Why FIT
(Faecal Immunochemical Test)
is the best biomarker for CRC screening

Prof. Stephen Halloran
• Royal Surrey County Hospital
• NHS Cancer Screening Programme
• University of Surrey
Guaiacum Officinale
- Lignum Vitae
Guaiac Faecal Occult Blood Test

Haemoglobin - Haem

- Haem (containing iron)
- Release of oxygen from H₂O₂
- Oxidise a dye (guaiac)
- Change in colour (blue)
$2\text{H}_2\text{O}_2 = 2\text{H}_2\text{O} + \text{O}_2$
Will they do the test???

They’ll never do it!

It’s just too gross!
1990’s
Large
Randomised
Controlled Trials Using
FOBT

US (Minnesota)
UK (Nottingham)
Denmark (Funen)
France (Dijon)

Sept. 19, 2013 369;12  Nishihara et al
30 year update - Minnesota RCT

Annual gFOBT
•  After 13 years - 33% reduction of CRC mortality
•  After 30 years - 32%

Biennial gFOBT
•  Both 13 and 30 years about 22%
Message – polypectomy effective in reducing CRC
**Strengths**

- Cheap test
- Mailing – simple & cheap
- Records patient ID and date
- 3 Opportunities to find blood
gFOBT - A significant analytical challenge!

Mean Positivity / Reader / Week

Spot Positivity (%)

Reader Identification

Imprecise

Negative Bias
The English ‘three-kit algorithm’

- **Guaiac FOBT Kit 1**
  - Negative
  
- **WP [1-4 spots positive]**
  - **Retest Kit 2**
    - **WP,N**
      - **Retest Kit 3**
        - **WP,N,N**
          - Negative repeat in 2 years
        
    - **WP,P [any spot P]**
      
  
- **P [5-6 spots positive]**
  - Investigation

5% dropout

3% dropout
Why we need a
Better Test for Haemoglobin

No Automation

Can’t adjust positivity

Operator Variability

3 samples,
3 kits, 3 letters,
3 analysis
Colorectal Cancer

The Ideal Population Marker

- Detect all CRC & ‘pre-cancers’
  - Early stage Dukes A & B cancers
  - Advanced adenomas
  - No false positives

- Simple Sampling
  - Home
  - GP Clinic

- Analysis Easy & Reliable

- No interference
  - Sample stable
  - Temperature
  - Light
  - Diet or drugs
  - Other diseases

- Affordable!
DNA: Franklin, Crick & Watson 1953
Method of Screening
Non-Invasive Investigations

Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer

Methylation of vimentin

Epigenomics Licenses Septin 9 Diagnostics

Calprotectin Intestinal Inflammation Assay

p53 gene
K-ras /KRAS gene
APC gene

Proteins (M2-PK)

Epidermal growth factor receptor (EGFR)

carcinoembryonic antigen (CEA)

Carbohydrate antigen 19-9 (CA 19-9)
Method of Screening

Non-Invasive Investigations

FDA Advisers Back Exact Sciences Colon Cancer Test

WASHINGTON March 27, 2014 (AP)

Exact Sciences Moves Closer to Preventing the No. 2 Cancer Killer

Multi-target Stool DNA & FOBT 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/NEJMoa1311194
Blood in faeces
...still the best marker!
Haemoglobin - Globin

- Antibody recognition of the tertiary structure produced by the folding of the amino acid chain in the globin protein.
European guidelines for quality assurance in colorectal cancer screening and diagnosis. Chapter 4. Faecal occult blood testing.

Endoscopy 2012; 44 (S 03):SE65-SE87
## FIT Measures Concentration of Haemoglobin

<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>
<td></td>
</tr>
<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, MD¹, Seungho Ryu, MD², Young-Ho Kim, MD³, Suck-Ho Lee, MD⁴, Chang Kyun Lee, MD⁴, Chang Soo Eun, MD⁵ and Dong Soo Han, MD⁵
# Study relating OC Sensor FIT concentration and outcome at colonoscopy

Hemoccult-II and OC-SENSA MICRO

<table>
<thead>
<tr>
<th>Endoscopic Classification</th>
<th>No. of Patient Outcomes</th>
<th>Positive gFOBT</th>
<th>Mean FIT Conc. ug/g</th>
<th>Positives at 15 ug/g Cut-off</th>
<th>Positives at 20 ug/g Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukes A &amp; B</td>
<td>10 (77%)</td>
<td>3 (30.0%)</td>
<td>138</td>
<td>9 (90.0%)</td>
<td>8 (80.0%)</td>
</tr>
<tr>
<td>Dukes C &amp; D</td>
<td>3 (23%)</td>
<td>1 (33%)</td>
<td>281</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>11 (85%)</td>
<td>3 (27%)</td>
<td>167</td>
<td>10 (90.9%)</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Distal</td>
<td>2 (15%)</td>
<td>1 (50.0%)</td>
<td>191</td>
<td>2 (100%)</td>
<td>1 (50.0%)</td>
</tr>
</tbody>
</table>
Hb Cut-off concentration determines the performance of FIT in a colorectal cancer Screening Programme

Van Rossum et al Gastroenterology 2008 135:82-90

Lower cut-off concentrations – More cancers detected

Haemoglobin Cut-off Concentration (ug/g faeces)
Effect of Cut-off on Number needed to Scope

Van Rossum - BJ Cancer (2009)

No. of Colonoscopies

Effect of Cut-off on Number needed to Scope

Van Rossum - BJ Cancer (2009)

Increasing proportion of false +ve

Haemoglobin Cut-off Concentration (ug/g faeces)
Effect of Cut-off on Number needed to Scope

*Van Rossum - BJ Cancer (2009)*

![Graph showing the effect of cut-off on number needed to scope. The graph demonstrates an increasing proportion of false positives with higher cut-off concentrations for colorectal cancer and CRC+advanced adenomas.](image)
‘Age? You mean now... or when we first sat down?’
The much-ballyhooed provincial colon cancer screening program has hit some hitches that will delay its start-up.

The government first announced the program last spring. The Vancouver Island Health Authority volunteered to be the first region to implement it a few months ago. But two hospitals in Victoria have been swamped with referrals for colonoscopies. Demand has so outstripped the available supply of hospital space, doctors and nurses that the government has told other health authorities to do a better job anticipating demand before rolling out similar programs.

"From what I understand, VIHA put up their hands and said 'we want to be the first to do this,'" said Health Minister Terry Lake in a recent interview. "And as it turned out, there were renovations going on in some operating rooms that decreased the availability of ORs," he said.

While the provincial program was supposed to have been implemented throughout the province by this summer, it is now expected to roll out across the Lower Mainland, the North and the Interior in late September.

Lake said other health authorities are learning from the experiences on Vancouver Island.

"We've talked to the other health authorities. So now when we roll it out elsewhere, we do know some of the challenges that will need to be overcome," said Health Minister Terry Lake.

Dr. Max Coppes, CEO of the BC Cancer Agency, said Monday that the government is giving the agency $2 million a year to coordinate and manage the program, maintain a registry, and set quality assurance standards.

"In hindsight, our modelling projections underestimated the actual numbers. So we're looking at our predictions before other health regions implement the program."
Van Rossum et al Gut 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 5004

FIT 5007

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 10,301

FIT 10,322

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 5004

FIT 5007

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 10,301

FIT 10,322

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 5004

FIT 5007

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off

Study Cohort

Invited

gFOBt 10,301

FIT 10,322

15,011

20,623

Participation

20ug/g Cut-off

Positive test

gFOBt

FIT

Follow-up examination

Advanced adenomas & cancers

Detected cancers

False Positives

Van Rossum et al Gastroenterology 2008 135:82-90

L Hol et al Gut 2010;59:62–68

20ug/g Cut-off
Screening for colorectal cancer

<table>
<thead>
<tr>
<th>FIT (10ug/g cut-off)</th>
<th>Sensitivity (CI)</th>
<th>Specificity (CI)</th>
<th>PPV (CI)</th>
<th>NPV (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>88 (47-99)</td>
<td>91 (89-92)</td>
<td>6 (3-12)</td>
<td>100 (99-100)</td>
</tr>
<tr>
<td>Advanced neoplasia</td>
<td>38 (29-47)</td>
<td>93 (92-95)</td>
<td>37 (29-46)</td>
<td>93 (92-95)</td>
</tr>
</tbody>
</table>

FIT sensitivity
Left and Right-sided lesions

Study
De Wijkerslooth T et al. DDW 2011

Colonoscopy
1256

Advanced Adenoma
119

Left
38% (29-47)

Right
37% (28-46)

Study
Haug U et al. Br J Cancer 2011

Colonoscopy
2310

Advanced Adenoma
228

Left
33% (26-41)

Right
20% (11-31)
Detection rate with 1 or 2 day FIT screening

Detection rate with 1 or 2 day FIT screening

Detection rate with 1 or 2 day FIT screening

Detection rate with 1 or 2 day FIT screening

FIT Cut-off Predicts Incident cancers
Taiwanese Population Screening Cohort

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

Chen L-S et al. Lancet Oncol June 2011
Units of measurement and reporting

μg Haemoglobin /g of Faeces (µg/g)

Depends on the volume of buffer provided in the collection device

Interested in the concentration in faeces not buffer!

Depends on quantity of faeces collected on the sample stick
FIT and NHS

Bowel Cancer Screening in England

Pilot Design

- FIT *in place* of guaiac FOBT
- 40,000 FIT tests
- Minimal impact upon BCSP
- 1 in 28 invitations will be FIT
- Complete in 6 months
- Use 2 Hubs
- Single kit
Available FIT Systems

FOB Gold NG/ BioMajesty  NS PLUS-C15
HM-JACKarc  OC Sensor DIANA
FIT System for NHS Pilot

- FOB Gold NG/ BioMajesty
- HM-JACKarc
- NS PLUS-C15
- OC Sensor DIANA
FIT System for NHS Pilot

- FOB Gold NG/ BioMajesty
- HM-JACKarc

- NS PLUS-C15
- OC Sensor DIANA
Stability of FIT (OC Sensor)
Grazia Grazzini et al Gut. 2010 Jul 5

Average value of HB in intervals of 5° Celsius

- Winter vs Summer
  - 17% more +ve tests
  - 13% more cancers
Seasonal variation in positivity rates in the Netherlands

Date: 17th July - 31st July 2013

Postal Services Temperature Monitoring Project 2013
Individual Stool Samples
Spiked to 150 ng/mL
2006 and 2012 Eiken Buffers at 25°C
Individual Stool Samples
Spiked to 150 ng/mL
2006 and 2012 Eiken Buffers at 25°C

Spiked Stool Concentration (ng/mL)

- Stool A (Buffer 2006)
- Stool B
- Stool C
- Stool D
- Stool E

2006

2012
FIT Stability Studies

HM-JACKarc (*Hb spiked buffer*)

Magdalen Carroll et al GMEC/NHS Report October 2013

-20°C
4°C
20°C

Concentration (µg Hb/g faeces) vs Days

Days: 1 2 3 4 6 7 8 9 10 12 14 16 18 20 22 24 29
FIT Stability Studies

HM-JACKarc (Hb spiked buffer)

Magdalen Carroll et al GMEC/NHS Report October 2013

Concentration (µg Hb/g faeces)

Days

-20C
4C
20C

35C
Stability of FIT - Lab Experiment


• 71 positives at Room Temperature over 25 days
• Average - Hb falls by 5.9% /day
• None negative, at low concentration of 10 ug/g, within 10 days
FIT Stability Studies
HM-JACKarc (*Hb spiked faeces*)

Magdalen Carroll et al GMEC/NHS Report October 2013
FIT Stability Studies
HM-JACKarc (*Hb spiked faeces*)

Magdalen Carroll et al GMEC/NHS Report October 2013

-20C
4C
20C

Concentration (µg Hb/g faeces)

Days
Maximising Uptake

Miscellaneous
• Change from gFOBT to FIT - 4 to 8% increase
• GP involvement? – depends on GP
• Pre-invitation – 6% already done!
• CO₂ insufflation – comfort factors
• Target local ‘Problem Population’

Test design and packaging
• Elderly – Arthritis, Parkinson’s disease etc

Information
• Learning difficulties – Alternative literature?
• Language – different languages, different letters?
• Braille, sign language, translators, DVD – Done!
• ....but avoid excessive information!

Coverage
• Disabilities – local initiative
• Prisoners
Maximising Uptake

Miscellaneous
- Change from gFOBT to FIT - 4 to 8% increase
- GP involvement? – depends on GP
- Pre-invitation – 6% already done!
- CO₂ insufflation – comfort factors
- Target local ‘Problem Population’

Test design and packaging
- Elderly – Arthritis, Parkinson’s disease etc

Information
- Learning difficulties – Alternative literature?
- Language – different languages, different letters?
- Braille, sign language, translators, DVD – Done!
- ….but avoid excessive information!

Coverage
- Disabilities – local initiative
- Prisoners
Make packaging
Attractive
Informative
Safe for mailing
Simple to use
Reliable
Innovative Packaging Principle

Participant

UK Mail

Hub Return Address

Bowel Cancer Screening Hub
20 Priestley Road
Research Park
Surrey GU2 7YS
CRC Population Screening

- Good test is one that gets done
- Choice agenda
  - CRC screening menu
- Flexi sigmoidoscopy, colonoscopy, new faecal & blood tests

- FIT will be the primary tool for CRC screening for next 10-15 years *(SPH Prediction)*

Gastro Central
CRC Screening Menu

**Tonight’s Specials…**
1. Colonoscopy - Chef’s Special €800
   Served with midazolam
1. Flexi Sigmoidoscopy €200
   Bring your own enema!

**Takeaway menu…**
1. Blood Screen €100
   Be the first to check this one out!
2. New Stool FIT & DNA Test – not yet available
3. FIT €10
   (Free colonoscopy with every positive FIT)
This is only the beginning...

Today...
FIT is used as a single risk factor with a simple cut-off

Tomorrow...
CRC risk will combine FIT with other parameters to provide a new more powerful predictor of colorectal cancer (FIT & DNA)

Stegeman et al, 2013 GUT online
Multivariate Risk Scores
Exploiting the potential of FIT

Faecal Immunochemical Test for Haemoglobin
- FIT concentration
- Age & Sex
- Screening history
  - Time & outcome of last 3 FIT screens
  - Time & outcome of last colonoscopy/ FS etc
- Index of Multiple Deprivation
  - Sociodemographic /Geodemographics (Postcode)

Available on Screening database

Available in Clinic / GP

- Medical History – IBD, Crohns, DM, etc
- Family History – 1\textsuperscript{st} and 2\textsuperscript{nd} degree relatives
- Life style - Smoking, exercise, diet, obesity
Multivariate Risk Scores
Exploiting the potential of FIT

Available on Screening database
Available in Clinic / GP

Multivariate Bowel Cancer Risk Score

Improved PPV & Cost Effectiveness of Colonoscopy Referrals
FIT – A Good Biomarker & Device?

Good Design
- Easy to use
- pack
- mail
- test

Reliable
- Participant
- Lab
- Clinician

Affordable
- Device
- Package
- Mailing
FIT for Population Screening…

Quantitative or Qualitative FIT

- Automated
- Objective measurement
- Positivity tailored to clinical targets and resource
- Monitored analytical performance
  - Internal Quality Control
  - External Quality Assessment
- Operational performance monitoring
  - Response monitoring
  - Clinical outcome monitoring
- Combine with other risk factors
- Cheaper… if subject to comprehensive costing
FIT and NHS Bowel Cancer Screening in England

- **2012/13/14** – Preparations for a FIT pilot
  - Pilot design
  - Develop and test FIT programme software
  - Evaluation of 4 FIT systems

- **2014** – FIT Pilot April to October
Economic modelling of gFOBT and FIT


Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)
Economic modelling of gFOBT and FIT

Economic modelling of gFOBT and FIT


Life years saved per 1000 individuals aged 45-80 in 2005

Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)
Economic modelling of gFOBT and FIT

Economic modelling of gFOBT and FIT


Costs per 1000 individuals aged 45-80 in 2005 (euro's, 3% discount)
Economic modelling of gFOBT and FIT

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)
FIT and NHS Bowel Cancer Screening in England

Why a Pilot?

Organisation
Write, test and refine the BCSS-FIT software
Mailing logistics & use of barcodes

FIT device and analysis
FIT design of packaging
Literature inc. instructions
Testing analytical systems

Performance in pre-screened pop’n (resource implications)
Uptake – how much will it increase (SES gradient)?
Positivity – is it the same or different to other studies?
Outcome – is it similar to other studies?

Cost
Economic assessment
Financial implications of change - gFOBT to FIT