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PII: S0016-5107(21)01695-3
DOI: https://doi.org/10.1016/j.gie.2021.09.038
Reference: YMGE 12940

To appear in: Gastrointestinal Endoscopy

Received Date: 27 May 2021
Accepted Date: 27 September 2021

Please cite this article as: Njor SH, Rasmussen M, Friis-Hansen L, Andersen B, Varying fecal immunochemical test screening cut-offs by age and gender: a way to increase detection rates and reduce number of colonoscopies, Gastrointestinal Endoscopy (2021), doi: https://doi.org/10.1016/j.gie.2021.09.038.

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Running title: varying FIT cut-offs by age and gender

keywords: Colorectal cancer, FIT Screening, cut-off values, Epidemiology, Prevention

Financial support: Sisse Helle Njor was funded by the Health Research Fund of Central Denmark Region (no. A1518). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Conflict of interest: Sisse Njor has received a speaking fee from Norgine. Morten Rasmussen has received speaking fees from Norgine and Ferring Pharmaceuticals. Lennart Friis-Hansen and Berit Andersen has no conflicts of interest.

Word count: 2997

Abbreviations:
FIT: fecal immunochemical test
Hb: hemoglobin
ABSTRACT

Background and aims: Most colorectal cancer screening programs based on the fecal immunochemical test use the same cut-off value for all participants. This study aimed at finding age and gender specific cut-off values that can improve population-based colorectal cancer screening.

Methods: This observational study used data from the first 2 years of the Danish Fecal immunochemical test based colorectal cancer screening program to estimate sensitivity, specificity, number of positive tests, number of screen-detected cancers and adenomas as well as number of interval cancers for various cut-off values for different male and female age groups.

Results: Data from 531,828 participants showed that lower cut-off values for older residents and higher cut-off values for younger residents increased the overall sensitivity and specificity, decreased number of needed colonoscopies by 7%, increased number of screen-detected cancer by 1.1%, increased number of screen-detected adenomas by 5% and decreased number of interval cancers by approximately 1.5%. However, these cut-off values also increased the inequality in sensitivity and specificity. Choosing cut-off values that ensured equal sensitivity between the groups did however increase inequality in, eg, the interval cancer rate.

Conclusion: In a fecal immunochemical test based colorectal cancer screening program it is possible to decrease the number of needed colonoscopies while at the same time increase overall sensitivity and specificity and detect more cancers and adenomas, by
using different cut-off values for different male and female age groups. However, this will increase inequality in sensitivity and specificity, whereas other strategies like ensuring equal sensitivity could be considered.

INTRODUCTION
Colorectal cancer (CRC) screening aims at finding CRCs at an earlier stage or already as precursors in order to initiate early treatment and thereby decrease the mortality and incidence of CRC. Using colonoscopy as the initial screening test will detect most cancers and advanced precursors, but is also costly both for the health care systems, which have to perform a lot of colonoscopies, and for the population that will have unnecessary colonoscopies and eventual adverse events from the colonoscopy. To avoid this, population based CRC screening programs use an initial screening test that screens for blood in the stool, as colorectal adenomas and CRC often bleed. The fecal immunochemical test (FIT) is frequently used as it has a better sensitivity and is easier to use than the guaiac-based test for occult blood.

In FIT screening the amount of blood in the stool is used to stratify the population into a group with low risk of CRC and adenomas and another group with high risk of CRC and adenomas, who are referred to colonoscopy. The prespecified cut-off value should be chosen so that most participants without cancer or precursors are declared negative, ie, have a high specificity, while at the same time most participants who have cancer or
precursors are declared positive, ie, have a high sensitivity. Choosing the optimal cut-off value is a delicate decision requiring considerations of both benefits and harms.\(^7\)

Although it has been shown that sensitivity and specificity of FIT tests vary by age and gender\(^8\text{--}^{12}\), and studies have emphasized the need for more tailored screening strategies\(^8\), most population-based CRC screening programs have chosen to use the same cut-off value for all participants. The aim of this study was to develop age and gender specific cut-off values, using data from the prevalent round of the Danish FIT based CRC screening program and to test their performance in silico.

**MATERIAL AND METHODS**

**Setting**

The National Danish CRC screening program targeting residents aged 50 to 74 years was implemented from March 2014.\(^{13}\) The first screening round was planned to take almost 4 years ending in December 2017. All residents aged 50 to 74 years on January 1, 2014 were invited randomly to the first screening round according to birth month, although residents not yet invited when turning 75 and residents turning 50 were invited just before their birthday. As from 2018 residents are invited 2 years after the latest invitation or latest FIT test whatever is most recent.

Invitations are mailed directly to the residents and include an invitation letter with instructions, a test kit to obtain a fecal sample and a prepaid return envelope. In the invitation letter residents already enrolled in a colonoscopy surveillance program are advised not to participate and residents with inflammatory bowel disease (IBD) are advised...
to discuss with the physician in charge of their surveillance or treatment of IBD, whether participation is relevant. Residents who do not return a fecal sample within 45 days receive one digital reminder. Returned stool samples are analyzed in one of five regional laboratories, using the OC Sensor (Eiken Chemical Company, Tokyo, Japan) fecal immunochemical test (FIT). The 5 regional laboratories use the exact same analysis and monitor quality continuously to ensure equal calibration between laboratories. Residents returning an FIT test that contains more than 100 ng hemoglobin(Hb)/mL are referred to a colonoscopy and have by law the right to have the colonoscopy performed within 14 days.

In the Danish health care system, all screening tests, diagnostic colonoscopies or similar as well as treatments are free of charge.

**Study design and population**

The study population included all residents who participated in the first round of the National Danish CRC Screening program and send in an analyzable stool sample before 31. December 2015. The study population was followed for CRC and advanced adenoma diagnoses in the Danish National Pathology Data Bank. The study population was followed from the date the sample was analyzed and 2 years onward.

**Data**

The study population was identified using the Danish CRC screening database, which contains information on invitation date, date when the returned samples were analyzed and the amount of blood in the sample.\(^\text{14}\) FIT values below 35 ng Hb/mL were only known as \(\leq 35\) ng Hb/mL and FIT values above 1000 ng Hb/mL were only known as \(\geq 1000\) ng Hb/mL.
Hb/mL. The Danish CRC screening database received this information from the administrative database used to issue invitations, whereas the quality is considered high.

Information on subsequent CRCs and adenomas were retrieved from the Danish National Pathology Data Bank, using the unique Danish personal registration number issued to all Danish residents at birth or immigration. The register is deemed to have a high completeness and reliability.\textsuperscript{15}

**Definitions**

CRC cases were defined as samples from the colon or rectum with a SNOMED code M8*3 (cancer). Adenomas were defined as samples from the colon or rectum with one of these SNOMED codes: M8213F (flat adenoma), M82110 (tubular adenoma), M82130 (traditional serrated adenoma), M8213M (sessile serrated lesion with dysplasia), M82630 (tubulovillous adenoma), and M82611 (villous adenoma).

A FIT test was defined as positive if the measured amount of blood was above the cut off level. The number of true positive/false positive FIT tests was estimated by the number of positive FIT tests where the participant was diagnosed/not diagnosed with CRC 0-24 months after the test. Similarly, the number of false negative/true negative FIT tests was estimated by the number of nonpositive FIT tests where the participant was diagnosed/not diagnosed with CRC 0 to 24 months after the test.

**Analyses**
To avoid a very low number of cancers diagnosed in the span between 2 cut-off values, the analyses were limited to the following cut-off values: 40, 45, 50, 55, 60, 65, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 600, 700, 800, 900, 1000.

Sensitivity, specificity, number of positive tests, number of screen-detected CRCs and adenomas as well as number of interval cancers were estimated for all selected cut-off values and age groups both for men and women. We used 2 different perspectives to identify the optimal individual cut-off values that for each gender were either increasing, stable or decreasing by age. In "the public health perspective" we searched through all cut-off values that fulfilled this, aiming at finding cut-off values that would improve sensitivity and specificity without increasing the number of needed colonoscopies in the entire population. Cut-off values leading to a higher decrease in number of colonoscopies were preferred over cut-off values leading to a lower decrease, when sensitivity and specificity were otherwise similar. In 'the equity perspective' we chose cut-off values that minimized the variation in sensitivity across age groups and gender most, while at the same time maintained the overall sensitivity.

As many of the cancers are at an early stage when detected at screening it seems unlikely that all screen-detected cases with cut-off values between 100 ng Hb/mL and 100+x ng Hb/mL would have emerged as cancer within 2 years (ie, a false negative test) if the cut-off value had been 100+x ng Hb/mL. Due to this we did not know how many false negative cases there would have been, had the cut-off value been above 100 ng Hb/mL. Similarly, we did not know how many true positive cases there would have been with a cut-off value
below 100 ng Hb/mL, because participants with a negative test did not have a colonoscopy. We therefore had to estimate the number of false negative cases for cut-off values above 100 ng Hb/mL and the number of true positive cases for cut-off values below 100 ng Hb/mL.

In a previous article we showed that the ratio between number of true positive cases and number of false negative cases was approximately 2.8 for cut-off values close to 100 ng Hb/mL. This ratio is probably larger below 100 ng Hb/mL and smaller above 100 ng Hb/mL, whereas we assumed that the ratio decreases linearly going through 2.8 at 100 ng Hb/mL and 1.0 at 1000 ng Hb/mL (full line figure 1). We made 2 sensitivity analyses in order to check how sensitive our results were towards violations to this assumption. One where we assumed the ratio to be 2.8 for all cut-off values (dotted line, figure 1) and another where we assumed the ratio to follow a curve, but still going through 2.8 at 100 ng Hb/mL (dashed line, figure 1).

The adenoma detection rate was 7.1 times higher than the cancer detection rate (14827 vs 2086) when 100ng Hb/mL was used as cut-off value (Table 1). The ratio between number of detected adenomas and cancers probably decreases with increasing cut-off values. To give a conservative estimate on the number of adenomas detected for cut-off values below 100ng Hb/mL, we assumed the ratio between number of detected adenomas and cancers to be 7.1.
Data was processed using SAS (version 9.4). All authors had access to the study data and reviewed and approved the final manuscript.

Ethical approvals

According to EU's General Data Protection Regulation (article 30), the project was listed at the record of processing activities for research projects in the Central Denmark Region (J. No: 1-16-02-68-20).

RESULTS

After excluding the 488 residents who only send in unanalyzable stool samples, the study population included 531,828 residents of which 35,582 residents (6.7%) returned a stool sample containing ≥100 ng Hb/mL and were referred to colonoscopy (Figure 2). Of these 32,057 (90.1%) had at least 1 colonoscopy within 6 months with an average time from the day the FIT test was analyzed to first colonoscopy of 20.65 days. Among all residents invited in 2014 to 2015, 64% chose to participate, but the participation rate in the Danish CRC screening program is a bit higher among women (66.6% in 2014-2016) than among men (58.4 in 2014-2016), whereas our study population consisted of 286,308 (53.8%) women and 245,520 (46.2%) men (Table 1). Due to the invitation system, the study population included a higher proportion of residents aged 50 to 54 years and 70 to 74 years than the general population. The FIT positive rate as well as detection rate and interval cancer rate increased by age both for men and women.

Applying ‘the public health perspective’ and improving the overall sensitivity and specificity, these cut-off values could be suggested: decreasing the cut-off value to 75 ng Hb/mL for
males aged 70 to 74 years and females aged 65 to 74 years and increasing the cut-off value to 300 ng Hb/mL for males aged 50 to 59 years and females aged 50 to 54 years (table 2). Using these cut-off values instead of 100 ng Hb/mL for all residents, increased the overall sensitivity slightly from 81.9% to 82.3% (Table 2), increased specificity from 93.7% to 94.1%, decreased number of positive test and thereby number of needed colonoscopies by 7%, increased number of screen-detected cancer by 1.1%, increased number of screen-detected adenomas by 5% and decreased number of interval cancers by 1.5%.

The numbers only changed marginally when the assumption in sensitivity analysis 1 and 2 was used (Table 2). The inequality in sensitivity and specificity between the different ages and gender groups did however increase (Figs. 3 and 4), whereas the inequality in colonoscopies needed to detect 1 cancer and interval cancer rate decreased.

Using “the equity perspective” and aiming for equal sensitivity for all residents the following cut-off values could be suggested: decreasing the cut-off value to 45 ng Hb/mL for women below 65 years and to 50 ng Hb/mL for women above 65 years, whereas increasing the cut-off values to 300 ng Hb/mL for males aged 50 to 54 years; 250 ng Hb/mL for males aged 55 to 64 years and 150 ng Hb/mL for males aged 65 to 74 years (Table 3). Using these cut-off values instead of 100 ng Hb/mL for all residents increased the overall sensitivity slightly from 81.9% to 82.4% (Table 3) decreased specificity from 93.6% to 93.0%, increased number of positive test by 10%, increased number of screen-detected cancer by 1.4%, decreased number of screen-detected adenomas by 7% and decreased number of interval cancers by 2.2%. The numbers only changed marginally when the
assumption in sensitivity analysis 1 and 2 was used (Table 3). Using these cut-off values leveled out the inequality in sensitivity, whereas the overall sensitivity was maintained. However, at the same time this also increased inequality in interval cancer rate and number of colonoscopies needed to detect one cancer (Figs. 3 and 5).

With the present cut-off value of 100 ng Hb/mL used for all residents, women aged 50 to 54 years have the highest “number of colonoscopies needed to detect one cancer.” Increasing the cut-off value for this group to lower the “number of colonoscopies needed to detect one cancer” would, however, decrease the sensitivity in this group and thereby increase the inequality in sensitivity. Residents aged 70 to 74 years had the highest interval cancer rate. Decreasing the cut-off values among these residents to lower the interval cancer rate, would though reduce specificity in this group and thereby increase the inequality in specificity.

**DISCUSSION**

**Main finding**

This nationwide study including 531,828 participants from the first part of the prevalent round of the FIT based Danish CRC screening program showed that it is possible to optimize the program and increase the overall sensitivity and specificity while at the same time decrease the number of positive tests by 7%, increase the number of screen-detected cancers by 1.1%, increase number of screen-detected adenomas by 5% and decrease the number of interval cancers by 1.5%.

It was not possible to achieve equality on all studied parameters for all groups of residents (ie, sensitivity, specificity, number of colonoscopies needed to detect one cancer, interval
cancer rate) at the same time. If, for example, choosing cut-off values that ensured
equality in sensitivity, then the inequality in “the number of colonoscopies needed to detect
one cancer” increased.

Other studies
Only a few studies have examined the value and performance of gender and age specific
cut-offs and provided suggestions on gender and age specific cut-off values.\textsuperscript{10,17} Using
the equity perspective on data from the Taiwanese nationwide screening program and
aiming at 80% sensitivity, Chen et al found that the cut-off values should be: 100ng Hb/mL
for men/women aged 50 to 59 years and 80ng Hb/mL/50ng Hb/mL for men/women aged
60 to 69 years.\textsuperscript{10} Using the equity perspective in our study resulted in cut-off values that
were much lower for women than for men. This difference is due to a similar sensitivity
among women and men in the Taiwanese program, whereas sensitivity was much lower in
women compared with men in the Danish program. These differences probably reflect that
the Taiwanese program used the outreach approach and only invited residents who did
not use or underused medical services, whereas the Danish program invited all
residents.\textsuperscript{18} As recognized by Chen et al their positive rate is quite lower than reported in
previous studies whereas the age/gender-specific cut-off values may not be generalized to
other countries. Alvarez-Urturi et al\textsuperscript{17} used data from men and women randomized to FIT
screening in the ColonPrevstudy. Their estimated cancer and adenoma detection rate as
well as numbers needed to screen/scope to find one cancer were very much in line with
our results. As only 36 cancers were included in the Alvarez-Urturi et al study, they found
ranges of FIT values without cancers, eg, they found no cancers among women aged 50
to 60 years with FIT values between 75 and 200ng Hb/mL. They therefore suggested that
the cut-off value could be increased to 200ng Hb/mL for women below 60 years. In our study including 2086 screen-detected cancers we found 17 screen-detected cancers among women aged 50 to 59 years with FIT values between 100 and 200ng Hb/mL and a too low sensitivity (71%) if increasing the cut-off value to 200ng Hb/mL. Alvarez-Urturi et al found that any increase in the FIT cut-off value decreased the number of screen-detected cancers among men 61 to 69 years and therefore concluded that the cut-off value should be kept low. In our study we also found a high cancer detection rate in this group and therefore proposed rather low cut-off values, but when also taking interval cancers and specificity into account it was not evident that the cut-off value should be lowest for men above 60.

Strength and weakness

The major strength of this study is the large number of screened residents and the use of high-quality databases to get information on screen-detected cancers and interval cancers.

The major weakness is that FIT negative residents were not assessed with colonoscopy. We therefore did not know how many false negative cases/ true positive cases there would have been, had the cut-off value been above/below 100 ng Hb/mL and had to estimate these numbers. However, in our main analysis and sensitivity analyses we used three very different distributions of the ratio between number of true positive cases and number of false negative cases and showed that this only affected our results slightly. However, the fact that we had to estimate the number of false negative and true positive cases and thereby sensitivity and specificity did not seem to have significantly affected our results.
As we neither knew how many adenomas we would detect with a cut-off value below 100 ng Hb/mL, we had to estimate these numbers. Our estimates are conservative whereas the estimated numbers of detected adenomas are probably too low, especially for lowest cut-off values 40 to 70 ng Hb/mL.

Due to the invitation system, residents aged 50 to 54 years and 70 to 74 years are overrepresented compared with the general population. Decreasing the proportion of residents aged 50 to 54 years and 70 to 74 years by 40% to get a population that resembles the general Danish population, only changed the results marginally when using the Public Health perspective. Number of positive tests decreased by 6% instead of 7%, the number of screen-detected cancers increased by 0.9% instead of 1.1%, the number of screen-detected adenomas increased by 3% instead of 5% and the number of interval cancers decreased by 1.1% instead of 1.5%.

Given the uncertainty of our estimates, there might be gender and age specific cut-off values that will improve CRC screening more than the cut-off values we propose.

Because almost 10% of the participants with a FIT value above 100 ng Hb/mL did not have a follow-up colonoscopy within 6 months, our results might not be applicable to screening programs with a different proportion of participants having a follow-up colonoscopy after a positive FIT test.

Our results are only based on residents participating in the first half of the prevalent round of the Danish CRC screening program and might therefore not be applicable to incident
rounds. Because our results might be affected by a lower colonoscopy quality during the first years of our national screening program, it will be interesting to see whether similar results can be found in other more mature screening programs. When it is available, we will use data from the incident round of the Danish screening program to investigate this.

**CONCLUSION**

This study shows that it is possible to decrease the number of needed colonoscopies while at the same time increase the overall sensitivity and specificity, by using different cut-off values for men and women and for different age groups. This will, however, increase the inequality in sensitivity and specificity whereas other strategies like ensuring equal sensitivity could be considered.

**DATA AVAILABILITY**

The data that support the findings of this study are available from The Danish Health Data Authority and The Danish Clinical Quality Program– National Clinical Registries (RKKP). Restrictions apply to the availability of these data, which were used under license for this study. Data may be available upon reasonable request to The Danish Health Data Authority and The Danish Clinical Quality Program– National Clinical Registries (RKKP).

**ACKNOWLEDGEMENTS**

This study was funded by the Health Research Fund of Central Denmark Region (no. A1518). The funders had no role in study design, data collection and analysis, decision to
publish, or preparation of the manuscript. Data was provided by the Danish colorectal cancer screening database.

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Table 1: Number and proportion of participants, FIT-positive tests, screen-detected cancers, interval cancers and screen-detected adenomas at cut-off 100 ng Hb/mL by age and gender.

| Group          | Participants (n=531,828) | FIT-positive | Cancers detected | Interval cancers | Adenomas detected |
|----------------|--------------------------|--------------|------------------|------------------|-------------------|
| Men            | 245,520 (46.2%)          | 19,913 (8.1%)| 1264 (0.51%)     | 199 (0.08%)      | 9,436 (3.8%)      |
| Men, 50–54 years| 73,508 (13.8%)           | 3,481 (4.7%) | 1264 (0.51%)     | 12 (0.02%)       | 1,331 (1.8%)      |
| Men, 55–59 years| 38,062 (7.2%)            | 2,402 (6.3%) | 97 (0.25%)       | 14 (0.04%)       | 1,105 (2.9%)      |
| Men, 60–64 years| 38,325 (7.2%)            | 3,231 (8.4%) | 179 (0.47%)      | 20 (0.05%)       | 1,634 (4.3%)      |
| Men, 65–69 years| 42,955 (8.1%)            | 4,271 (9.9%) | 311 (0.72%)      | 57 (0.13%)       | 2,173 (5.1%)      |
| Men, 70–74 years| 52,670 (9.9%)            | 6,528 (12.4%)| 577 (1.10%)      | 96 (0.18%)       | 3,193 (6.1%)      |
| Women          | 286,308 (53.8%)          | 15,669 (5.5%)| 822 (0.29%)      | 262 (0.09%)      | 5,391 (1.9%)      |
| Women, 50–54 years| 90,550 (17.0%)           | 3,523 (3.9%) | 88 (0.10%)       | 31 (0.03%)       | 873 (1.0%)        |
| Women, 55–59 years| 45,252 (8.5%)            | 1,998 (4.4%) | 80 (0.18%)       | 25 (0.06%)       | 701 (1.5%)        |
| Women, 60–64 years| 44,592 (8.4%)            | 2,358 (5.3%) | 123 (0.28%)      | 34 (0.08%)       | 860 (1.9%)        |
| Women, 65–69 years| 47,526 (8.9%)            | 3,007 (6.3%) | 179 (0.38%)      | 63 (0.13%)       | 1,163 (2.4%)      |
| Women, 70–74 years| 58,388 (11.0%)           | 4,783 (8.2%) | 352 (0.60%)      | 109 (0.19%)      | 1,794 (3.1%)      |
| Total          | 531,828 (100%)           | 35,582 (6.7%)| 2,086 (0.39%)    | 461 (0.09%)      | 14,827 (2.8%)     |
Table 2: New cut-off values using the public health perspective as well as sensitivity, specificity, number of positive FIT-tests, number of screen-detected cancers, number of adenomas and number of interval cancers (IC), when using these new cut-off values and when using 100 ng Hb/ml as cut-off value for all residents.

|                | 50-54 Years | 55-59 years | 60-64 years | 65-69 years | 70-74 Years |
|----------------|-------------|-------------|-------------|-------------|-------------|
| Men            | 300 ng Hb/ml| 300 ng Hb/ml| 100 ng Hb/ml| 100 ng Hb/ml| 75 ng Hb/ml |
| Women          | 300 ng Hb/ml| 100 ng Hb/ml| 100 ng Hb/ml| 75 ng Hb/ml | 75 ng Hb/ml |

|                  | Cut-off 100 ng Hb/mL for all | New cut-off: straight line | New cut-off: 2.1 for all (sensitivity analysis 1) | New cut-off: curve (sensitivity analysis 2) |
|------------------|-------------------------------|----------------------------|-----------------------------------------------|------------------------------------------|
| Sensitivity      | 81.9%                        | 82.3%                      | 82.3%                                         | 82.1%                                    |
| Specificity      | 93.7%                        | 94.1%                      | 94.1%                                         | 94.1%                                    |
| positive tests   | 35,582                       | 33,251 (±7%)               | 33,251 (±7%)                                 | 33,251 (±7%)                             |
| Screen detected cancers | 2,086                      | 2,108 (+1.1%)              | 2,108 (+1.1%)                               | 2,109 (+1.1%)                           |
| Screen detected adenomas | 14,827                     | 15,523 (+5%)               | 15,521 (+5%)                                | 15,531 (+5%)                            |
| Interval cancers | 461                          | 454 (±1.5%)                | 453 (±1.7%)                                 | 458 (±0.7%)                             |
Table 3: New cut-off values using the equity perspective as well as sensitivity, specificity, number of positive FIT-tests, number of screen detected cancers, number of adenomas and number of interval cancers, when using these new cut-off values and when using 100 ng Hb/ml as cut-off value for all residents.

| Age Group          | Cut-off 100 ng Hb/mL for all | New cut-off: straight line | New cut-off: 2.1 for all (sensitivity analysis 1) | New cut-off: curve (sensitivity analysis 2) |
|--------------------|-------------------------------|---------------------------|--------------------------------------------------|--------------------------------------------|
| 50-54 years        | 300 ng Hb/mL                  | 250 ng Hb/mL              | 250 ng Hb/mL                                     | 150 ng Hb/mL                               |
| 55-59 years        | 250 ng Hb/mL                  | 250 ng Hb/mL              | 250 ng Hb/mL                                     | 150 ng Hb/mL                               |
| 60-64 years        | 250 ng Hb/mL                  | 250 ng Hb/mL              | 250 ng Hb/mL                                     | 150 ng Hb/mL                               |
| 65-69 years        | 150 ng Hb/mL                  | 150 ng Hb/mL              | 150 ng Hb/mL                                     | 150 ng Hb/mL                               |
| 70-74 years        | 150 ng Hb/mL                  | 150 ng Hb/mL              | 150 ng Hb/mL                                     | 150 ng Hb/mL                               |

| Measure             | 50-54 years                   | 55-59 years               | 60-64 years                                     | 65-69 years                                | 70-74 years                                |
|---------------------|-------------------------------|---------------------------|--------------------------------------------------|--------------------------------------------|
| Sensitivity         | 81.9%                         | 82.4%                     | 82.5%                                            | 82.2%                                      |
| Specificity         | 93.6%                         | 93.0%                     | 93.0%                                            | 93.0%                                      |
| Positive tests      | 35,582                        | 39,209 (+10%)             | 39,209 (+10%)                                    | 39,209 (+10%)                              |
| Screen detected cancers | 2,086                     | 2,115 (+1.4%)             | 2,114 (+1.3%)                                    | 2,119 (1.6%)                               |
| Screen detected adenomas | 14,827                     | 13,852 (+7%)              | 13,942 (+6%)                                     | 13,980 (+1%)                               |
| Interval cancers    | 461                           | 451 (+2.2%)               | 449 (+2.6%)                                      | 459 (+0.4%)                                |
FIGURE LEGENDS

Figure 1: The assumed ratio between number of true positive cases and number of false negative cases for cut-off values 0-1000 ng Hb/mL.

Figure 2: Flow chart

Figure 3: Sensitivity, specificity, number of colonoscopies per screen-detected case and interval cancer rate by 5-year age groups for men and women when using a cut-off value of 100 ng Hb/mL for all groups

Figure 4: Sensitivity, specificity, number of colonoscopies per screen-detected case and interval cancer rate by 5-year age groups for men and women when using the specified individual cut-off values (Public health perspective).

Figure 5: Sensitivity, specificity, number of colonoscopies per screen-detected case and interval cancer rate by 5-year age groups for men and women when using the specified individual cut-off values (equity perspective).
assuming the ratio follows a straight line (main analysis)
assuming the ratio is constantly 2.6 (sensitivity analysis 1)
assuming the ratio follows a hyperbola (sensitivity analysis 2)
Citizens participation in CRC screening January 1, 2014 to December 31, 2015 532,316

Citizens only sending in unanalyzable samples 488

Participants 531,828

FIT value < 100 mg Hb/L 496,246 (93.3%)
FIT value ≥100 mg Hb/L 35,582 (6.7%)

Colonoscopy in 6 months 32,057 (90.1%)
No colonoscopy in 6 months 3525 (9.9%)
| Age Group | 50-54 Years | 55-59 Years | 60-64 Years | 65-69 Years | 70-74 Years |
|-----------|-------------|-------------|-------------|-------------|-------------|
| Men       | 300 µg Hb/L | 300 µg Hb/L | 100 µg Hb/L | 100 µg Hb/L | 75 µg Hb/L  |
| Women     | 300 µg Hb/L | 100 µg Hb/L | 100 µg Hb/L | 75 µg Hb/L  | 75 µg Hb/L  |
Abbreviations:

CRC: Colorectal cancer
FIT: fecal immunochemical test
Hb: hemoglobin