Faecal testing in colorectal cancer screening:

State of the Art

Cancer Screening Programmes
Faecal Immunochemical Test (FIT)

1. Marked increase in **analytical specificity** of FIT
2. Enables its use at low concentrations
3. Marked increase in **clinical sensitivity**

Where do the **false positives** come from? Clinical, dietary, drug interference? Could they be eliminated?

Globin *(Human)*

Haem
All studies confirm superior performance of FIT over gFOBT

- Improved uptake
- Improved cancer & adenoma detection
- Improved PPV (threshold dependent)

### Study Cohort

<table>
<thead>
<tr>
<th>Test</th>
<th>Study Cohort</th>
<th>Invited Participation</th>
<th>Follow-up examination</th>
<th>Advanced adenomas &amp; cancers</th>
<th>Detected cancers</th>
<th>False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBt</td>
<td>10,011</td>
<td>10,301</td>
<td>62 (95%)</td>
<td>28 (1.2%)</td>
<td>6 (0.3%)</td>
<td>34 (55%)</td>
</tr>
<tr>
<td>FIT</td>
<td>20,623</td>
<td>10,322</td>
<td>137 (96%)</td>
<td>14 (1.4%)</td>
<td>67 (0.5%)</td>
<td>46 (45%)</td>
</tr>
</tbody>
</table>

Clinical sensitivity and specificity in screening?

- No consensus - influenced by:
  - study population
  - analytical and colonoscopy performance

---

*Van Rossum et al Gastroenterology 2008 135:82-90*

Choose a cut-off to meet your clinical requirements

Park DI et al. Am J Gastroenterol. 2010

Adjustable sensitivity – Greatest asset of FIT!

Adjust threshold to meet changing circumstances
- Clinical aspirations
- Endoscopic resource

Use numeric value in multi-variable risk assessment

<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>
</tr>
<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>

The “best” faecal haemoglobin cut-off value for detecting colorectal cancer with three quantitative FIT
FIT sensitivity
Left and Right-sided lesions

Study
T De Wijkerslooth 2011

Colonoscopy
1256

Advanced Adenoma
119

Left
38% (29-47)

Right
37% (28-46)

Study
Haug U 2011

Colonoscopy
2310

Advanced Adenoma
228

Left
33% (26-41)

Right
20% (11-31)

De Wijkerslooth T et al. DDW 2011

Haug U et al. Br J Cancer 2011
Locations ‘lesions’ removed
FIT Pilot England 2014/5

‘Polyp’ location – relatively small change across the thresholds

<table>
<thead>
<tr>
<th>FIT</th>
<th>Rectum</th>
<th>Sigmoid</th>
<th>Descending</th>
<th>Splenic</th>
<th>Transverse</th>
<th>Hepatic</th>
<th>Ascending</th>
<th>Caecum</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>16.30%</td>
<td>30.3%</td>
<td>8.98%</td>
<td>3.06%</td>
<td>13.6%</td>
<td>3.28%</td>
<td>13.05%</td>
<td>9.9%</td>
</tr>
<tr>
<td>40</td>
<td>16.08%</td>
<td>30.6%</td>
<td>9.15%</td>
<td>3.12%</td>
<td>13.3%</td>
<td>3.51%</td>
<td>12.95%</td>
<td>9.6%</td>
</tr>
<tr>
<td>60</td>
<td>15.23%</td>
<td>31.9%</td>
<td>9.73%</td>
<td>3.07%</td>
<td>13.0%</td>
<td>3.07%</td>
<td>12.91%</td>
<td>9.2%</td>
</tr>
<tr>
<td>80</td>
<td>14.85%</td>
<td>33.3%</td>
<td>9.14%</td>
<td>2.67%</td>
<td>13.9%</td>
<td>3.05%</td>
<td>12.41%</td>
<td>9.0%</td>
</tr>
<tr>
<td>100</td>
<td>14.54%</td>
<td>33.9%</td>
<td>9.04%</td>
<td>2.42%</td>
<td>14.1%</td>
<td>3.08%</td>
<td>12.30%</td>
<td>9.0%</td>
</tr>
<tr>
<td>120</td>
<td>14.45%</td>
<td>33.8%</td>
<td>8.27%</td>
<td>2.72%</td>
<td>14.5%</td>
<td>3.35%</td>
<td>12.57%</td>
<td>9.0%</td>
</tr>
<tr>
<td>140</td>
<td>14.51%</td>
<td>34.4%</td>
<td>8.61%</td>
<td>2.95%</td>
<td>15.0%</td>
<td>3.20%</td>
<td>12.67%</td>
<td>7.0%</td>
</tr>
<tr>
<td>160</td>
<td>14.05%</td>
<td>34.8%</td>
<td>8.19%</td>
<td>3.00%</td>
<td>15.3%</td>
<td>3.27%</td>
<td>13.23%</td>
<td>6.6%</td>
</tr>
<tr>
<td>180</td>
<td>14.37%</td>
<td>34.0%</td>
<td>8.77%</td>
<td>3.18%</td>
<td>15.3%</td>
<td>3.33%</td>
<td>13.01%</td>
<td>6.5%</td>
</tr>
<tr>
<td>200+</td>
<td>15.18%</td>
<td>34.1%</td>
<td>8.94%</td>
<td>3.20%</td>
<td>15.4%</td>
<td>3.54%</td>
<td>12.48%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Data Prepared by Claire Nickerson (BCSP) 2017
**Locations ‘lesions’ removed**

FIT Pilot England 2014/5

‘Polyp’ location – relatively small change across the thresholds

<table>
<thead>
<tr>
<th>FIT</th>
<th>Right</th>
<th>Transverse</th>
<th>Left Inc.</th>
<th>Left Exc.</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>26.23%</td>
<td>13.60%</td>
<td>58.64%</td>
<td>42.34%</td>
<td>16.30%</td>
</tr>
<tr>
<td>40</td>
<td>26.06%</td>
<td>13.30%</td>
<td>58.95%</td>
<td>42.87%</td>
<td>16.21%</td>
</tr>
<tr>
<td>60</td>
<td>25.18%</td>
<td>13.00%</td>
<td>59.60%</td>
<td>43.85%</td>
<td>15.95%</td>
</tr>
<tr>
<td>80</td>
<td>24.46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>24.38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>24.92%</td>
<td>14.50%</td>
<td>59.24%</td>
<td>44.79%</td>
<td>14.45%</td>
</tr>
<tr>
<td>140</td>
<td>22.87%</td>
<td>15.00%</td>
<td>60.47%</td>
<td>45.96%</td>
<td>14.51%</td>
</tr>
<tr>
<td>160</td>
<td>23.10%</td>
<td>15.30%</td>
<td>60.04%</td>
<td>45.99%</td>
<td>14.05%</td>
</tr>
<tr>
<td>180</td>
<td>22.84%</td>
<td>15.30%</td>
<td>60.32%</td>
<td>45.95%</td>
<td>14.37%</td>
</tr>
<tr>
<td>200+</td>
<td>21.72%</td>
<td>15.40%</td>
<td>61.42%</td>
<td>46.24%</td>
<td>15.18%</td>
</tr>
</tbody>
</table>

Right sided lesions increase as FIT threshold falls

Data Prepared by Claire Nickerson (BCSP) 2017
FIT Cut-off Predicts Interval Cancers
Taiwanese Population Screening Cohort

- FIT Cut-off Predicts Interval Cancers
- Taiwanese Population Screening Cohort

Prospective cohort study
- 2001 and 2007
- 45,992 participants

Cumulative Incidence of neoplasm / 1000 person years

Interval cancer rate influenced by...

- FIT threshold
- Frequency of screening (biennial / annual)
- Adherence to screening

1 - 6 Years since FIT

Chen L-S et al. Lancet Oncol June 2011
Detection rate with 1 or 2 day FIT screening

Single FIT – OK in screening!


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)

Most efficient strategy
Economic modelling of gFOBT and FIT

Whatever you invest in screening

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

Life years saved per 1000 individuals aged 45-80 in 2005
(3% discount)

Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)

DNA: Franklin, Crick & Watson
1953

Search for a better test...
Method of Screening
Non-Invasive Investigations

Carbohydrate antigen 19-9 (CA 19-9)

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

Methylated vimentin

p53 gene
K-ras /KRAS gene
APC gene

Proteins (M2-PK)

Epidermal growth factor receptor (EGFR)
Multi-target Stool DNA & FIT test

(Cologuard)

Multi-target Stool DNA & FIT test

- FOBT (FIT)
- Methylated BMP3 & NDRG4
- Mutant KRAS & B-Actin

The NEW ENGLAND JOURNAL of MEDICINE

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/NEJMo1311194

FDA Advisers Back Exact Sciences Colon Cancer Test

WASHINGTON March 27, 2014 (AP)
Comparative Sensitivity of Multitarget Stool FIT /DNA Test and a Single (FIT)

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, $P<0.001$

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

Increased sensitivity
But... a significant increase in... referral & false positivity rate

Imperiale TF et al. NJMed2014;370:1287-97
Blood in faeces...

...still the best marker for population screening!
‘They say it is easier with FIT!’
In good company

Faecal
Immunochemical
Test

European guidelines for quality assurance in colorectal cancer screening and diagnosis.
Chapter 4. Faecal occult blood testing.
Endoscopy 2012; 44 (S 03):SE65-SE87
Case for quantitative FIT in screening has strengthened

1. Better analytically quality
2. Control endoscopy referrals
3. Ready for ‘risk-based’ screening

Selling FIT Products
What species of FIT? Quantitative or Qualitative

Questions to ask

1. Good Evidence-base?
2. Many successful programmes?
3. Reproducible quality
4. Simple to manage batch changes
5. Objective measurement?
6. High quality quality control
7. QA monitor by organisation?
8. Fast analysis?
9. Can adjust sensitivity & positivity
10. Use in ‘Risk Score’
11. Cheapest solution

<table>
<thead>
<tr>
<th>Quantitative</th>
<th>Qualitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Overdue for enhancement

1. Optimised for lower / high thresholds
2. Faster and larger capacity analysers
3. Combinations with other blood markers

Quantiative FIT
We need - FIT device improvements

1. More reliable sampling
2. Non-tamper lids
3. Better device ID systems (RFID marker)
4. Easier to write collection date & name
IFCC FIT Working Group
(International Federation of Clinical Chemistry)

Chair
Sally C. Benton  UK

Group Members
Marieke Fasa  NL
Barcey Levy  USA
Han Mo Chiu  Taiwan
Josep-Maria Auge  Spain
Erin Symonds  Australia
Petr Kocna  Czech Republic
Natasha Djedovic  UK
Judith Strachan  UK
Heinz Schimmel  Belgium
Shizuka Takehara  Japan
Samantha Jones  UK

Corporate members
Maurizio Gramegna  Italy Sentinel
Takuo Ichiyanagi  Japan Eiken
Tsuyoshi Fukuda  Japan Kyowa
Yasunobu Masuda  Japan Kyowa
Mr Yosuke Doi  Japan Alfresa
Dr Tetsuya Kosaka  Japan Alfresa

First meeting held in Athens in June 2017

Terms of Reference
• To attempt to **standardize** analysis of haemoglobin in faecal samples by immunochemistry (FIT)
• To identify all **sources of pre-analytical variation** and **standardise** if possible
• To establish **external quality assurance** and **3rd party internal quality control** programmes
• To determine impact of **assay interference of Hb variants** and other factors
Stability of FIT (OC Sensor)
Grazia Grazzini et al Gut. 2010 Jul 5

Average value of HB in intervals of 5° Celsius

Winter v Summer
- 17% more +ve tests
- 13% more cancers
Seasonal Variation in FIT Positivity Rate

Chyke A. Doubeni, MD, MPH
Perelman School of Medicine
University of Pennsylvania
Seasonal Variation in FIT Positivity Rate

Chyke A. Doubeni, MD, MPH
Perelman School of Medicine
University of Pennsylvania

Winter

Summer

Modified Dickey-Fuller test p-value <0.01
Stability in Individual Stool Samples
Spiked to 30 ug/g
2006 and 2012 Eiken Buffers at 25°C
Individual Stool Samples
Spiked to 30 ug/g
2006 and 2012 Eiken Buffers at 25°C
Stability of FIT - Lab Experiment

- 71 FIT +ve samples at ‘room temperature’ for 25 days
- Average Hb falls by 5.9% /day
- None <10 ug/g within 10 days
Stop Invitation During Summer?

Yes (3)

- Australia - *Selected if Temp >30°*
- Italy (E-R) - *Reduced July /August*
- Japan (*most municipalities*)

No (14)

- England
- Canada - *Saskatchewan, PEI, Alberta, L&N*
- Czech Republic
- Denmark
- Ireland
- Italy - *Veneto, Piedmont*
- Malta
- The Netherlands (*but stop for Christmas!*)
- New Zealand
- Singapore
- Slovenia
- Spain - *Basque*
- Taiwan
- Uruguay
FIT Kit Delivery

Pharmacy

Public Health

Hospital

Mail

GP

10

1

1

1

4
FIT Return Instructions?

- None: 4
- <7 days: 2
- <2 - 3 days: 1
- Return <2 days: 2
- Post <24 hours: 2
- Post immediately: 1
- Post Office not street box: 2
- Not if hot weather: 1
- Not at weekend: 7

Programmes
Colorectal Cancer Screening
A global overview of existing programmes

Scheuders EH et al
GUT 2015;64:1637-1649

Iceland
Slovenia
France
Germany & Poland
Holland
Scandinavia
Australia
New Zealand
Canada
Japan
Taiwan
Hong Kong
USA
Italy
Malta

Budget 2017: Bowel screening programme rolled out

No screening or unknown
Opportunistic: gFOBT/FIT-based
Opportunistic: colonoscopy (+gFOBT/FIT)
Population-based organised, pilot
Population-based organised, roll-out ongoing
Population-based organised, roll-out complete
Pondering the Future
FIT... in the Future!

- More programmes with **higher FIT thresholds** >20ug/g
- Organised programmes consider ‘**Risk Scores**’ in personalised screening – recent *FIT concentrations*, *personal demographics*, *screening history*, *family and personal medical history /lifestyle*
- Focus on **adherence** to FIT screening (not just uptake)
- See more publications on **FIT screening outcomes** – but much **variation** because of **quality differences** in coverage, uptake, adherence, **ADR** and quality of aftercare
- Adoption of low threshold **FIT in primary care**
- Comparative assessments of FIT and **new combined FIT /faecal DNA**
The future is FIT
Challenges
Southern Ireland

Review finds 12 bowel cancers missed at Wexford General Hospital

Delay in bowel screening at UHG for over half of patients

Lessons must be learned from bowel screening mistakes, warns Irish Cancer Society
Tuesday, September 26, 2017 9:30 – 11:30
Chairs: O. Májek, S. Halloran

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30 – 9:50</td>
<td>Faecal testing in colorectal cancer screening: state of art</td>
<td>S. Halloran</td>
</tr>
<tr>
<td>9:50 – 10:00</td>
<td>Czech National Coordination Centre for Prevention of Serious Diseases: platform for systematic introduction of innovations to early disease detection</td>
<td>O. Májek</td>
</tr>
<tr>
<td>10:00 – 10:20</td>
<td>Implementation of population-based faecal occult blood testing and transition to immunochemical tests: experience from England</td>
<td>S. Halloran</td>
</tr>
<tr>
<td>10:20 – 10:35</td>
<td>Role of general practitioners in population-based colorectal cancer screening: current situation and future prospects</td>
<td>B. Seifert</td>
</tr>
<tr>
<td>10:35 – 10:50</td>
<td>Quantitative immunochemical tests: evidence on accuracy and implementation considerations in the Czech Republic</td>
<td>P. Kocna</td>
</tr>
<tr>
<td>10:50 – 11:05</td>
<td>Quality-assured immunochemical testing – proposal for a pilot project in the Czech Republic</td>
<td>O. Májek, Š. Suchánek</td>
</tr>
<tr>
<td>11:05 – 11:30</td>
<td>Structured discussion &amp; wrap-up</td>
<td></td>
</tr>
</tbody>
</table>

26th Tuesday 12:00 - press conference - Thierry Ponchon could give insight into goals of UEG.
SPH programme in England and how important is to have a good governance, quality assurance and political support.

Session title: Why do we have different levels of participation in Europe? Influence of the population type. How to tackle inequalities.

Date: Wednesday, September 27
Time: 14:20 – 15:50
FIT in Primary Care

Recommendations for Primary care referral (appointment < 2 weeks)
OC Sensor, HM-JACKarc and FOB Gold FIT (threshold of 10 ug/g) in primary care for suspected colorectal cancer with unexplained symptoms and no rectal bleeding and do not meet the criteria for suspected cancer referral (appointment within 2 weeks).

Criteria for a suspected Colorectal cancer referral
- aged ≥ 40 with unexplained weight loss and abdominal pain or
- aged ≥ 50 with unexplained rectal bleeding or
- aged ≥ 60 and over with:
  - iron-deficiency anaemia or
  - changes in their bowel habit, or
  - occult blood in their faeces

- adults with a rectal or abdominal mass

- aged < 50 with rectal bleeding and
  - abdominal pain or
  - change in bowel habit or
  - weight loss or
  - iron-deficiency anaemia
Economic modelling of gFOBT and FIT

Life years saved per 1000 individuals aged 45-80 in 2005 (3% discount)

Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)