Challenges for Colorectal Cancer Screening...

...a Biomarker with...

No Standards!

Prof. Emeritus Stephen P. Halloran

University of Surrey
W. Europe Top 20 Cancers

*World Health Organization*

**Incidence & Mortality** (2012)

**Western Europe**

*International Agency for Research on Cancer*

**Incidence** & **Mortality**

*Estimated age-standardised rates/100,000*

**Men**

- Breast
- Prostate
- **Colorectum**
- Lung
- Melanoma of skin
- Bladder
- Kidney
- Non-Hodgkin lymphoma
- Leukaemia
- Pancreas
- Stomach
- Thyroid
- Corpus uteri
- Lip, oral cavity
- Brain, nervous system
- Liver
- Other pharynx
- Testis
- Oesophagus
- Ovary

**Women**

- Breast
- Prostate
- Colorectum
- Lung
- Melanoma of skin
- Bladder
- Kidney
- Non-Hodgkin lymphoma
- Leukaemia
- Pancreas
- Stomach
- Thyroid
- Corpus uteri
- Lip, oral cavity
- Brain, nervous system
- Liver
- Other pharynx
- Testis
- Oesophagus
- Ovary

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**World - Bowel Cancer**

- 3rd commonest cancer
- 4th cause of Ca deaths

**Western Europe**

- 3rd commonest cancer
- 2nd commonest cancer death
- 1st commonest cancer in non-smoking men?
Survival 5 years after treatment

93%

77%

48%

7%

Dukes’ Stage

A

B

C

‘D’

Case for Screening

Bowel Cancer Pathogenesis

Polyp

10 years
Candidate Screening Tests

Carbohydrate antigen 19-9 (CA 19-9)

carcinoembryonic antigen (CEA)

Methylated vimentin

Epigenomics Licenses Septin 9 Diagnostics

Cologuard: The Stool DNA-Based Approach

ScheBo® Tumor M2-PK™ EDTA Plasma Test

exact sciences

Calprotectin
Intestinal Inflammation Assay

THE SEPTIN 9 TEST

Blood-based colorectal cancer screening is available for your patients who are unwilling or unable to have a colonoscopy

Proteins (M2-PK)

Epidermal growth factor receptor (EGFR)

p53 gene
K-ras /KRAS gene
APC gene
Blood in faeces
...still the best screening marker for cancer & adenomas!
Faecal Immunochemical Test (FIT)

Haemoglobin - Globin
- Specific to human blood
- Detects small bleeds
- Quantitative measurement

Hemoglobin

Haem

Globin
Available FIT Systems

- FOB Gold NG/ BioMajesty
- NS PLUS-C15
- HM-JACKarc
- OC Sensor DIANA
Faecal Immunochemical Test

The International Choice!

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 (37-25)</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>Histology</th>
<th>Mean FIT Conc. ug Hb /g faeces</th>
<th>+ve at 20 ug /g Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGD</td>
<td>27</td>
<td>14.1%</td>
</tr>
<tr>
<td>HGD</td>
<td>197</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size</th>
<th>Mean FIT Conc. ug Hb /g faeces</th>
<th>+ve at 20 ug /g Cut-off</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Mean FIT Conc. ug Hb /g faeces</th>
<th>+ve at 20 ug /g Cut-off</th>
</tr>
</thead>
<tbody>
<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>

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**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\(^5\)
Power of **Quantitative** FIT

Multivariate Risk Scores

- **Quantitative** FIT concentration
- Age & Sex
- Screening history
- Indices of Deprivation – Geodemographics (*Postcode*)
- Medical History – IBD, Crohns, DM, etc
- Family History – 1st and 2nd degree relatives
- Life style – Smoking, exercise, diet, obesity

Multivariate Bowel Cancer Risk Score

Better Screening!
- PPV
- Cost Effectiveness
- Colonoscopy Referrals
FIT – Why the challenge?

1. Haemoglobin is unstable in solution
FIT – Why the challenge?

1. Haemoglobin is unstable in solution

- 13% less cancers detected in Summer vis Winter

Grazzini, Halloran et al Gut. 2010

Australia
475,000 suspect FIT results!
FIT – Why the challenge?

1. Haemoglobin is unstable in solution
2. Same faeces, same units... different
   Hb buffer concentrations ($ng/mL$)

Buffer Volumes - Different

Faecal Sample Mass - dependent upon design of sampling device
FIT – Why the challenge?

1. Haemoglobin is unstable in solution
2. Same faeces, same units... different Hb buffer concentrations ($ng/mL$)
3. Assay calibration poorly defined

What was used for Hb calibration?
FIT – Why the challenge?

1. Haemoglobin is unstable in solution
2. Same faeces, same units... different Hb buffer concentrations \((ng/mL)\)
3. Assay calibration poorly defined
4. No ‘mature’ External Quality Assessment Scheme (EQAS).

Does FIT have a reliable EQAS?
**WEO CRCSC Expert working Group ‘FIT for Screening’**

**Remit**

Population screening for CRC using guaiac-based faecal occult blood tests (gFOBT) reduces disease-specific mortality but the superior performance characteristics of faecal immunochemical tests for haemoglobin (FIT) makes them a better choice for population screening. However, there is a need for FIT refinement and standardisation. To ensure, inter alia, traceability of analytical results, consistency in faecal sample mass evaluation, assessment of haemoglobin (Hb) stability and common units for reporting Hb concentrations. The EWG ‘FIT for Screening’ was convened to address these problems.

**Founding members**

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Faecal Immunochemical Tests

Standardisation

• **Product**
  – Hb Traceability
  – Sample mass?
  – Units of reporting
  – EQAS

• **Performance Claims**
  – Stability
  – Sample mass
  – Clinical sensitivity
  – Analytical accuracy

• **Procurement**
  – Critical attributes
  – Desirable attributes
  – Local requirements
FIT Publications 2012

- Young GP, Fraser CG, Halloran SP, Cole S. Guaiac based faecal occult blood testing for colorectal cancer screening: an obsolete strategy? Gut 2012 16(7):959-60

- Allison JE, Fraser CG, Halloran SP, Young GP. Comparing fecal immunochemical tests: improved standardization is needed. Gastroenterol 2012;142:422-424

- Fraser CG, Allison JE, Halloran SP, Young GP. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. JNCI 2012 104(11):810-4

% Europe Population over 65

How many FIT Screening Tests?
Conservative estimate...
Population 850 million
20% eligible 170 million
40% uptake, 2 yearly
4% positivity

70 million tests p.a.
(3 m colonoscopies p.a.)