Intelligent use of FIT

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No conflicts of interest!
Intelligent use of FIT

Kicked gFOBT into the long grass!
But... we are using a new ball but...
...playing by the rules of the ‘guaiac’ game!
‘...given the continuous nature of the FIT result, it seems wasteful of both information and endoscopy resource to have a single threshold...

- above - returned to normal screening
- below - receives a full colonoscopy.’

But... we are using a new ball but... ...playing by the rules of the ‘guaiac’ game!
<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>

Dong Il Park, MD\(^1\), Seungho Ryu, MD\(^2\), Young-Ho Kim, MD\(^3\), Suk-Ho Lee, MD\(^4\), Chang Kyun Lee, MD\(^5\), Chang Soo Eun, MD\(^6\) and Dong Soo Han, MD\(^7\)
<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>

...we need to apply a stratified approach for different risk-cohorts
Population screening... changes and increases risk differences!

Population Screening

- DIFFERENT Screening History
- DIFFERENT Health Issues
- DIFFERENT Ages
- Socioeconomic DIFFERENCES
- DIFFERENT Lifestyle
- DIFFERENT Family History
- Men... & Women

CRC Risk Reduction

FIT participation
Annual Colorectal Cancer Rates
UK 2012-2014

Age-Specific Incidence Rates /100,000 Population

Male Rates
Female Rates

Higher Risk of Harm

Benefit? Harm?

Lower Risk of CRC

Higher range in women?
Proportion of colorectal cancers that occur in Women
(C18-C20 2011-2013)

Source: cruk.org/cancerstats

60:40 split
Men:Women

Age Range (years)
Cancer 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

Cancers detected /5,000 male & 5,000 female participants (completed FIT)

FIT Concentration ug/g

2014 Pilot Data

Cancers detected in men

Cancers detected in women
Cancer 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 Concentration ug/g

Cancers detected /5,000 male & 5,000 female participants (completed FIT)

60% of cancers are detected in men

<<40% of cancers are detected in women

>60% of cancers are detected in men

FIT increases gender inequality for colorectal cancer
Cancer Detection in 10,000 FIT Screened Participants

(50:50 male & female)

2014 Pilot Data

Opportunity for intelligent use of FIT?

Cancers detected /5,000 male & 5,000 female participants

FIT Concentration ug/g

Cancers detected in men

Cancers detected in women

60%

40%

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

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

Opportunity for intelligent use of FIT?
The gender dilemma

Gender Dilemma

Make sensitivity the same in men and women?

Higher FIT threshold in men - PPV difference & male miss rate increase

Make male & female ‘miss rate’ the same?

Lower FIT threshold in men - similar PPV but lower sensitivity in women

Opportunity for intelligent use of FIT?

Why not start screening in women 4-8 years later?

...your choice!
Age & FIT Threshold – Cancer Detection Rate

Opportunity for intelligent use of FIT?
Personalised Risk Prediction

Flemish CRC Screening Programme

Opportunity for...

...tailored ‘personalised screening’

Predicted probability of colonoscopy findings

Flemish Screening Programme
- 57,400 colonoscopies
- Explore improvement to:
  - Referral accuracy
  - Cost-effectiveness

Logistic regression modelling
- Age, gender & quantitative FIT

Wessel Van de Veerdonk et al  Risk stratification for colorectal neoplasia detection in the Flemish CRC screening programme. *Ca Epi* 2018;56:90-96
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

% Cancer Detection Rate vs. FIT

- First Invitation
- No response to previous invitations
- Participated previously
Screen Episode & FIT threshold – Cancer Detection Rate

Previous non-responders benefit most from a low FIT threshold.
Risk markers associated with screening history

Include in FIT algorithm...
1. Period since last screen?
2. Previous screening outcomes
3. Surveillance details

In ‘hot countries’...
1. Ambient temperature
2. Travel time to laboratory

All held on screening database!

% Uptake over 3 episodes

Adherence to screening

Opportunity?

Increasing Risk of CRC

Very Poor Adherence
Poor Adherence
Full Adherence

At least once At least twice At least 3 times
The algorithm offers an additional means of identifying risk of colorectal cancer, and...

...could support other approaches to early detection, including screening...‘
Personal cancer history - (colon, rectum, ovary, endometrium, or breast)

Metabolic syndrome 33-41%

Type II diabetes 22-33%

Ulcerative colitis 70%

Crohn's colitis

Family history of colon cancer 25%

Lynch Syndrome etc

Gallstones 33%

Metabolic syndrome 33-41%

Ethnicity (Ashkenazi Jew)

Personal Medical Records

Colon Cancer Risk Factors

Full Blood Counts Parameters
# Colon Cancer Risk Factors

<table>
<thead>
<tr>
<th>Preventable cases of bowel cancer, UK</th>
<th>Red and processed meat</th>
<th>Excess bodyweight</th>
<th>Low fibre</th>
</tr>
</thead>
<tbody>
<tr>
<td>54%</td>
<td>21%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Bowel cancer cases linked to eating red and processed meat, UK</td>
<td>Bowel cancer cases linked to excess bodyweight, UK</td>
<td>Bowel cancer cases linked to eating too little fibre, UK</td>
<td></td>
</tr>
</tbody>
</table>

Life Style

### Bowel cancer risk factors

- **Prevention**: 54%
- **Red and processed meat**: 21%
- **Excess bodyweight**: 13%
- **Low fibre**: 12%
Optimising FIT-based screening

*What is our measure of success?*

**Maximising...**
1. Cancers /adenomas detection
2. Early detection /down-staging of cancer
3. QALYS (Quality adjusted life years)

**Reducing...**
1. Mortality from CRC
2. Incidence of CRC
3. Economic burden from CRC
Future of Quantitative FIT?
FIT-based Multivariate Risk Assessment

- Quantitative FIT concentrations... & trends
  (ambient temp / elapse time?)

- Age & Sex
- Screening history
- Indices of Deprivation – Postcode
- Medical History – IBD, Crohns, DM, etc
- Family History – 1st & 2nd deg. relatives
- Life style – Smoking

Stage 1 - Assess risk at FIT invitation
If low risk... ...delay invitation

Stage 2 - Assess risk 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


**Collaborators...**
Jennifer Cooper, Nick Parsons, Sian Taylor-Phillips

**Multivariable Risk Prediction Model**
- Logistic linear regression
- Artificial neural networks
- Machine learning

**Neural networks in the lead...**

Risk-adjusted colorectal cancer screening using the FIT and routine screening data: development of a risk prediction model


**Neural Network**

Feed forward
5-3-1
neural network,
18 weights.
Weight decay 0.01

Bias Node 1
Bias Node 2

FIT result
I1

Age at Episode Start
I2

Sex
I3

Previous non responder compared with a first time screen
I4

Previous responder compared with a first time screen
I5

Hidden Layer Node 1
H1

Hidden Layer Node 2
H2

Hidden Layer Node 3
H3

O1

Colorectal cancer/advanced adenoma detected at colonoscopy

**Neural Network Approach**
(uses some screening history data)

**Conventional FIT Approach**
If we play the FIT game properly...

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
Better Test
Better Application
Better Outcome