GI UPDATE 2014

FIT FOR CRC SCREENING

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FACULTY/PRESENTER DISCLOSURE

- **Faculty/Presenter: Dr. Clarence Wong**
  - **Cancer Screening Programs/Tumour Markers**
- **Relationships with commercial interests:** -
  - **Grants/Research Support**: *Vantage, Covidien (BarrX)*
  - **Speakers Bureau/Honoraria:** *Takeda (Nycomed)*
  - **Consulting Fees:** *Ferring Pharmaceuticals, Boston Scientific*
  - **Other:**
    - *Advisory Board: Takeda Pharmaceutical, Pendopharm*
    - *Employer: Alberta Health Services*

DISCLOSURE OF COMMERCIAL SUPPORT

- **This program has received no additional financial support**
- **This program has received no in-kind support**
- **<u>Potential for conflict(s) of interest</u>:**
  - No funding or payment relevant to this program
  - No developed/licenses/distributes/benefits from the sale relevant to this program

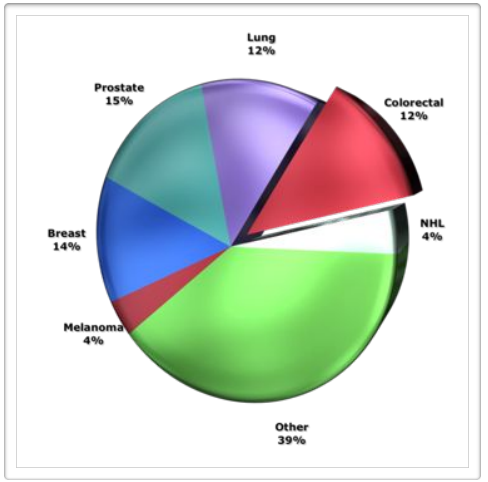
MITIGATING POTENTIAL BIAS

- *This topic (**Colon cancer screening**) has no relationship or potential bias with the companies disclosed.*
- *Information presented is evidence-based and guideline based. All data has been sourced from evidence.*

OBJECTIVES

- At the end of this workshop, participants will have a better understanding of:
  - Screening tests for CRC
  - Fecal Immunochemical test indications
  - When not to use FIT

ALBERTA CRC DIAGNOSES 2012

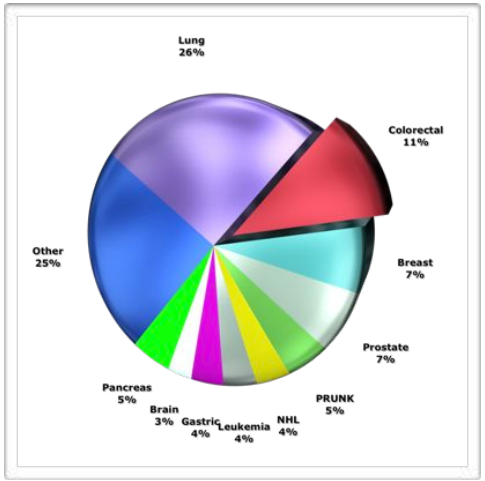


1930 Diagnosed

Colon Cancer is the 3rd most commonly diagnosed cancer

ACB Registries, 2012

ALBERTA CRC DEATHS 2012



720 Deaths

Colon Cancer is the 2nd most common cause of cancer related deaths

ACB Registries, 2012

RISK OF CRC

Men
1 in 13

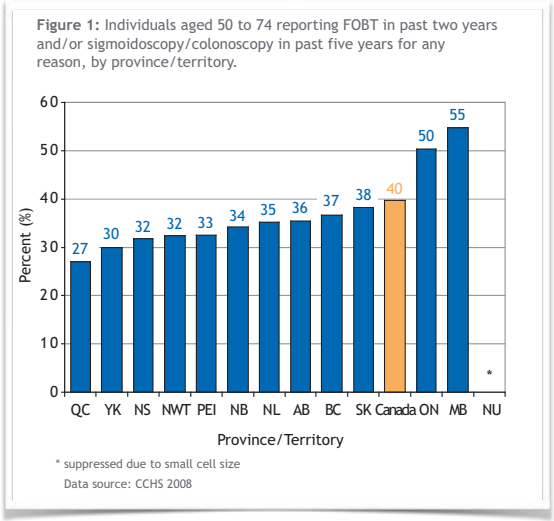
Women
1 in 16

Age Group (Years)	Males	Females
Lifetime Risk (all ages)	**1 in 13**	**1 in 16**
0-20	Less than 1 in 10,000	Less than 1 in 10,000
20-30	1 in 5,428	1 in 4,506
30-40	1 in 1,613	1 in 1,355
40-50	1 in 450	1 in 410
50-60	1 in 161	1 in 158
60-70	1 in 77	1 in 77
70-80	1 in 45	1 in 46
80+	1 in 28	1 in 25

Table 1: Probability of Developing Colorectal Cancer by Age and Sex, Alberta 2006 – 2010
Reproduced with permission from Alberta Cancer Registry, Alberta Health[2]

Canadian Cancer Statistics 2013

ARE CANADIANS SCREENED FOR CRC?



CPAC Colorectal Cancer Snapshot, 2010, cancerview.ca

WHAT TESTS SHOULD WE USE TO SCREEN FOR CRC IN 2014?

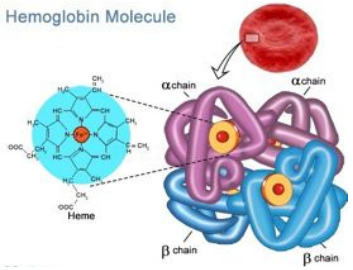
CRC Screening Tests - Comparison

Endoscopy	Radiology	Blood	Fecal Based
Colonoscopy Sigmoidoscopy	DCBE CTC	CEA Cologic	Guaiac FIT
Access Wait Lists Invasive	DCBE-not for screening CTC-radiation	CEA-No! Cologic-? powered studies, $$	Guaiac-low SEN FIT-high SEN

WHAT IS FIT?

WHAT IS FIT?

- Fecal Immunochemical Test
- Antibody to human globin
  - Not a chemical reaction
  - No dietary restrictions
- Colonic bleeding (LGIB) specific
  - Globin degrades from upper GI tract
- Detects 33-200 ng of blood per mL (guaiac 0.3 - 1 mg)

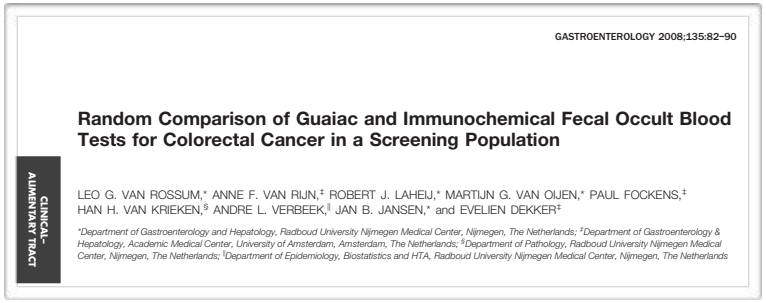


FIT FOR CRC SCREENING

- ELISA based
- Immunochemical
- Qualitative or quantitative
  - Adjustable cutoff
- Mass testing
- FIT for Alberta:
  - Polymedco (Eiken) OC FIT-CHEK

HOW DOES FIT COMPARE TO OTHER SCREENING MODALITIES?

FIT VS GFOBT



GASTROENTEROLOGY 2008;135:82–90

Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population

CLINICAL-ALIMENTARY TRACT

LEO G. VAN ROSSUM,* ANNE F. VAN RIJN,‡ ROBERT J. LAHEIJ,* MARTIJN G. VAN OIJEN,* PAUL FOCKENS,‡ HAN H. VAN KRIEKEN,§ ANDRE L. VERBEEK,‖ JAN B. JANSEN,* and EVELIEN DEKKER‡

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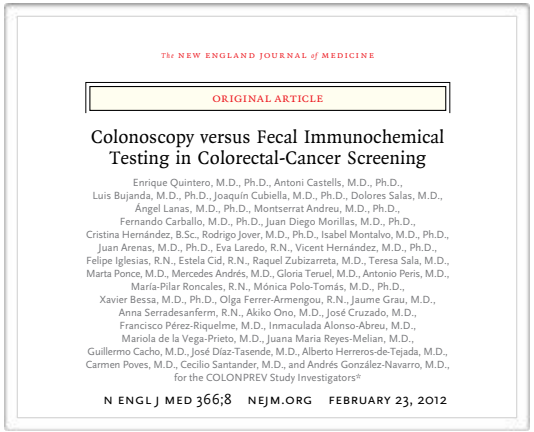
- gFOBT vs FIT; population based study
- 10,993 tests

VAN ROSSUM ET AL. 2008
GFOBT VS FIT RESULTS

TEST	GFOBT	FIT
POSITIVITY RATE	2.4%	5.5%
PARTICIPATION	46.9	59.6
ALL POLYPS +CRC	1.7	3.5
AA+CRC AA=Advanced Adenoma	1.2	2.4
CRC	0.2	0.4

FIT DETECTED 2X CRC THAN GUAIAC

FIT VS COLONOSCOPY



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening

Enrique Quintero, M.D., Ph.D., Antoni Castells, M.D., Ph.D., Luis Bujanda, M.D., Ph.D., Joaquín Cubiella, M.D., Ph.D., Dolores Salas, M.D., Ángel Lanas, M.D., Ph.D., Montserrat Andreu, M.D., Ph.D., Fernando Carballo, M.D., Ph.D., Juan Diego Morillas, M.D., Ph.D., Cristina Hernández, B.Sc., Rodrigo Jover, M.D., Ph.D., Isabel Montalvo, M.D., Ph.D., Juan Arenas, M.D., Ph.D., Eva Laredo, R.N., Vicent Hernández, M.D., Ph.D., Felipe Iglesias, R.N., Estela Cid, R.N., Raquel Zubizarreta, M.D., Teresa Sala, M.D., Marta Ponce, M.D., Mercedes Andrés, M.D., Gloria Teruel, M.D., Antonio Peris, M.D., María-Pilar Roncales, R.N., Mónica Polo-Tomás, M.D., Ph.D., Xavier Bessa, M.D., Ph.D., Olga Ferrer-Armengou, R.N., Jaume Grau, M.D., Anna Serradesanferm, R.N., Akiko Ono, M.D., José Cruzado, M.D., Francisco Pérez-Riquelme, M.D., Inmaculada Alonso-Abreu, M.D., Mariola de la Vega-Prieto, M.D., Juana Maria Reyes-Melian, M.D., Guillermo Cacho, M.D., José Díaz-Tasende, M.D., Alberto Herreros-de-Tejada, M.D., Carmen Poves, M.D., Cecilio Santander, M.D., and Andrés González-Navarro, M.D., for the COLONPREV Study Investigators*

N ENGL J MED 366;8 NEJM.ORG FEBRUARY 23, 2012

57,404 subjects randomly assigned to COL or FIT

Table 1. Diagnostic Yield of Colonoscopy and Fecal Immunochemical Testing (FIT), According to the Intention-to-Screen Analysis.*

Colorectal Lesion	Colonoscopy (N=26,703)		FIT (N=26,599)		Odds Ratio (95% CI)†	P Value
	Subjects no.	Rate %	Subjects no.	Rate %		
Cancer	30	0.1	33	0.1	0.99 (0.61–1.64)	0.99
Advanced adenoma‡	514	1.9	231	0.9	2.30 (1.97–2.69)	<0.001
Advanced neoplasia§	544	2.0	264	1.0	2.14 (1.85–2.49)	<0.001
Nonadvanced adenoma	1109	4.2	119	0.4	9.80 (8.10–11.85)	<0.001
Any neoplasia	1653	6.2	383	1.4	4.67 (4.17–5.24)	<0.001

* The diagnostic yield was calculated as the number of subjects with true positive results divided by the number of subjects who were eligible to undergo testing. Subjects were classified according to the most advanced lesion.
† Odds ratios were adjusted for age, sex, and participating center. CI denotes confidence interval.
‡ Advanced adenoma was defined as an adenoma measuring 10 mm or more in diameter, with villous architecture (>25%), high-grade dysplasia, or intramucosal carcinoma.
§ Advanced neoplasia was defined as advanced adenoma or cancer.

Quintero et al., NEJM, 2012

COLONOSCOPY VS FIT

	COLONOSCOPY 26, 703	FIT 26, 599
NNSCOPE FOR 1 CANCER	191	18
COMPLICATIONS	0.5%	0.1%
RATE OF PARTICIPATION	24.6	34.2
SCREENED	5059	10,611

IN AN EVENLY RANDOMIZED POPULATION, CRC DETECTION BY FIT WAS THE SAME AS COLONOSCOPY

Quintero et al., NEJM, 2012

FIT HAS CUTOFF VALUES

British Journal of Cancer (2009) 101, 1274 – 1281

www.bjcancer.com

Clinical Studies

Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme

LGM van Rossum*[,1], AF van Rijn[2], RJF Laheij[1], MGH van Oijen[1], P Fockens[2], JBMJ Jansen[1], ALM Verbeek[3] and E Dekker[2]

[1]Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, P.O.Box 9101, 6500 HB, Nijmegen, The Netherlands; [2]Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [3]Department of Epidemiology and Biostatistics and MTA, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

BACKGROUND: The cutoff of semi-quantitative immunochemical *faecal occult blood tests* (iFOBTs) influences colonoscopy referrals and detection rates. We studied the performance of an iFOBT (OC-Sensor) in colorectal cancer (CRC) screening at different cutoffs.
METHODS: Dutch screening participants, 50–75 years of age, with average CRC risk and an iFOBT value ⩾ 50 ng ml^{-1} were offered colonoscopy. The detection rate was the percentage of participants with CRC or advanced adenomas (⩾ 10 mm, ⩾ 20% villous, high-grade dysplasia). The *number needed to scope* (NNTScope) was the number of colonoscopies to be carried out to find one person with CRC or advanced adenomas.
RESULTS: iFOBT values ⩾ 50 ng ml^{-1} were detected in 526 of 6157 participants (8.5%) and 428 (81%) underwent colonoscopy. The detection rate for advanced lesions (28 CRC and 161 with advanced adenomas) was 3.1% (95% confidence interval: 2.6–3.5%) and the NNTScope was 2.3. At 75 ng ml^{-1}, the detection rate was 2.7%, the NNTScope was 2.0 and the CRC miss rate compared with 50 ng ml^{-1} was < 5% ($N = 1$). At 100 ng ml^{-1}, the detection rate was 2.4% and the NNTScope was < 2. Compared with 50 ng ml^{-1}, up to 200 ng ml^{-1} CRC miss rates remained at 16% ($N = 4$).
CONCLUSIONS: Cutoffs below the standard 100 ng ml^{-1} resulted in not only higher detection rates of advanced lesions but also more colonoscopies. With sufficient capacity, 75 ng ml^{-1} might be advised; if not, up to 200 ng ml^{-1} CRC miss rates are acceptable compared with the decrease in performed colonoscopies.
British Journal of Cancer (2009) **101,** 1274 – 1281. doi:10.1038/sj.bjc.6605326 www.bjcancer.com
Published online 15 September 2009

Keywords: colorectal cancer; faecal occult blood test; screening; epidemiology; colonoscopy

Table 3 The performance characteristics of the iFOBT, OC-Sensor, at different cutoff levels

	Cutoff values (ng ml^{-1})							
	50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
Positives adherent to colonoscopy[a] (N)	428	336	280	248	234	215	198	187
Colonoscopy rate[b] (%)	7.0%	5.5%	4.5%	4.0%	3.8%	3.5%	3.2%	3.0%
Number of lesions (n)								
Colorectal cancer	28	27	24	24	24	24	24	23
CRC+advanced adenomas	189	163	145	136	131	121	113	109
Detection rate[c] (%)								
Colorectal cancer	0.45%	0.44%	0.39%	0.39%	0.39%	0.39%	0.39%	0.37%
Confidence interval (95% CI)	0.3–0.6%	0.3–0.6%	0.2–0.6%	0.2–0.6%	0.2–0.6%	0.2–0.6%	0.2–0.6%	0.2–0.5%
CRC+advanced adenomas	3.1%	2.6%	2.4%	2.2%	2.1%	2.0%	1.8%	1.8%
Confidence interval (95% CI)	2.6–3.5%	2.3–3.1%	2–2.7%	1.8–2.6%	1.8–2.5%	1.6–2.3%	1.5–2.2%	1.4–2.1%
Number Needed To Scope[d] (N/n)								
Colorectal cancer	15.3	12.4	11.7	10.3	9.8	9.0	8.3	8.1
Confidence interval (95% CI)	11.3–23.8	9.1–19.5	8.4–18.9	7.5–16.7	7.1–15.7	6.5–14.4	6–13.2	5.9–13.2
CRC+advanced adenomas	2.3	2.1	1.9	1.8	1.8	1.8	1.8	1.7
Confidence interval (95% CI)	2.6–2.5	1.9–2.3	1.7–2.2	1.6–2.1	1.6–2	1.6–2	1.6–2	1.5–2
Specificity[e]								
CRC+advanced adenomas	96.0%	97.1%	97.8%	98.1	98.3	98.4	98.6	98.7
Confidence interval (95% CI)	95.5–96.5%	96.7–97.5%	97.4–98.1%	97.8–98.5%	98.0–98.6%	98.1–98.8%	98.3–98.9%	98.4–99.0%
CRC miss rate[f] (%)	N.A.	3.6%	14.3%	14.3%	14.3%	14.3%	14.3%	17.9%
Confidence interval (95% CI)	N.A.	–3.3–10.4%	1.3–27.2%	1.3–27.2%	1.3–27.2%	1.3–27.2%	1.3–27.2%	3.7–32%

Abbreviations: CI, confidence interval; CRC, colorectal cancer; iFOBT, immunochemical faecal occult blood test. [a]Postives adherent to colonoscopy = patients with a positive iFOBT who underwent a colonoscopy. [b]Colonoscopy rate = percentage of participants with a positive iFOBT who underwent a colonoscopy. [c]Detection rate = percentage of participants with lesions of reference. [d]Number Needed To Scope = the number of patients to find one extra patient with lesions of reference. [e]Specificity was calculated under the rare disease assumption (Brecht and Robra, 1987). [f]CRC miss rate = the percentage of the colorectal cancer patients at that cutoff relative to the colorectal cancer patients at the minimal 50 ng ml^{-1} cutoff.

FIT+ in asymptomatic, AR first test group - 75ng cutoff:
~1 in 13 will have CRC
~1 in 2 should have polyp or CRC

Annals of Internal Medicine | REVIEW

Accuracy of Fecal Immunochemical Tests for Colorectal Cancer

Systematic Review and Meta-analysis

Jeffrey K. Lee, MD, MAS; Elizabeth G. Liles, MD, MCR; Stephen Bent, MD; Theodore R. Levin, MD; and Douglas A. Corley, MD, PhD

Background: Performance characteristics of fecal immunochemical tests (FITs) to screen for colorectal cancer (CRC) have been inconsistent.

Purpose: To synthesize data about the diagnostic accuracy of FITs for CRC and identify factors affecting its performance characteristics.

Data Sources: Online databases, including MEDLINE and EMBASE, and bibliographies of included studies from 1996 to 2013.

Study Selection: All studies evaluating the diagnostic accuracy of FITs for CRC in asymptomatic, average-risk adults.

Data Extraction: Two reviewers independently extracted data and critiqued study quality.

Data Synthesis: Nineteen eligible studies were included and meta-analyzed. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of FITs for CRC were 0.79 (95% CI, 0.69 to 0.86), 0.94 (CI, 0.92 to 0.95), 13.10 (CI, 10.49 to 16.35), 0.23 (CI, 0.15 to 0.33), respectively, with an overall diagnostic accuracy of 95% (CI, 93% to 97%). There was substantial heterogeneity between studies in both the pooled sensitivity and specificity estimates. Stratifying by cutoff value for a positive test result or removal of discontinued FIT brands resulted in homogeneous sensitivity estimates. Sensitivity for CRC improved with lower assay cutoff values for a positive test result (for example, 0.89 [CI, 0.80 to 0.95] at a cutoff value less than 20 $\mu g/g$ vs. 0.70 [CI, 0.55 to 0.81] at cutoff values of 20 to 50 $\mu g/g$) but with a corresponding decrease in specificity. A single-sample FIT had similar sensitivity and specificity as several samples, independent of FIT brand.

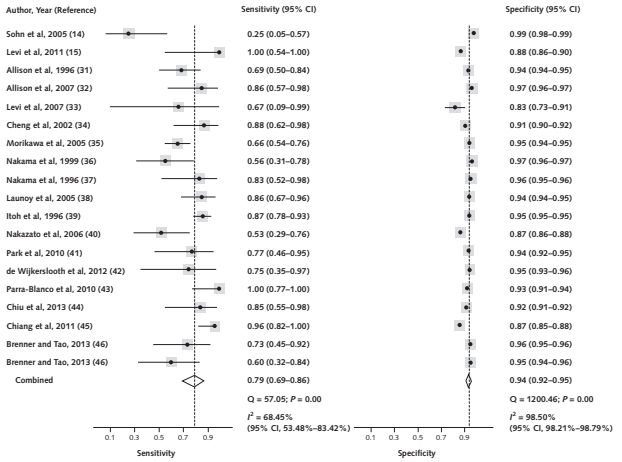
Limitations: Only English-language articles were included. Lack of data prevented complete subgroup analyses by FIT brand.

Conclusion: Fecal immunochemical tests are moderately sensitive, are highly specific, and have high overall diagnostic accuracy for detecting CRC. Diagnostic performance of FITs depends on the cutoff value for a positive test result.

Primary Funding Source: National Institute of Diabetes and Digestive and Kidney Diseases and National Cancer Institute.

Ann Intern Med. 2014;160:171-181. www.annals.org
For author affiliations, see end of text.

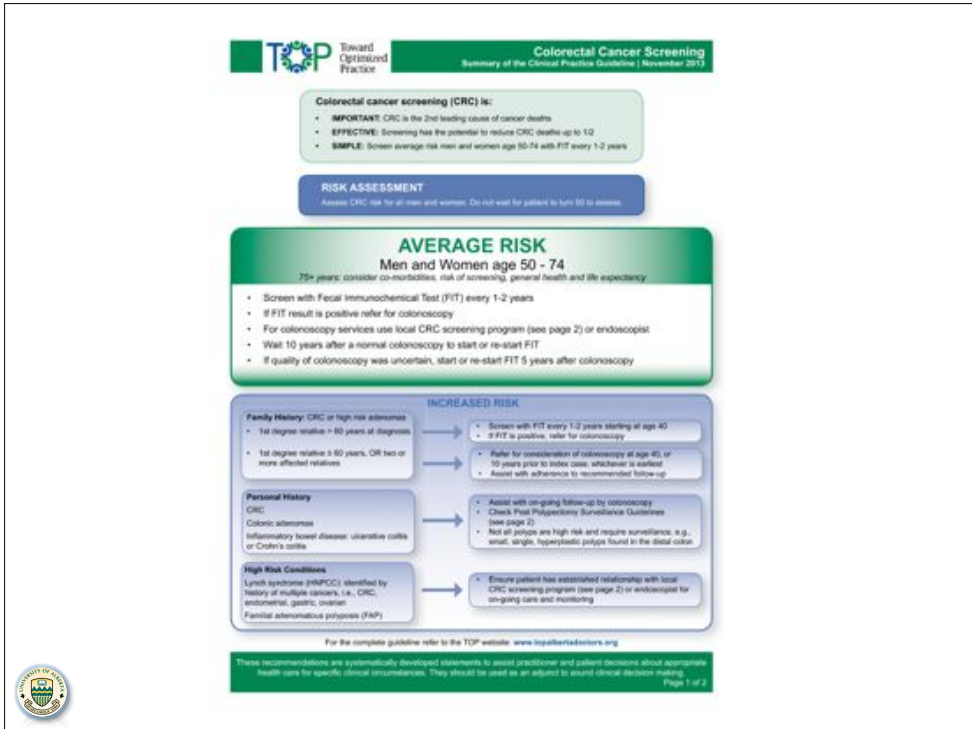
Figure 2. **Pooled sensitivity and specificity for fecal immunochemical tests for the detection of colorectal cancer for all included studies.**



The circles in squares represent the point estimate, the horizontal lines represent the 95% CI, the dotted lines represent the pooled estimate, and the diamonds represent the 95% CI of the pooled estimate.

SEN 0.79
SPEC 0.94
PLR 13.1
NLR 0.23
Accuracy 95%

WHO SHOULD GET A FIT?



WHO SHOULD GET A FIT TEST?

- All average risk Albertans
  - age 50-74
- Moderate risk Albertans (FDR CRC or AA > age 60)
  - age 40-74

WHEN NOT TO USE FIT

NO FIT FOR...

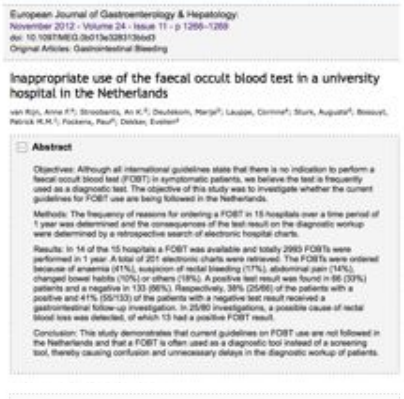
- Out of age range patients (<40 or over age 85)
  - needs careful consideration in 75-84 group
- Symptomatic patients
- Acute care settings
- Interval FIT
- If quality of life is poor or life expectancy is less than 10 years

FIT OUT OF RANGE

- FIT can be ordered for screening in age 40+ if FDR with CRC over age 60
- No evidence for use under 40
- If testing over 75, needs assessment of quality of life, comorbidities, risks of sedation and life expectancy
- Soon - hard cutoff - no tests released for under 40 over 85 and older

SYMPTOMATIC PATIENTS FOBT MISUSE

- Guaiac fecal testing discontinued in community settings as of 2014
- Lack of evidence for use in symptomatic patients



European Journal of Gastroenterology & Hepatology:
November 2012 - Volume 24 - Issue 11 - p 1266–1269
doi: 10.1097/MEG.0b013e328313fde0
Original Articles: Gastrointestinal Bleeding

Inappropriate use of the faecal occult blood test in a university hospital in the Netherlands

van Rijn, Anne F.[a]; Stroobants, An K.[a]; Deutekom, Marjo[b]; Lauppe, Corinne[a]; Sturk, Augusta[a]; Bossuyt, Patrick M.M.[c]; Pockens, Paul[a]; Dekker, Evelien[a]

Abstract

Objectives: Although all international guidelines state that there is no indication to perform a faecal occult blood test (FOBT) in symptomatic patients, we believe the test is frequently used as a diagnostic test. The objective of this study was to investigate whether the current guidelines for FOBT use are being followed in the Netherlands.

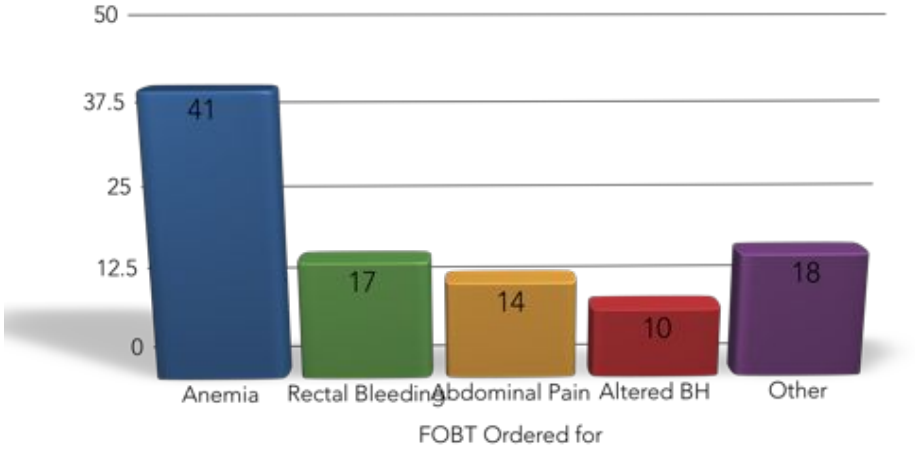
Methods: The frequency of reasons for ordering a FOBT in 15 hospitals over a time period of 1 year was determined and the consequences of the test result on the diagnostic workup were determined by a retrospective search of electronic hospital charts.

Results: In 14 of the 15 hospitals a FOBT was available and totally 2993 FOBTs were performed in 1 year. A total of 201 electronic charts were retrieved. The FOBTs were ordered because of anaemia (41%), suspicion of rectal bleeding (17%), abdominal pain (14%), changed bowel habits (10%) or others (18%). A positive test result was found in 66 (33%) patients and a negative in 133 (66%). Respectively, 38% (25/66) of the patients with a positive and 41% (55/133) of the patients with a negative test result received a gastrointestinal follow-up investigation. In 25/80 investigations, a possible cause of rectal blood loss was detected, of which 13 had a positive FOBT result.

Conclusion: This study demonstrates that current guidelines on FOBT use are not followed in the Netherlands and that a FOBT is often used as a diagnostic tool instead of a screening tool, thereby causing confusion and unnecessary delays in the diagnostic workup of patients.

VAN RIJN ET AL., INAPPROPRIATE FOBT USE

- Impact and followup of 2993 FOBT over 1 year



VAN RIJN ET AL., INAPPROPRIATE FOBT USE

POSITIVE RESULT
38% HAD WORKUP

NEGATIVE RESULT
41% HAD WORKUP

ALL CASES HAD DELAY IN REFERRAL

ACUTE CARE SETTING-FOBT USE

EDITORIAL

Putting an end to the misuse of the fecal occult blood test in diagnostic medicine

Catherine Dubé MD MSc FRCPC

ORIGINAL ARTICLE

Use of fecal occult blood test in hospitalized patients: Survey of physicians practicing in a large central Canadian health region and Canadian gastroenterologists

IP ET AL., FOBT SURVEY

- Survey of Cdn physicians
  - EM, FM, Gen Surg, GI

TABLE 3
Comparison of survey responses between Winnipeg Regional Health Authority (WRHA) physicians and Canadian Association of Gastroenterology (CAG) member respondents

Question	WRHA physicians* (n=118)†	CAG members (n=60)†	P
Do not use FOBT in hospitalized patients	44	74	<0.001
Believe FOBT is of value among emergency room patients	58	25	<0.001
Believe FOBT is of value among inpatients	76	26	<0.001

FIT SHOULD **NOT** BE USED FOR SYMPTOMATIC PATIENTS OR IN ACUTE CARE

- Delays referral/consultation
- Can not be used at point of care
- Does not detect UGIB
- Higher rates of False positivity
- Not for interpretation/use after DRE
- Urgent colonoscopy does not apply to this subset

INTERVAL FIT

- Use of FIT after a normal colonoscopy
- Prior studies had discussed use of gFOBT between colonoscopy sessions
    - No discussion of quality metrics for colonoscopy
    - Additional pickup rate was 1%
- In Calgary screening centre, rate was 0.04%!

INTERVAL FIT

- If colonoscopy was of high quality, interval testing NOT recommended
    - High quality colonoscopy
        - documentation of cecal intubation
        - documentation of bowel prep quality
        - done as part of program based screening

SUMMARY

- In this session, we have reviewed:
    - Impact of CRC
    - FIT testing for colorectal cancer
    - Stratifying who gets FIT for colorectal cancer screening
    - Who should not get FIT