Epidemiological and clinical aspects of quantitative FIT test for CRC screening

Kocna P., Májek O., Blaha M., Ngo O., Dušek L.
### Criteria for disease screening

1. The condition screened for should be an important one
2. There should be an acceptable treatment for patients with the disease
3. The facilities for diagnosis and treatment should be available
4. There should be a recognised latent or early symptomatic stage
5. There should be a suitable test or examination which has few false positives (specificity) and few false negatives (sensitivity)
6. The test or examination should be acceptable to the population
7. The test should be cheap/cost effective

*Screening - Wilson & Jungen (WHO, 1968)*
Laboratory of Gastroenterology of the Institute of Medical Biochemistry and Laboratory Diagnostics shows long-standing – 40 years experiences with FOBT analytics

40 years ago

1st GENERATION - GUAIAC TEST, g-FOBT

Haemoccult exclusively has been recommended for CRC screening with highest reproducibility

Frič, P.: The use of haemoccult test in the early diagnosis of colorectal cancer – experience from six pilot studies in Czechoslovakia,
in: Haemoccult screening for the early detection of colorectal cancer Schattauer, Stuttgart 1986, p. 73-74
Quantitative immunochemical - qiFOBT are 3x more reliable to guaiac FOBT

Colorectal Cancer Screening and Diagnosis Guidelines Seminar - April 2011
prof. Stephen Halloran - NHS criticized qualitative FOBTs:
No Automation - Operator Variability - Can't adjust positivity
The evidence to date suggests that faecal occult blood testing using FIT will remain the best test for CRC population-based screening for the next decade. Quantitative FIT provides the important opportunity of incorporating results into a CRC risk algorithm.
qi-FOBT / FIT POCT & LABORATORY ANALYSERS

OC-Sensor Eiken
QuikRead Orion
OC-DIANA Eiken

SmartPlus Eurolyser
i-Chroma Boditech
QuikReadGo Orion

SENTi-FIT 270 Sentinel
SENTi-FIT mini Sentinel
Map of the Czech Republic with 95 marked locations where the quantitative analysis of Hb in stool, controlled with the SEKK external control quality, is available.
Quantitative determination of Hb in stool
Eiken OC-Sensor micro analyser
General Faculty Hospital Prague
32,000 tests in distributed in 6 years
Test recovery - 60.1%
13271 individuals were tested
107 CRC diagnosed by FIT
EQAS - 100 % success rate
The relative error of Hb analysis - 4.04 %

Kocna P., Májek O., Blaha M.: Clinical and epidemiological importance of analyzing laboratory data with the data source I-COP.
Sborník Medsoft 2014 - March 25; 110-122
### POSITIVITY OF FIT (OC-SENSOR TEST)

#### AGE 30 – 50 YEAR (n = 2091)

<table>
<thead>
<tr>
<th>µg/g</th>
<th>n</th>
<th>positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>219</td>
<td>10.47 %</td>
</tr>
<tr>
<td>15</td>
<td>178</td>
<td>8.51 %</td>
</tr>
<tr>
<td>20</td>
<td>152</td>
<td>7.27 %</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>43</td>
<td>2.06 %</td>
</tr>
</tbody>
</table>

#### AGE 50 – 90 YEAR (n = 13282)

<table>
<thead>
<tr>
<th>µg/g</th>
<th>n</th>
<th>positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2374</td>
<td>17.87 %</td>
</tr>
<tr>
<td>15</td>
<td>1954</td>
<td>14.71 %</td>
</tr>
<tr>
<td>20</td>
<td>1669</td>
<td>12.57 %</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>448</td>
<td>3.37 %</td>
</tr>
</tbody>
</table>

Laboratory information system - OpenLIMS Stapro
18 029 samples of FIT - OC-Sensor method
13271 individuals were tested between 2008 - 2014
### Positivity of FIT (OC-Sensor Test)

#### Age 50 – 90 Year (n = 5273)

<table>
<thead>
<tr>
<th>μg/g</th>
<th>n</th>
<th>Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>510</td>
<td>9.67 %</td>
</tr>
<tr>
<td>15</td>
<td>390</td>
<td>7.40 %</td>
</tr>
<tr>
<td>20</td>
<td>310</td>
<td>5.88 %</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>64</td>
<td>1.21 %</td>
</tr>
</tbody>
</table>

#### Age 50 – 90 Year (n = 7938)

<table>
<thead>
<tr>
<th>μg/g</th>
<th>n</th>
<th>Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1855</td>
<td>23.37 %</td>
</tr>
<tr>
<td>15</td>
<td>1556</td>
<td>19.60 %</td>
</tr>
<tr>
<td>20</td>
<td>1351</td>
<td>17.02 %</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>382</td>
<td>4.81 %</td>
</tr>
</tbody>
</table>

Patients of the Center for Preventive Care & GPs

Patients specialized hospital clinics outpatient and inpatients
DATA-MINING TOOL I-COP

One health care
different focus
different data sources
?

Czech National
Cancer Registry
(CNCR)

I-COP
analytical and datamining tool

Hospital HIS/LIS
Laboratory
Administrative data

Laboratory values
Patient treatment
Hospital processes
Approximated cost

Tumor diagnosis
TNM classification
Clinical stage
Patient referral
### ACCURACY OF QUANTITATIVE FIT
#### A HISTORICAL COHORT STUDY

**cut-off 10 μg/g**

<table>
<thead>
<tr>
<th></th>
<th>CRC +</th>
<th>CRC -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test</td>
<td>41</td>
<td>916</td>
<td>957</td>
</tr>
<tr>
<td>Negative test</td>
<td>10</td>
<td>5,130</td>
<td>5,140</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>6,046</td>
<td>6,097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Positivity</td>
<td>15.7</td>
<td>14.8-16.6</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80.4</td>
<td>66.9-90.2</td>
</tr>
<tr>
<td>Specificity</td>
<td>84.8</td>
<td>83.9-85.7</td>
</tr>
<tr>
<td>PPV</td>
<td>4.3</td>
<td>3.1-5.8</td>
</tr>
</tbody>
</table>

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011
### ACCURACY OF QUANTITATIVE FIT

**A HISTORICAL COHORT STUDY**

**cut-off 15 μg/g**

<table>
<thead>
<tr>
<th></th>
<th>CRC +</th>
<th>CRC -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive test</strong></td>
<td>39</td>
<td>755</td>
<td>794</td>
</tr>
<tr>
<td><strong>Negative test</strong></td>
<td>12</td>
<td>5,291</td>
<td>5,303</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51</td>
<td>6,046</td>
<td>6,097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Positivity</td>
<td>13.0</td>
<td>12.2-13.9</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76.5</td>
<td>62.5-87.2</td>
</tr>
<tr>
<td>Specificity</td>
<td>87.5</td>
<td>86.7-88.3</td>
</tr>
<tr>
<td>PPV</td>
<td>4.9</td>
<td>3.5-6.7</td>
</tr>
</tbody>
</table>

- 6097 adult patients with their first FIT performed during 2009-2011
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# ACCURACY OF QUANTITATIVE FIT

**A HISTORICAL COHORT STUDY**

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**cut-off 20 μg/g**

<table>
<thead>
<tr>
<th></th>
<th>CRC +</th>
<th>CRC -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test</td>
<td>38</td>
<td>646</td>
<td>684</td>
</tr>
<tr>
<td>Negative test</td>
<td>13</td>
<td>5,400</td>
<td>5,413</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>6,046</td>
<td>6,097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Positivity</td>
<td>11.2</td>
<td>10.4-12.0</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74.5</td>
<td>60.4-85.7</td>
</tr>
<tr>
<td>Specificity</td>
<td>89.3</td>
<td>88.5-90.1</td>
</tr>
<tr>
<td>PPV</td>
<td>5.6</td>
<td>4.0-7.5</td>
</tr>
</tbody>
</table>

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011
### ACCURACY OF QUANTITATIVE FIT

A HISTORICAL COHORT STUDY

#### cut-off 30 μg/g

<table>
<thead>
<tr>
<th></th>
<th>CRC +</th>
<th>CRC -</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive test</strong></td>
<td>36</td>
<td>515</td>
<td>551</td>
</tr>
<tr>
<td><strong>Negative test</strong></td>
<td>15</td>
<td>5,531</td>
<td>5,546</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51</td>
<td>6,046</td>
<td>6,097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT Positivity</td>
<td>9.0</td>
<td>8.3-9.8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>70.6</td>
<td>56.2-82.5</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.5</td>
<td>90.7-92.2</td>
</tr>
<tr>
<td>PPV</td>
<td>6.5</td>
<td>4.6-8.9</td>
</tr>
</tbody>
</table>

- 6097 adult patients with their first FIT performed during 2009-2011
- patients without prior CRC, minimal 1 year follow-up through CNCR records
- accuracy characteristics according to cut-off – 2 year follow up
- 2 year follow-up may be incomplete in patients tested in 2011
### DETECTED COLORECTAL CANCERS

#### AGE 50 – 90 YEAR (n = 4145)

<table>
<thead>
<tr>
<th>μg/g</th>
<th>n</th>
<th>FIT +</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>510</td>
<td>9.67%</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>64</td>
<td>1.21%</td>
</tr>
</tbody>
</table>

**Patients of the Center for Preventive Care & GPs**

**Detected CRC – 13/83**

**Detection rate - 2.47/1000 FIT**

#### AGE 50 – 90 YEAR (n = 6561)

<table>
<thead>
<tr>
<th>μg/g</th>
<th>n</th>
<th>FIT +</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1855</td>
<td>23.37%</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>382</td>
<td>4.81%</td>
</tr>
</tbody>
</table>

**Patients specialized hospital clinics outpatient and inpatients**

**Detected CRC – 70/83**

**Detection rate - 8.81/1000 FIT 3.6x more compare to GPs**

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Kocna P., Májek O., Blaha M., Zima T., Dušek L.: Characteristics of colorectal cancer detected by quantitative faecal haemoglobin test in hospital opportunistic screening. *WorldLab 2014, June, Istanbul*
The frequency of tumors in different localisations according to ICD-10 codes
The frequency of tumors in different localisations corresponding published papers

Johns Hopkins Colon Cancer Center
http://www.hopkinscoloncancercenter.org
Hb μg/g values are not significantly different according to tumor localisation.

The OC-Sensor FIT could be used reliably for CRC screening in any tumor localisation.
False negativity - is 21.69%
cut-off value 15 µg/g
recommended by the CRC Commission
False negativity - is 21.69%
cut-off value 20 µg/g
The sensitivity for CRC - is 78.31%
OC - SENSOR FIT FALSE NEGATIVITY

False negativity - is 21.69%
cut-off value 20 \( \mu g/g \)
The sensitivity for CRC - is 78.31%

The percentage of unrecognized cancers - 23.5%
for one test with cut-off 20 \( \mu g/g \)

Kelley L, Swan N, Hughes DJ. - Colorectal Dis. 2013 Sep; 15(9): e512-21
An analysis of the duplicate testing strategy of an Irish immunochemical FOBT colorectal cancer screening programme
CRC TUMOR STAGE & FIT VALUE

Hb \( \mu g/g \) values are not significantly different according to tumor stages.

<table>
<thead>
<tr>
<th>CRC Stage</th>
<th>n</th>
<th>Mean (( \mu g/g ))</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>18</td>
<td>202.8 (13.2 - 339.2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>24</td>
<td>227.4 (99.6 - 327.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>250.6 (66.8 - 476.8)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>53.2 (1.8 - 237.4)</td>
<td></td>
</tr>
</tbody>
</table>
OC - SENSOR FIT FALSE NEGATIVITY

CRC stage I
(n=18)
5/18
27.8%

CRC stage II
(n=24)
2/24
8.3%

CRC stage III
(n=23)
5/23
21.7%

CRC stage IV
(n=18)
6/18
33.3%
FOBT - THE PAST
20 YEARS WE USED g-FOBT
WITH LOW SENSITIVITY
BUT THE SAME RELIABILITY IN ALL
REGIONS OF THE CZECH REPUBLIC

FOBT - THE PRESENT
IN 2013 WE CHANGED TO i-FOBT, FIT
WITH 2-TIMES HIGHER SENSITIVITY
BUT DISTINCTLY INCREASING VARIABILITY
IN REGIONS OF THE CZECH REPUBLIC

FOBT - THE FUTURE
QUANTITATIVE FIT SHOULD BE USED ONLY
MODIFY THE SCREENING RULES
Automated analysers for qiFOBT are ready to start CRC screening with qiFOBT optimised for Czech Republic screening. EQAS control system is since January 2012 available.

Committee for CRC screening
Ministry of Health
of the Czech Republic

National screening programme in the Czech Republic should be modified to use quantitative qiFOBT technology.

Quantitative immunochemical qi-FOBT OC-Sensor
Meeting with EC & EP – Prague, January 11, 2012
We analysed 180 scientific publications, available on web
Publications focusing on CRC screening by FIT
Publications published in the last 6 years (2008-2014)
The presentation was focused only on studies of European countries

'EVIDENCE BASED' RECOMMENDATIONS AND EXPERIENCES ARE NOW AVAILABLE

Kocna P.: The European experiences with FIT tests.
Proceedings 2nd National Congress on Colorectal Cancer, Prague 2013, 359-369
FIT test before colonoscopy - 815 people, two centers (VFN and FTN)

Comparison of a two-FIT tests and different cut-off values

FIT test - OC-Sensor micro

<table>
<thead>
<tr>
<th>Hb cut off - ng/ml</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity CRC - FIT 1</strong></td>
<td>88.6% (73.2 - 96.7)</td>
<td>85.7% (69.7 - 95.1)</td>
<td>85.7% (69.7 - 95.1)</td>
<td>80.0% (63.1 - 91.5)</td>
<td>80.0% (63.1 - 91.5)</td>
</tr>
<tr>
<td><strong>Sensitivity CRC - FIT 2</strong></td>
<td>88.6% (73.2 - 96.7)</td>
<td>85.7% (69.7 - 95.1)</td>
<td>85.7% (69.7 - 95.1)</td>
<td>85.7% (69.7 - 95.1)</td>
<td>85.7% (69.7 - 95.1)</td>
</tr>
<tr>
<td><strong>Specificity CRC - FIT 1</strong></td>
<td>87.2% (83.6 - 90.2)</td>
<td>90.1% (86.8 - 92.8)</td>
<td>91.0% (87.9 - 93.6)</td>
<td>93.0% (90.1 - 95.2)</td>
<td>93.5% (90.6 - 95.6)</td>
</tr>
<tr>
<td><strong>Specificity CRC - FIT 2</strong></td>
<td>81.4% (77.3 - 85.0)</td>
<td>84.7% (80.9 - 88.1)</td>
<td>86.9% (83.3 - 90.0)</td>
<td>89.1% (85.7 - 91.9)</td>
<td>90.1% (86.8 - 92.8)</td>
</tr>
</tbody>
</table>

**Recommendation of Czech pilot study** - one FIT test with cut-off value 75 ng/ml


*Biomed Pap 2012 Jun; 156(2): 143 - 150: Improvements in colorectal cancer screening programmes - quantitative immunochemical faecal occult blood testing - how to set the cut-off for a particular population.*
EDUCATION ON IMPORTANCE OF FIT VALUES

Man 66 year (born 1946)

29.4.2009  - FIT: 0 µg/g
8.8.2011    - FIT: 271 µg/g
11.7.2012   - FIT: 370.8 µg/g

NO reaction

14.8.2012 - colonoscopy, sigmoid CRC
6.9.2012   - tumour resection, stage 3
FIT - surgery time: 12.96 months

Two cases with FIT value 0 µg/g and CRC

Man 72 year (born 1941)

13.5.2010  - FIT: 0 µg/g
14.11.2012 - FIT: 148.2 µg/g
5.3.2013   - FIT 327.4 µg/g

NO reaction

10.4.2013  - colonoscopy, sigmoid CRC
13.5.2013  - tumour resection, stage 3
FIT - surgery time: 5.92 months

FIT_surgery interval (median): 1.42
Range: 0.1 - 45.2 months

Kocna P., Májek O., Blaha M.: Clinical and epidemiological importance of analyzing laboratory data with the data source I-COP.
Sborník Medsoft 2014 - March 25; 110-122
- qFIT is 3 times more sensitive and reliable than gFOBT
- qFIT analysis is based on specific antibody technique
- qFIT on automatic analyser eliminates subjective evaluation
- qFIT allows the quantitative analysis
- qFIT could be possible to optimise selecting screening cut-off
- qFIT allows comparing the values on a European scale
- qFIT may be monitor by quality control system EQAS