ‘sample elapse time’ in FIT risk algorithm?

Falling Hb concentration

Proportion of colorectal cancers that occur in Women
(C18-C20 2011-2013)

Source: cruk.org/cancerstats
Cancers Detection in 10,000 FIT Screened Participants
(50:50 male & female)

2014 Pilot Data

- Expected Male Cancers detected in men
- Expected Female Cancers detected in women

Expect 60% of cancers to be in men
Expect 40% of cancers to be in women

‘Estimated cancers in men and women’ (dotted lines) based on the proportion of incident cancers in UK men and women of screening age
Cancers Detection in 10,000 FIT Screened Participants
(50:50 male & female)

2014 Pilot Data

- Expected Male
- Cancers detected in men
- Expected Female
- Cancers detected in women

FIT can increase gender inequality for detection of cancer
Cancers Detection in 10,000 FIT Screened Participants

(50:50 male & female)

2014 Pilot Data

Opportunity for intelligent use of FIT

Cancers detected in men

Men (60%) 10 cancers/5,000 participants

Cancers detected in women

Women (40%) 6.7 cancers/5,000 participants

FIT Concentration ug/g

Cancers detected /5,000 male & 5,000 female participants (completed FIT)
Screen Episode & FIT threshold – Cancer Detection Rate

- First Invitation (60 year olds)
- No response to previous invitations
- Participated previously

Opportunity for more intelligent use of FIT
Screen Episode & FIT threshold – Cancer Detection Rate

First Invitation (60 year olds)
- No response to previous invitations
- Participated previously

Previous non-responders benefit most from a low FIT threshold

Opportunity?
Age & FIT Threshold – Cancer Detection Rate

Should age, or QALY (Quality-adjusted Life Years Gained) influence threshold?

Opportunity?
Opportunity?

Risk & screening history...

Increasing risk
• First invitation to participate
• Poor adherence
  • Use period since last screen?

Decreasing risk
• Good adherence
• Previous ‘false positive’ FIT
• Bowel Scope participant
• Surveillance colonoscopy

All held on screening database!

% Uptake over 3 episodes

Adherence to screening

Increasing Risk of CRC

70% 1 in 3

61% 2 in 3

44% 3 in 3

Very Poor Adherence

Poor Adherence

Full Adherence

At least once  At least twice  At least 3 times
Personal Medical Colon Cancer Risk Factors

- Personal cancer history - (colon, rectum, ovary, endometrium, or breast)
- Ethnicity (Ashkenazi Jew)
- Family history of colon cancer
- Lynch Syndrome etc
- Gallstones
- Type II diabetes
- Metabolic syndrome
- Ulcerative colitis
- Crohn's colitis
- Lifestyle factors: Sugar consumption

Know Your Family Medical History

Ethnicity: Ashkenazi Jew
The algorithm offers an additional means of identifying risk of colorectal cancer, and could support other approaches to early detection, including screening... and active case finding.
Bowel cancer risk factors

**Prevention**
- 54%
- Preventable cases of bowel cancer, UK

**Red and processed meat**
- 21%
- Bowel cancer cases linked to eating red and processed meat, UK

**Excess bodyweight**
- 13%
- Bowel cancer cases linked to excess bodyweight, UK

**Low fibre**
- 12%
- Bowel cancer cases linked to eating too little fibre, UK
The Future of Quantitative FIT Multivariate Risk Scores

- Quantitative FIT concentrations...& trends
  (ambient temp /transit time)
- Age & Sex
- Screening history
- Indices of Deprivation – Postcode
- Medical History – IBD, Crohns, DM, etc
- Family History – 1st and 2nd deg. relatives
- Life style – Smoking, exercise, diet, obesity

Multivariate Bowel Cancer Risk Score

1. Assessment at point of invitation
   Very low risk…
   …delay invitation?
Developed a Multivariable Risk Prediction Model

- Logistic linear regression
- Artificial neural networks
- Machine learning

So far neural networks in the lead....
Marked increase in detection of advanced adenomas

2. Assessment on receipt of FIT
Referral to colonoscopy with improved PPV & cost effectiveness

Risk-adjusted colorectal cancer screening using the FIT and routine screening data: development of a risk prediction model
FIT – An opportunity to personalise population-based screening?

Better Screening by -
...focusing on **individuals**...
...as well as on **populations**?

‘**Personalising Population-based Screening**’

1. Intelligent use of FIT data
2. Incorporate personal risk
3. Personalised interpretation of the FIT Screen