

Screening for Colorectal Cancer

Part 1: Screening-Tests
and Program Design

3. updated edition



Ludwig Boltzmann Institut
Health Technology Assessment

HTA project report No.: 41a
ISSN 1992-0488
ISSN online 1992-0496

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Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, October 2012

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3. UPDATED EDITION

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This report should be referenced as follows:

Patera N., Schumacher I. Screening for Colorectal Cancer. Part 1: Screening Tests and Program Design, HTA project report. 2012; Nr.: 41a.

Conflict of Interest

All contributing authors declare that they have no conflicts of interest according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org)

Overall Project Management: Viterio-Schweiz GmbH, Martinsbruggstrasse 65, CH-9016 St. Gallen (1. and 2. editions)

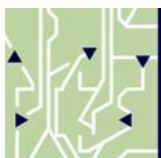
Commissioned by: Swiss Cancer League (Krebsliga Schweiz), Effingerstrasse 40, CH-3000 Bern, www.krebsliga.ch (1. and 2. editions); Main Association of Austrian Social Security Institutions (Hauptverband der österreichischen Sozialversicherungsträger), A-1030 Vienna, www.hauptverband.at (3. edition)

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Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6. Stock, A-1090 Vienna
<http://www.lbg.ac.at/gesellschaft/impressum.php>

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Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
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HTA project reports of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

HTA project reports of the LBI-HTA are available in a minimal amount in print and also available to the public via the Internet at "<http://eprints.hta.lbg.ac.at/>":

HTA project report No.: 41a

ISSN 1992-0488

ISSN online 1992-0496

http://eprints.hta.lbg.ac.at/view/types/hta_report.html

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Summary

Significance of colonoscopy in screening for colorectal cancer

Colonoscopy is – irrespective of first line screening test – the final common pathway of all screening for colorectal cancer (CRC) and is used for biopsy and polyp removal. For a screening-test in the (healthy) general population colonoscopy is invasive and prone to (unlikely) serious complications. Screening-yield and rates of complications are strongly dependent on the individual operator and on quality assurance. As a result, training and continued education of endoscopists as well as monitoring of both detection and complication rates are key to high screening-quality.

colonoscopy ...

... final common pathway in all CRC-screening

... invasive, (unlikely) serious complications

... operator-dependent

Effectiveness of screening for CRC

No data is currently available on the impact of CRC-screening on all-cause mortality. Four randomized controlled trials on screening for faecal occult blood as a first-line test (gFOBT) showed a relative risk reduction of 15% for disease-specific CRC-mortality. Absolute risk reduction was between 0.12-0.29%. Two large non-population based randomized controlled trial on once-only flexible sigmoidoscopy as a first-line screening-test showed a relative risk reduction of 31% and 22% (statistically not significant) for disease-specific CRC-mortality and a reduction of CRC incidence of 23% and 18%. Results from a large non-population based two round flexible sigmoidoscopy screening study showed a relative risk reduction of 26% of disease-specific CRC-mortality and a reduction of CRC incidence of 21%. Absolute risk reduction of CRC-mortality through flexible sigmoidoscopy was between 0.11-0.15%. Results from a population based randomized trials on flexible sigmoidoscopy are expected in 2013. To date there is no evidence from randomized controlled trials on CRC-screening using colonoscopy as a first-line screening test. Two randomized studies on screening with either colonoscopy or iFOBT as a first-line test will yield results starting ten years from now. There is only limited evidence on test characteristics (sensitivity, specificity, complication rates) in real life screening-settings. The ideal test strategie in CRC-screening is uncertain, the evidence base evolving.

limited evidence base for CRC-screening ...

... RCTs from gFOBT and recently flexible sigmoidoscopy show reduction in CRC-specific mortality ...

... for flexible sigmoidoscopy also for CRC-incidence

no RCT evidence for colonoscopy for another decade

ideal CRC-screening test strategy uncertain

Summary 1: results from CRC-screening-RCTs on effectiveness

Study Country Duration of follow-up	CRC-mortality (95% CI)	CRC-incidence (95% CI)	NNS (95% CI)
gFOBT			
gFOBT Nottingham UK ⁴ Follow-up: 11 yrs.	RR ³ : 0.86 (0.77-0.97) ARR: 0.12% ¹	RR ⁵ : 1.04 (0.95-1.14)	NNS (death from CRC): 840 ¹
gFOBT Funen DK ⁴ Follow-up: 17 yrs.	RR ³ : 0.84 (0.73-0.96) ARR: 0.22% ¹	RR ⁵ : 1.02 (0.93-1.12)	NNS (death from CRC): 449 ¹
gFOBT Gotenburg SWE ⁴ Follow-up: 15.5 yrs.	RR ³ : 0.84 (0.71-0.99) ARR: 0.14% ¹	RR ⁵ : 0.96 (0.86-1.06)	NNS (death from CRC): 711 ¹
gFOBT Minnesota USA ⁴ Follow-up: 18 yrs.	RR ³ : 0.75 (0.62-0.91) ARR: 0.29% ¹	RR ⁵ : 0.83 (0.73-0.94)	NNS (death from CRC): 350 ¹
Flexible sigmoidoscopy			
FS Atkin (2010) UK Follow-up: 11.2 yrs.	RR: 0.69 (0.59-0.82; p<0.0001) ARR: 0.15% ¹	RR: 0.77 (0.70-0.84; p<0.0001) ARR: 0.37% ¹	NNS (death from CRC): 489 (343-852) NNS (CRC-diagnosis): 191 (145-277)
FS Segnan (2011) ITA Follow-up: 11.4 yrs. mortality 10.5 yrs. incidence	RR: 0.78 (0.56-1.08) ARR: 0.105%	RR: 0.82 (0.69-0.96) ARR: 0.32% ¹	NNS (death from CRC): 952 ¹ NNS (CRC-diagnosis): 312 ¹
FS Schoen (2012) USA Follow-up: 11.9 yrs.	RR: 0.74 (0.63-0.87; p<0.001) ARR: 0.115% ¹	RR: 0.79 (0.72-0.85; p<0.001) ARR: 0.36% ¹	NNS (death from CRC): 871 ² NNS (CRC-diagnosis): 282 ²

ARR ... absolute risk reduction; CI ... confidence interval; CRC ... colorectal cancer; FS ... flexible sigmoidoscopy; gFOBT ... guaiac fecal occult blood test; NNS ... number needed to screen; RR ... relative risk

¹ own calculation

² author response to letter to the editors: <http://www.nejm.org/doi/full/10.1056/NEJMoa1114635#t=letters>

³ Bretthauer (2011), figure 3

⁴ Cochrane Review on gFOBT RCTs: Cochrane Systematic Review, Hewitson (2007)

⁵ Bretthauer (2011), table 3

International screening-activities

In many countries the evaluation of evidence, the planning and at times the coordination of CRC-screening are done by a national institution. A few countries – e.g. England, Scotland, Finland, Ireland, the Netherlands and Australia – run or are starting to run organized population-based programs. However, most screening is not population-based but opportunistic with low participation rates. Some countries – Japan, Italy and Germany – have programs that have been under way for many years. In the European Union about 70% of the population has access to some mode of CRC-screening. The most common first-line screening-test is gFOBT, to a growing degree also iFOBT. In some countries endoscopic-screening – colonoscopy, flexible sigmoidoscopy – is used as an alternative or in combination with FOBT. Also due to insurers’ remuneration decisions in the US, colonoscopy is the most common first-line screening-test there.

most screening-activity not population-based ...

... but opportunistic with low participation rates

... gFOBT most common, also iFOBT starting to be used ...

... US relies mostly on colonoscopy

Choice of first-line test

When considering first-line screening-tests on which to base an organized program, program sensitivity per invitee through the test’s impact on participation in screening (and re-screening) is more important than single test-sensitivity per screened participant. Complications rates are to be taken into account. Program-sensitivity largely depends on participation rates. Recent developments in first-line screening tests include quantitative iFOBTs. CT-colonoscopy, capsule endoscopy and new molecular tests are not yet viable alternatives for use in population-based mass-screening.

first-line screening test’s impact on program participation more important than sensitivity of single test

complication rates should be considered

Summary 2: CRC-screening participation rates observed in the real world

Screening-modality	Source Country	Participation-rate	Comment
Screening-programs			
gFOBT	von Wagner (2011) UK	54%	Oct. 2006 – Jan. 2009, mailing of first self-test kit population based program
gFOBT	Poncet (2012) France	37%	2007-2008, population based program
gFOBT	Cancer Society of Finland (2012) Finland	66.3%	2011 population based program in 154 of Finland's 444 municipalities
iFOBT	AIHW (2012) Australien	38.5%	Aug. 2006 – June 2011, population based program
iFOBT	Zorzi (2012) Italy	48%	2010, adjusted participation rate (only persons actually invited included), population based program
FS	Zorzi (2012) Italy	24%	2010, adjusted participation rate (only persons actually invited included), population based program
C	ZI (2012) Germany	18.3% of men 20.1% of females	cumulated attendance 2003-2010, program not population based

Screening-modality	Source Country	Participation-rate	Comment
RCTs			
gFOBT	Hol (2010) NL	49.5%	RCT in preparation of organized CRC-screening program in the NL, population based randomization, first round of invitation
iFOBT	Hol (2010) NL	61.5%	RCT in preparation of organized CRC-screening program in the NL, population based randomization, first round of invitation
iFOBT	Van Hal (2011) Belgium	44.3%	RCT pilot study for potential organized CRC-screening program in Belgium, population based randomization, (52.3% participation after invitation via mail, 27.7% after invitation via general practitioner)
FS	Hol (2010) NL	32.4%	RCT in preparation of organized CRC-screening program in the NL, population based randomization, first round of invitation
C	Stoop (2012) NL	22%	RCT in preparation of organized CRC-screening program in the NL, population based randomization, first round of invitation
CT-C	Stoop (2012) NL	34%	RCT in preparation of organized CRC-screening program in the NL, population based randomization, first round of invitation

C ... colonoscopy; CT-C ... virtual CT-colonoscopy; FS ... flexible sigmoidoscopy, gFOBT ... guaiac fecal occult blood test; iFOBT immunochemical fecal occult blood test

Summary 3: estimates of (single-)test characteristics of different screening-modalities

Screening-test	Sensitivity (%) CRC	Sensitivity (%) Advanced adenoma	Specificity (%) CRC	Specificity (%) Advanced adenoma
gFOBT	11-64	11-41	91-98	n.a.
iFOBT	56-89	27-56	91-97	n.a.
Flexible Sigmoidoskopie	60-70	50-81	60-70	50-80
Koloskopie	95	95	95-99	90-95

CRC ... colorectal cancer; gFOBT ... guaiac fecal occult blood test; iFOBT immunochemical fecal occult blood test; n.a. ... not applicable

Source: Bretthauer (2011), table 1

Summary 4: complications in CRC-screening-RCTs on flexible sigmoidoscopy: complications FS

Study	Perforations per 100,000	Bleedings per 100,000
Atkin (2010) ¹	2.48	30 ²
Segnan (2011)	10	n.a.
Schoen (2012)	2.8 2. FS round: 107.5 ³	n.a.

¹ reported in Atkin (2002)

² hospital admission

³ author response to letter to the editors: <http://www.nejm.org/doi/full/10.1056/NEJMoa1114635#t=letters>

Summary 5: complications in CRC-screening-RCTs on flexible sigmoidoscopy: complications colonoscopy following FS

Study	Perforations per 100,000	Bleedings per 100,000
Atkin (2010) ¹	168	377 ²
Segnan (2011)	120	n.a.
Schoen (2012)	108	n.a.

¹reported in Atkin (2002)

² hospital admission

Improving screening-effectiveness

An upper age-limit for CRC-screening is recommended. An integrated screening-program combines screening with screening-relevant considerations in diagnosis, treatment and surveillance. Along with standardized documentation and regular evaluation an integrated program-design provides the quality necessary to consider screening average risk-populations. Giving thorough attention to the design of the surveillance regime is important, because its thresholds determine the numbers of surveillance-colonoscopyes resulting from CRC-screening. Incremental implementation of a national population-based screening-program, with targeted research studies, pilot testing and incremental roll-out, like in the Netherlands, should be considered.

integrated screening – program considering diagnosis – treatment – surveillance

incremental implementation of national program recommended

Securing comprehensive program-financing

Population-based screening-programs require significant initial investment in overhead and sustainable financing of ongoing documentation, quality assurance and evaluation. Also, ongoing financing of both program- and provider-independent information dissemination to potential screening-participants enabling informed consent if or if not to participate in screening, and funds for regular program evaluation through an external institution need to be secured.

CRC-screening needs substantial initial net-investment, comprehensive and sustainable program funding needs to be secured

Zusammenfassung

Koloskopie ...

- ... ist Hauptbestandteil jedes CRC-Screening Pfads
- ... ist invasive Screening-Maßnahme mit (seltenen) schweren Komplikationen

Bedeutung der Koloskopie im Dickdarmkrebs-Screening

Koloskopie ist – unabhängig von der Wahl des first-line Tests – Bestandteil jedes Screenings. Koloskopie wird jedenfalls als second-line Test und gegebenenfalls zur Biopsie bzw. Entfernung entdeckter Polypen eingesetzt. Koloskopie ist für eine Screening-Maßnahme, die sich an die gesunde Normalbevölkerung richtet, invasiv und mit (seltenen) schweren Komplikationen verbunden. Die Entdeckungsraten von Polypen und die Komplikationsraten sind stark von der/dem individuellen UntersucherIn und von umfassender Qualitätssicherung abhängig. Die Aus- und Weiterbildung der Endoskopierenden und das Monitoring der Ergebnisraten sind zentral für die Qualität von Dickdarmkrebs-Screening.

- wenig Evidenz zur Effektivität von Dickdarmkrebs-Screening vorhanden

- ... 4 RCTs zu gFOBT und ...
- ... 3 RCTs zu flexibler Sigmoidoskopie belegen Reduktion der CRC-Mortalität durch Screening ...
- ... flexible Sigmoidoskopie auch der CRC-Inzidenz
- ... RCTs zu Koloskopie erst in 10 Jahren

Effektivität von Dickdarmkrebs-Screening

Zum Einfluss von Darmkrebs-Screening auf die Gesamtsterblichkeit liegen keine Daten vor. Vier randomisierte Studien belegen für Screening mit einem Test auf Blut im Stuhl (gFOBT) eine Senkung der Darmkrebs-spezifischen Sterblichkeit um 15% (relative Risikoreduktion). Die absolute Risikoreduktion liegt zwischen 0,12-0,29%. Zwei große nicht-populationsbezogene randomisierte Studien belegen für einmaliges Screening mit flexibler Sigmoidoskopie eine Senkung der CRC-spezifischen Sterblichkeit um 31% bzw. (statistisch nicht signifikant) 22%. Die Inzidenz von CRC ging um 23% bzw. 18% zurück. Eine große nicht-populationsbezogene randomisierte Studie zu Screening mit zwei Runden flexibler Sigmoidoskopie belegt 26% weniger CRC-spezifische Sterblichkeit und 21% weniger CRC-Inzidenz. Die absoluten Risikoreduktionen der CRC-spezifischen Sterblichkeit durch flexible Sigmoidoskopie liegen zwischen 0,11-0,15%. Ergebnisse einer weiteren, diesmal populationsbezogenen, randomisierter Studie zu flexibler Sigmoidoskopie werden 2013 erwartet. Zwei randomisierte Studien über Screening mit Koloskopie oder alternativ iFOBT als first-line Test werden erst in zehn Jahren Ergebnisse liefern. Über Charakteristika wie Sensitivität, Spezifität und Komplikationsraten der Tests im Kontext von Screening-Bedingungen in der Praxis gibt es wenig Evidenz. Eine ideale Teststrategie von CRC-Screening läßt sich derzeit aus der vorhandenen Evidenz nicht ableiten, das Forschungsgebiet entwickelt sich dynamisch.

Ergebnisse von CRC-Screening-RCTs zur Effektivität

Studie Land Follow-up	CRC-Mortalität (95% CI)	CRC-Inzidenz (95% CI)	NNS (95% CI)
gFOBT			
gFOBT Nottingham UK ⁴ Follow-up: 11 J.	RR ³ : 0,86 (0,77-0,97) ARR: 0,12% ¹	RR ⁵ : 1,04 (0,95-1,14)	NNS (CRC-Todesfall): 840 ¹
gFOBT Funen DK ⁴ Follow-up: 17 J.	RR ³ : 0,84 (0,73-0,96) ARR: 0,22% ¹	RR ⁵ : 1,02 (0,93-1,12)	NNS (CRC-Todesfall): 449 ¹
gFOBT Göteborg SWE ⁴ Follow-up: 15,5 J.	RR ³ : 0,84 (0,71-0,99) ARR: 0,14% ¹	RR ⁵ : 0,96 (0,86-1,06)	NNS (CRC-Todesfall): 711 ¹
gFOBT Minnesota USA ⁴ Follow-up: 18 J.	RR ³ : 0,75 (0,62-0,91) ARR: 0,29% ¹	RR ⁵ : 0,83 (0,73-0,94)	NNS (CRC-Todesfall): 350 ¹
Flexible Sigmoidoskopie			
FS Atkin (2010) UK Follow-up: 11,2 J.	RR: 0,69 (0,59-0,82; p<0,0001) ARR: 0,15% ¹	RR: 0,77 (0,70-0,84; p<0,0001) ARR: 0,37% ¹	NNS (CRC-Todesfall): 489 (343-852) NNS (CRC-Diagnose): 191 (145-277)
FS Segnan (2011) ITA Follow-up: 11,4 J. Mortalität 10,5 J. Inzidenz	RR: 0,78 (0,56-1,08) ARR: 0,105%	RR: 0,82 (0,69-0,96) ARR: 0,32% ¹	NNS (CRC-Todesfall): 952 ¹ NNS (CRC-Diagnose): 312 ¹
FS Schoen (2012) USA Follow-up: 11,9 J.	RR: 0,74 (0,63-0,87; p<0,001) ARR: 0,115% ¹	RR: 0,79 (0,72-0,85; p<0,001) ARR: 0,36% ¹	NNS (CRC-Todesfall): 871 ² NNS (CRC-Diagnose): 282 ²

ARR ... absolute risk reduction; CI ... Konfidenzintervall; CRC ... Colorectalcarcinom; FS ... flexible Sigmoidoskopie; gFOBT ... guaiac fecal occult blood test; NNS ... number needed to screen; RR ... relative risk

¹ eigene Berechnung

² author response to letter to the editors:

<http://www.nejm.org/doi/full/10.1056/NEJMoa1114635#t=letters>

³ Bretthauer (2011), Abbildung 3

⁴ Cochrane Review zu gFOBT RCTs: Cochrane Systematic Review, Hewitson (2007)

⁵ Bretthauer (2011), Tabelle 3

Screening-Aktivitäten international

Screening meist nicht populationsbezogen im Rahmen qualitätsgesicherter Programme ...
... sondern opportunistisch und mit niedrigen Teilnehmeraten
... gFOBT, iFOBT, in USA Koloskopie

In vielen Ländern erfolgt die Bewertung der Evidenz, die Planung und teilweise die Koordinierung von Screening durch eine nationale Institution. Nur wenige Länder – wie England, Schottland, Finnland, Irland, die Niederlande und Australien – verfügen über nationale populationsbezogene Programme. Meist erfolgt Screening aber nicht populationsbezogen im Rahmen eines qualitätsgesicherten Programms, sondern opportunistisch und mit niedriger Teilnehmerate. In einigen Ländern – wie etwa in Japan, Italien und Deutschland – bestehen Programme bereits seit vielen Jahren. In der Europäischen Union haben etwa 70% der Bevölkerung Zugang zu der einen oder anderen Form von Dickdarmkrebs-Screening. Als first-line Screening-Test wird am häufigsten gFOBT, zunehmend gefolgt von iFOBT, eingesetzt. Bisweilen besteht eine Wahlmöglichkeit zu Koloskopie oder flexibler Sigmoidoskopie. Nicht zuletzt aufgrund von Erstattungsentscheidungen von Krankenversicherungen in den USA ist dort Koloskopie der häufigste first-line Test.

Auswahl des Screening-Tests:
... Auswirkung auf Programmsensitivität über Teilnehmerate wichtiger ...
... als Einzelsensitivität des Tests
Komplikationsraten

Auswahl eines first-line Tests

Für die Auswahl eines first-line Screening-Tests ist seine Auswirkung auf die TeilnehmerInnenrate des Screening-Programms wichtiger als die Sensitivität eines einzelnen Tests. Die Sensitivität des Programms hängt maßgeblich von der TeilnehmerInnenrate über die Screeningrunden hinweg ab. Die Komplikationsraten von endoskopischen Tests (flexible Sigmoidoskopie und Koloskopie) sind in Betracht zu ziehen. Als neue first-line Screening-Tests bieten sich quantitative iFOBTs an. CT-Koloskopie, Kapselendoskopie und in Entwicklung befindliche molekulare Test werden in absehbarer Zeit (noch) keine Alternativen für einen breiten Screening-Einsatz sein.

Real beobachtete Teilnahmeraten an CRC-Screening

Screening-Modalität	Quelle Land	Teilnahmerate	Bemerkung
Screening-Programme			
gFOBT	von Wagner (2011) UK	54%	Okt. 2006 – Jan. 2009, Zusendung des ersten Selbsttest-Briefchens, populationsbezogenes Programm
gFOBT	Poncet (2012) Frankreich	37%	2007-2008, populationsbezogenes Programm
gFOBT	Cancer Society of Finland (2012) Finnland	66,3%	2011 populationsbezogenes Programm in 154 der 444 Munizipalitäten Finnlands
iFOBT	AIHW (2012) Australien	38,5%	Aug. 2006 – Juni 2011, populationsbezogenes Programm
iFOBT	Zorzi (2012) Italien	48%	2010, bereinigte Teilnahmerate (nur tatsächlich eingeladene Personen berücksichtigt), populationsbezogenes Programm
FS	Zorzi (2012) Italien	24%	2010, bereinigte Teilnahmerate (nur tatsächlich eingeladene Personen berücksichtigt), populationsbezogenes Programm
C	ZI (2012) Deutschland	18,3% der Männer 20,1% der Frauen	kumuliert 2003-2010, nicht populationsbezogenes Programm
RCTs			
gFOBT	Hol (2010) NL	49,5%	RCT in Vorbereitung auf organisiertes CRC-Screening Programm in den NL, populationsbezogene Randomisierung, erste Einladungsrunde
iFOBT	Hol (2010) NL	61,5%	RCT in Vorbereitung auf organisiertes CRC-Screening Programm in den NL, populationsbezogene Randomisierung, erste Einladungsrunde
iFOBT	Van Hal (2011) Belgien	44,3%	RCT Pilotstudie für ev. organisiertes CRC-Screening Programm in Belgien, populationsbezogene Randomisierung, (52,3% bei Einladung per Post, 27,7% bei Einladung über praktische Ärztin)
FS	Hol (2010) NL	32,4%	RCT in Vorbereitung auf organisiertes CRC-Screening Programm in den NL, populationsbezogene Randomisierung, erste Einladungsrunde
C	Stoop (2012) NL	22%	RCT in Vorbereitung auf organisiertes CRC-Screening Programm in den NL, populationsbezogene Randomisierung, erste Einladungsrunde
CT-C	Stoop (2012) NL	34%	RCT in Vorbereitung auf organisiertes CRC-Screening Programm in den NL, populationsbezogene Randomisierung, erste Einladungsrunde

C ... Koloskopie; CT-C ... virtuelle Koloskopie; FS ... flexible Sigmoidoskopie , gFOBT ... guaiac fecal occult blood test; iFOBT immunochemical fecal occult blood test

Geschätzte (Einzel-)Testcharakteristika unterschiedlicher Screening-Modalitäten

Screeningtest	Sensitivität (%) CRC	Sensitivität (%) Advanced Adenoma	Spezifität (%) CRC	Spezifität (%) Advanced Adenoma
gFOBT	11-64	11-41	91-98	n.a.
iFOBT	56-89	27-56	91-97	n.a.
Flexible Sigmoidoskopie	60-70	50-81	60-70	50-80
Koloskopie	95	95	95-99	90-95

CRC ... Colorectalcarcinom; gFOBT ... guaiac fecal occult blood test; iFOBT immunochemical fecal occult blood test; n.a. ... nicht anwendbar

Quelle: Bretthauer (2011), Tabelle 1

Komplikationen in CRC-Screening-RCTs zu flexibler Sigmoidoskopie: Komplikationen FS

Studie	Perforationen pro 100.000	Blutungen pro 100.000
Atkin (2010) ¹	2,48	30 ²
Segnan (2011)	10	k.A.
Schoen (2012)	2,8 2. FS Runde: 107,5 ³	k.A.

¹ berichtet in: Atkin (2002)

² Spitalsaufnahme

³ author response to letter to the editors: <http://www.nejm.org/doi/full/10.1056/NEJMoa1114635#t=letters>

Komplikationen in CRC-Screening-RCTs zu flexibler Sigmoidoskopie: Komplikationen Koloskopie nach FS

Studie	Perforationen pro 100.000	Blutungen pro 100.000
Atkin (2010) ¹	168	377 ²
Segnan (2011)	120	k.A.
Schoen (2012)	108	k.A.

¹ berichtet in: Atkin (2002)

² Spitalsaufnahme

**Screening-Programm
soll Vernetzung mit
Diagnose, Behandlung
und Surveillance sicher
stellen
... schrittweise
Einführung empfohlen**

Ansätze zur Steigerung der Effektivität

Das Festlegen einer oberen Altersgrenze für die Teilnahme am Dickdarmkrebs-Screening wird empfohlen. Ein mehrstufiges Programm, das die verschiedenen AkteurInnen des Screenings und die nachgelagerten diagnostischen, behandlerischen und Surveillance-Prozesse vernetzt, ermöglicht Qualitätssicherung, Dokumentation der Ergebnisse und deren Evaluation. Besondere Bedeutung kommt der Gestaltung der dem Screening nachgelagerten Surveillance zu. Die dort formulierten Schwellenwerte legen die Anzahl der durch Screening induzierten Surveillance-Koloskopien fest. Bei der Einführung eines populationsbezogenen Programms ist ein schrittweises Vorgehen, mit gezielter Begleitforschung und Pilottestungen und anschließendes schrittweises Ausrollen, wie in den Niederlanden, überlegenswert.

Komponenten der Programmfinanzierung

Für den nicht unbeträchtlichen Overhead eines qualitätsgesicherten populationsbezogenen Programms zum Dickdarmkrebs-Screening ist eine nachhaltige Finanzierung Voraussetzung. Gleiches gilt für die Finanzierung der extern programmabhängigen Bereitstellung von Informationen für potenzielle TeilnehmerInnen am Screening, die informed consent über Screening-Teilnahme oder nicht ermöglichen, und für die Finanzierung der regelmäßigen Evaluation des Programms durch eine externe unabhängige Institution.

CRC-Screening erfordert anfänglich beträchtliche Nettoinvestition

... ausreichende Finanzierung für Erfolg des Screening-Programms notwendig

1 Introduction

1.1 Rationale for Colorectal Cancer-Screening

Colorectal cancer (CRC) or colorectal adenocarcinoma is a malignant tumor arising within the walls of the large intestine, including the segments in the cecum, ascending colon, transverse colon, descending colon, sigmoid and rectum. CRC does not include tumors in the tissues of the anus or the small intestine.¹ CRC is common in industrialized countries. In terms of age-standardized incidence rates, there exists little difference from one European country to another, nor is there a clear geographic pattern.² Among both men and women CRC was the third most common non-skin cancer and also the third-highest cause of cancer death in the US in 2009.³

CRC has a recognizable, protracted pre-malignant stage (adenoma) that is relatively easy to remove through polypectomy. If an adenoma has progressed to carcinoma, it is an average of nearly 7 years before the disease becomes symptomatic.⁴ If CRC is detected early, a person's chances of survival are considerably higher than if it is detected at a later stage: Five-year survival of CRC exceeds 90% if diagnosed at an early stage (no tumor extension beyond the bowel wall). Survival is only about 60% for patients with tumors with lymph node involvement and under 10% if metastases are present.⁵ Symptoms of CRC develop late in the course of the disease, early detection is therefore often not achieved.⁶ This is why screening for CRC has been introduced in various modes of organization in a number of countries.

CRC-screening has the potential of both detecting CRC early (as in the case of screening for breast-cancer) and (unlike the case of breast cancer) of prevention of CRC, i.e. intervening before a precursor lesion (polyp) becomes malignant, by detecting and removing it (through polypectomy).⁷

burden of colorectal cancer (CRC) high

CRC believed to have protracted pre-malignant stage ...

... can be relatively easy removed via polypectomy (prevention goal of CRC-screening)

... early detection of CRC raises chance of survival (early detection goal of CRC-screening)

1.2 Background and structure of this report

The Swiss Cancer League (Krebsliga Schweiz)⁸ requested a review of the secondary literature (health technology assessments, systematic reviews, meta-analyses) on CRC-screening to inform about policy options in this realm. (It later commissioned an update in December 2010, the Main Association of Austrian Social Security Institutions – Hauptverband der österreichischen Sozialversicherungsträger⁹ commissioned a second update in

review of secondary literature on CRC-Screening for Swiss Cancer League ... with two updates

¹ USPSTF Whitlock (2008a) p. 2

² Health Council of the Netherlands (2009) p. 32

³ AHRQ Holden (2010) p. 25

⁴ Health Council of the Netherlands (2009) p. 77

⁵ Bretthauer (2011) citing a review of US cancer statistics.

⁶ Bretthauer (2011)

⁷ Bretthauer (2011)

⁸ www.krebsliga.ch

⁹ www.hauptverband.at

... on choice of
screening-test and
general issues of
program design

report focuses on three
recent HTAs

October 2012.) The study questions guiding this report are:

1. What screening-tests are available for CRC, what are the respective test characteristics and what are the respective test's wider implication for a CRC-screening program?
2. What questions and central aspects are to be considered in the context of designing an organized population-based screening-program for CRC?

After the ensuing methods section on the literature search in chapter 2, the quality of the three major health technology assessments¹⁰ – which are the main sources of information this report focuses on – is appraised in chapter 3. This is done according to the PRISMA-statement on preferred reporting items for systematic reviews and meta-analyses.¹¹ Chapter 4 (results part I) addresses the first study question and condenses the results of the literature review on important facts about CRC-screening. Chapter 5 (results part II) addresses the second study question. Part of the focus here lies on distilling important questions to ask about CRC-screening and about population-based screening-program design from the literature. The final chapter 6 concludes with a brief take-home message from the literature review for designing quality assured population-based CRC-screening programs.

¹⁰ Health Council of the Netherlands (2009), Ontario Health Technology Advisory Committee OHTAC (2009), United States Preventive Services Task Force USPSTF Whitlock (2008a)

¹¹ The PRISMA statement: Moher (2009)

2 Methods

2.1 Initial literature search and inclusion Dec. 2009

A systematic search of the literature was conducted on Dec. 22nd 2009 with the following PICO¹² –question:

PICO question for literature search

“Can (newer) faecal occult blood tests/ colonoscopy/ flexible sigmoidoscopy/ CT- or MRT- colonoscopy – virtual colonoscopy – colonography/ capsule endoscopy/ DNA-analysis – genetic tests – laboratory tests – biomarker alone or in combination detect CRC in asymptomatic adult average risk populations early and positively influence the further course of CRC?”

Table 2.1-1: PICO-question for CRC-screening report

Population	healthy adults OR risk groups/ healthy adults with family history in colon cancer
Interventions early diagnosis	(newer) faecal occult blood tests/FOBT colonoscopy flexible sigmoidoscopy capsule endoscopy CT- or MRT- colonoscopy/ virtual colonoscopy/ colonography DNA-analysis, genetic tests/testing laboratory tests/ biomarker
Control interventions	natural history placebo all interventions see above
Outcomes	colon carcinoma mortality colon carcinoma, no/less invasive surgery screening harm(s) OR adverse outcomes OR adverse advents OR bleeding OR haemorrhage OR perforation OR bowel perforation(s) OR procedural complication(s) OR surgery OR admission to hospital OR sedation related event(s) OR chemical colitis OR infection(s) OR death
Study design	only HTA, systematic reviews, meta-analysis 1999-2009

The search was limited to secondary literature (health technology assessments, systematic reviews, meta-analyses) published from 1999-2009. The following databases were searched:

Systematic search limited to secondary literature published from 1999-2009

Primary Databases: HTA, DARE, EED, Cochrane (NICE, CADTH, AHRQ, DIMDI), EuroScan

Secondary Databases: Medline, EmBase

¹² PICO: Patient, Population or Problem / Intervention or exposure / Comparison Intervention/ Outcome

after high-quality HTAs from 2008 and 2009 were identified, search was narrowed to articles published thereafter (2008, 2009)

This systematic search yielded 242 results. When three recent and reliable HTA-reviews (Health Council of the Netherlands 2009, Ontario Health Technology Advisory Committee OHTAC 2009, United States Preventive Services Task Force USPSTF 2008a – marked in bold in list of references at the end of the report) were identified, covering the evidence at least until the end of 2007, the search was narrowed to sources published thereafter, i.e. in 2008, 2009. Of the initial 242 results 33 remained. Of these 2 articles were duplicates, after their removal 31 articles remained

systematic search produced 13 articles

The abstracts of these 31 articles were reviewed independently by two researchers. Disagreements about inclusion were resolved through discussion and consensus. 18 articles were excluded on the basis of their abstracts as not relevant for the PICO-question of this report. 13 articles were included in the analysis for this report. These 13 references are marked “[SS-2009]” – for systematic search in Dec. 2009 – in the list of references at the end of this report.

additional unsystematic search on new molecular screening-tests produced 3 articles

Due to a special interest in recent developments in the field of molecular screening-tests expressed by the Swiss Cancer League (Krebsliga Schweiz), the above systematic search for secondary literature was supplemented by a small, unsystematic search for primary literature on new molecular screening-tests:

- ✿ Medline: Gen*tests OR Biomarker AND Colon Cancer AND Screening; limits: RCT, CT
- ✿ Google: “Gentest” and the above

This unsystematic search yielded 3 articles, all of which were included. These 3 references are marked “[MOHS-2009]” – for molecular hand search in Dec. 2009 – in the list of references at the end of this report.

hand search produced an additional 38 relevant articles

Both searches were supplemented with a hand search for topic specific primary articles informing on details of issues covered in this report, yielding 38 references- The 25 references used for this report are marked “[BG-2009]” – for background 2009 – in the list of references at the end of this report. The remaining 13 references not used in this report can be found in appendix B together with a brief description of their content.

In the course of the compilation of this report further references were included.

2.2 Update literature search and inclusion Nov. 2010

update search with identical PICO question in Nov. 2010

Following a request from the Swiss Cancer League (Krebsliga Schweiz) an update search of the literature was conducted on Nov. 12th 2010 adhering to the procedure detailed above.

This systematic update search yielded 46 results that were published in 2009 and 2010 and had not been included in the results of the initial literature search in December of 2009.

systematic update search produced 3 relevant articles

The abstracts of these 46 articles were reviewed – this time by only one researcher. 43 were excluded on the basis of their abstracts as not relevant for the PICO-question of this report. 3 results were included in the analysis for

this report. These 3 references are marked “[SS-2010]” – for systematic search in Nov. 2010 –in the list of references at the end of this report. Among these three references was a publication by the Canadian Agency for Drugs and Technologies in Health on the next generation of fecal DNA tests¹³. This reference addresses the special interest in recent developments in the field of molecular screening-tests expressed by the Swiss Cancer League (Krebsliga Schweiz).

In the course of the compilation of the 2010-update of the report a further 8 topic specific primary and secondary articles – identified by a hand search – informing on details of issues covered in this report were included. To differentiate these articles in the reference list at the end of this report they were marked “[BG-2010]” – for background 2010. The most important of these was the publication of results of a multicentre randomized controlled trial on once-only flexible sigmoidoscopy screening from the UK.¹⁴

hand search produced an additional 8 relevant articles

2.3 Second update literature search and inclusion Aug. 2012

Following a request from the Main Association of Austrian Social Security Institutions (Hauptverband der österreichischen Sozialversicherungsträger) a second update search of the literature was conducted on Aug. 8th 2012 adhering to the procedure detailed above. The focus was on recent evidence about recommended CRC-screening tests (FOBT, flexible sigmoidoscopy, colonoscopy).

second update search with identical PICO question in Aug. 2012

This systematic update search yielded 469 results that were published in 2010-2012. This large number of results compared to the two previous searches underlines the importance CRC-screening enjoys as a dynamic research field at present. No new HTA-reports were identified.

The abstracts of these articles were reviewed by two researchers independently. Disagreements about inclusion were resolved through discussion and consensus. 460 results were excluded as not relevant for the PICO-question of this report with the focus of this update in mind. 9 results were included in the analysis for this report. Two of these references¹⁵ had already been identified in the previous systematic update search from Nov. 2010, which partly overlapped for publications from 2010. This way 8 new references remained and are marked “[SS-2012]” – for systematic search in Aug. 2012 – in the list of references at the end of this report.

systematic update search produced 7 new relevant articles

In the course of the compilation of the 2012-update of the report a further 20 topic specific primary and secondary articles – identified by a hand search – informing on details of issues covered in this report were included. To differentiate these articles in the reference list at the end of this report they were marked “[BG-2012]” – for background 2012.

hand search produced an additional 20 relevant articles

¹³ Morrison, A. Next-generation fecal DNA tests – an evolving technology [Environmental Scan issue 7]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010

¹⁴ Atkin (2010)

¹⁵ Atkin (2010), Spada (2010)

3 Appraisal of three core HTAs

The core of this report is based on three health technology assessments/ systematic reviews on the broader issue of CRC-screening by major health technology assessment or related institutions: Health Council of the Netherlands¹⁶, United States Preventive Services Task Force¹⁷ and Ontario Health Technology Advisory Committee¹⁸. The three publications were identified in the initial systematic search of the literature for this report in Dec. 2009. The systematic update searches in Nov. 2010 and Aug. 2012 did not identify additional health technology assessments/ systematic reviews with this broad scope. The three publications are appraised according to the PRISMA-statement on preferred reporting items for systematic reviews and meta-analyses in table 3-1 below.¹⁹

These three HTAs and additional relevant health technology assessments on narrower aspects within CRC-screening are listed in appendix A.

3 HTAs by Health Council of the Netherlands, USPSTF, Ontario HTAC form the core of report

¹⁶ Health Council of the Netherlands (2009)

¹⁷ United States Preventive Services Task Force USPSTF Whitlock (2008a)

¹⁸ Ontario Health Technology Advisory Committee OHTAC (2009)

¹⁹ The PRISMA statement: Moher (2009), table 1, p. 266

Table 3-1: Appraisal of three core HTAs relied on for this report

Institution	Study Quality Appraisal PRISMA for SRs and MAs	Comment
Health Council of the Netherlands (2009)	PRISMA checklist mostly not fulfilled as report is not published as systematic review	This advisory report to the Dutch Minister of Health, Welfare and Sport on whether and if, how to implement a national screening program is based on extensive literature and thorough evaluation of it. While not technically published as a systematic review, the results and discussion sections are similar. The additional value of this report is the explicit program focus and the incorporation of data from several pilot programs specifically undertaken to inform the decision making process in the Netherlands. Publication bias was not assessed.
Ontario Health Technology Advisory Committee OHTAC (2009)	PRISMA checklist fulfilled except: section 1: report declared as "evidence based analysis" not as "systematic review" section 2: structured abstract completely lacking section 12, 15, 19, 22: risk of bias in and across studies not extensively addressed point 27: role of funder in process of review not detailed	
United States Preventive Services Task Force USPSTF (2008 und 2008a)	PRISMA checklist fulfilled except section 12, 15, 19, 22 (risk of bias in and across studies) – compare comment	The review question was clear and supported by detailed inclusion criteria which are potentially reproducible. The search strategy included some relevant sources for published studies, but there was no apparent attempt to locate unpublished material. Publication bias was not assessed. Appropriate validity assessment tools were used to assess the quality of effectiveness and diagnostic studies. However, the results of this were not given in detail, making it difficult to verify the reported global assessment. The reported review process demonstrated attempts to minimize errors and bias. Heterogeneity was taken into account in the proposed methods of synthesis. The authors' conclusions reflected the results from a small number of included studies. The conclusions are probably reliable, but under reporting in relation to study quality may warrant a cautious interpretation. ²⁰

20 from Database of Abstracts of Reviews of Effects (DARE), produced by the Centre for Reviews and Dissemination, University of York
www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12008106882 – accessed March 14th 2010

4 Results part I: Facts about colorectal cancer-screening

4.1 Colorectal cancer

It is believed that the vast majority of CRC develops from benign precursor lesions (adenomatous polyps or adenomas) through a series of genetic changes over a long-time period.²¹ It is estimated that only 5% of all adenomas actually become malignant. The removal of these 5% of adenomas is sufficient to prevent CRC. The problem is that it is impossible to know which adenomas will become malignant and which will not. This inevitably results in a degree of over-diagnosis.²² In the case of most adenomas, removing them would have no effect on the survival of the individual concerned. The rates of over-diagnosis liable to result from CRC-screening cannot currently be quantified accurately.²³

Most CRC develops in average risk individuals, patients (approximately 75-80% or more) who have no close relatives with this disease. This majority of cases are classified as 'sporadic CRC'.²⁴

Approximately 20% of patients with CRC have some type of family history of CRC. For family-history CRC the lifetime risk of developing CRC depends on the number of relatives with this cancer, their degree of kinship and the age at which CRC was diagnosed.²⁵ Hereditary, genetically determined forms of CRC, i.e. Lynch syndrome – until recently referred to as hereditary non-polyposis colorectal carcinoma – and the various forms of polyposis are predisposed by genetical mutation and account for approximately 5% of all cases of CRC.²⁶ Individuals with Lynch syndrome are germ-line mutation carriers. They have a 25-70% lifetime risk of CRC. In people suffering from familial adenomatous polyposis that risk is virtually 100%.²⁷ For these hereditary, genetically determined forms of CRC-syndromes the issues involved in identifying candidates at risk, genetic testing, diagnosis and management are different than in general CRC-screening of average risk populations.²⁸

The remainder of CRC-cases develops in persons who have predisposing inflammatory bowel disease.²⁹

cancer-screening by definition results in over diagnosis ...

... degree difficult to quantify for CRC

80% of CRC sporadic

20% have family history of CRC ...

... these are not target of general screening: 5% hereditary CRC with 25-100% lifetime-risk of developing CRC

90% of newly diagnosed CRC-patients over 55 years ...

²¹ Bretthauer (2011) p. 87

²² Health Council of the Netherlands (2009) p. 32

²³ Health Council of the Netherlands (2009) p. 80

²⁴ USPSTF Whitlock (2008a) p. 3, Health Council of the Netherlands (2009) p. 34, Bretthauer (2011) p. 87

²⁵ Health Council of the Netherlands (2009) p. 34, Baglietto (2006), Butterworth (2006)

²⁶ Lynch (2003), Hampel (2005), USPSTF Whitlock (2008a) p. 3

²⁷ Health Council of the Netherlands (2009) p. 35

²⁸ e.g. Lynch (2009)

²⁹ USPSTF Whitlock (2008a) p. 3

... effective risk profiling for screening only via age and gender

More than 90% of all new CRC-patients were above 55 years of age in 2009.³⁰ Age and gender are the only effective risk factors in risk profiling prior to CRC-screening. The research literature contains reports of various attempts to develop a model for risk profiling. As yet, however, there are no usable, validated examples.³¹

4.2 Polyp size and CRC-screening

little evidence on optimal referral threshold to colonoscopy

A colorectal polyp is a fleshy growth occurring on the lining of the colon or rectum. A subtype of polyps are adenomas, benign tumors of glandular origin. Adenomas can grow from many organs including the colon.³²

referral to colonoscopy based on polyp sized

Without the benefit of biopsy results, referral to colonoscopy is based on polyp size. Referral thresholds of screen-detected lesions to colonoscopy are largely based on expert opinion rather than clinical outcomes.³³

... 80% of found polyps are < 6mm, consensus: no referral

Polyp size < 6mm: 80% of found abnormalities

- ✿ consensus by most, but not all experts³⁴: no referral required
- ✿ risk of being malignant in screening-population 0.03-0.2%

no consensus on polyps 6-10mm

Polyp size 6-10 mm: small polyps

- ✿ no consensus; necessity and benefit of removing small polyps is not clear³⁵
- ✿ data from large screening-studies: 3 – 9% are advanced neoplasia (composite outcome: adenocarcinoma/ invasive carcinoma/ CRC and advanced adenoma³⁶)
 - ✿ there have been no prospective studies describing the natural history of advanced neoplasia, and no longitudinal studies have validated the clinical benefit of targeting advanced neoplasia in screening-populations³⁷

“wait-and-see policy” seems indicated

- ✿ On the basis of data on the natural course of small polyps, there is no reason why a “wait-and-see policy” should not be adopted. For instance, a study involving the annual endoscopic surveillance of ‘small’ polyps found that, after 3 years, their average diameter even tended to decline slightly.³⁸

30 data for the Netherlands as example, Health Council of the Netherlands (2009) p. 33

31 Health Council of the Netherlands (2009) p. 37

An example for an area in which the evidence base is evolving would be the question if to suggest different screening-age limits for women and men.

32 compare: www.wikipedia.org

33 USPSTF Whitlock (2008)

34 USPSTF Whitlock (2008)

35 USPSTF Whitlock (2008a) p. 4

36 e.g. USPSTF Whitlock (2008a) p. 2

37 USPSTF Whitlock (2008a) p.6

38 Hofstad (1996) cited in Health Council of the Netherlands (2009) p. 70

Polyp size >10mm: large polyps

- ✿ consensus: should be removed
- ✿ 10-15% probability of being or becoming malignant
- ✿ evidence that removal of large adenomas has a particularly marked impact on the incidence of CRC³⁹ (caveat! – data on the reduction of CRC-incidence through colonoscopy and polypectomy rely on weak evidence⁴⁰)

consensus: large polyps > 10mm should be removed

Unanswered questions remain about the natural history of adenomas under 10mm and therefore about their clinical significance. Clarifying the risk associated with smaller polyps will be critical for estimating the true sensitivity and specificity of current and future CRC-screening methods that directly visualize lesions.

clarifying risk associated with smaller polyps important question for future research

Treatment costs for highly advanced stages of CRC (i.e. the very cases that screening can often prevent) are expected to rise sharply when the latest very expensive generation of chemotherapy agents is deployed. This increase in the cost of CRC treatment makes screening for CRC more cost-effective.⁴¹

sharply rising cost of CRC-treatment

4.3 CRC-screening trials

Measuring the outcome of CRC-screening trials

screening aims to save lives

Screening aims to save lives, i.e. screening strives to reduce all-cause mortality. There are three commonly used measures for evaluating the impact of CRC-screening on a population's health: 'all-cause mortality' directly and its surrogates, 'disease-specific mortality' and 'detection rate' – detection of advanced adenomas' or more narrowly 'detection of CRC'.

optimal outcome measure: all-cause mortality

The optimal outcome measure for screening-trials is all-cause mortality. Data on all-cause mortality is reliably and readily available. This endpoint requires very large samples, though. Of all causes of death, CRC represents very roughly 3%, a small fraction.⁴² The best available evidence suggests that the effect size of CRC-screening is a 15% reduction of CRC-mortality.⁴³ Even if directly translated into a reduction of all-cause mortality, assuming CRC-screening would not induce additional mortality, the effect of CRC-screening would represent only approximately 0.45% of all-cause mortality, a very small effect size to prove in a randomized controlled trial. When, as in this case, the disease-specific mortality is proportionally very low, only a very slight increase in non-cancer mortality is required to offset a reduction in cancer mortality and vice versa.⁴⁴ As a result the necessary sample size to

requires very large studies to prove effect: 300,000 per group

³⁹ Health Council of the Netherlands (2009) p. 80

⁴⁰ USPSTF Whitlock (2008a) p. 4

⁴¹ Health Council of the Netherlands (2009) p. 51 A debate in cost-effectiveness research concerns which costs to include in evaluations. If lost productivity through CRC were to be incorporated, which is at present not state of the art, cost-effectiveness of CRC-screening would become more favorable.

⁴² US CRC-lifetime mortality rate 2.4%, females 3.3%, USPSTF Whitlock (2008a)

⁴³ Cochrane Systematic Review, Hewitson (2007)

⁴⁴ Black (2002)

**as yet no data available
on impact of CRC-
screening on all-cause
mortality because of
huge study size required**

give a study sufficient power would have to be 300,000 per group in the case of CRC-screening.⁴⁵ Studies of all-cause mortality that are sufficiently large to have the required precision would not be feasible in many situations.⁴⁶ Since screening trials are expensive, require long follow-up and can include only a few comparison tests, validated microsimulation models may be used as an additional source of information for policy makers.⁴⁷ This leads to an unresolved dilemma: Presently there is no evidence from randomized controlled trials showing a reduction of all-cause mortality through CRC-screening. This lack of high-grade evidence leads to two interpretations: On one side the lack of high-grade evidence may suggest caution about CRC-screening. On the other side the fear is expressed, that a number of truly effective cancer-screening tests will incorrectly be deemed ineffective if emphasis is given to all-cause mortality, because it is not generally feasible to do studies that are large enough to reliably document the impact of screening on all-cause mortality.⁴⁸

**surrogate end point:
disease-specific
mortality**

It has been assumed that disease-specific mortality is a good surrogate end point for all-cause mortality. Because fewer patients are required for a study to provide adequate power, disease-specific mortality rather than all-cause mortality has been the accepted end point of screening-studies. Disease-specific mortality data are obtained via the cause-of-death statistics. These are less reliable than death statistics because of attribution problems of cause of death in practice. Even if disease-specific mortality is used for reasons of pragmatism, a decrease in all-cause mortality should be the ultimate aim of screening-programs, whether measured directly or not. A death from a non-malignant cause is just as important as a cancer-related death.⁴⁹

**attribution problems of
cause of death in
practice ...
... results in tendency to
overestimate screening
benefit**

Biases in screening trials

lead time bias ...

A concept from cancer screening epidemiology that is relevant for interpreting the results of screening trials is “lead time”. Lead time is the interval from diagnosis of a screening detected cancer to the the point in time when cancer would have been diagnosed without screening. In the case that the patient dies from CRC at the same time regardless if the cancer was detected early through screening or later, lead time bias would result in survival estimates favouring screening, because the cancer is detected earlier than without screening (even though in this case screening did not provide any survival benefit).⁵⁰

**... results in tendency to
overestimate screening
benefit**

slippery linkage bias ...

A problematic bias in screening-studies is the so called “slippery linkage bias”.⁵¹ Screening-activity and cancer treatment can be associated with excess non-cancer mortality (e.g. car accidents after sedation for screening-colonoscopy, stroke during colonoscopy, heart attack during CRC-surgery). If these deaths are not accurately linked to cancer-screening and cancer treatment, if “the link slips”, a cancer-screening or cancer treatment-induced death is not recorded under disease-specific mortality and consequently makes screening or cancer-treatment appear more beneficial than it actually is.

**... results in tendency to
overestimate screening
benefit**

⁴⁵ Church (2002)

⁴⁶ Gail (2002)

⁴⁷ Zauber (2010)

⁴⁸ Weiss (2002)

⁴⁹ Juffs (2002)

⁵⁰ Bretthauer (2011)

⁵¹ Black (2002)

Where studies are too small (in terms of number of participants and/ or length of follow-up) to detect CRC-screening impact on disease-specific mortality, it is often necessary to use even weaker intermediate end points to approximate the desired screening-outcome of reduced all-cause mortality. In the case of CRC-screening these intermediate endpoints are ‘detection of advanced adenomas’ and ‘detection of CRC’. These two measures are often combined and referred to as ‘detection of advanced neoplasia’. The assumption would be that higher detection of advanced neoplasia translates into lower CRC-mortality. That is not always grounded in fact, as by no means all advanced adenomas become malignant. In the case of most adenomas, removing them would have no effect on the survival of the individual concerned. Including all advanced adenomas as relevant screening-yield causes the effect of screening to be overestimated. At the other end of the disease spectrum, late stage CRC is also included as relevant yield, while only a small number of such cases can be cured. This too tends to overestimate the effect of screening. The goal of screening is not simply to detect abnormalities, it is to reduce people’s risk of developing CRC and of dying from this disease.⁵²

The introduction phase of a population based CRC-screening program is suggested as a setting for evidence generation at relatively little additional cost compared to setting up large clinical trials. Screening for CRC using any primary test modality is suggested to be launched in a public health program with randomization of the target population at the implementation phase. This experimental design is considered to be a prerequisite for evaluation of such a screening-program because the effectiveness of preventing deaths is likely to be small and results may otherwise remain inconclusive.⁵³

Establishing the net-effect of screening healthy people – only a few of whom can be helped, some of whom will be harmed, and most of whom will experience little effect – will often exceed the limits of medical science. Thus there is all the more reason for full disclosure of both what is known and what is unknown about screening for informed decision making.⁵⁴

Need for screening-trials to be population based

Screening needs to be effective in the general population at average risk for a disease. Ideally screening studies recruit individuals directly from the population registry. In this case they are population based. For the pragmatic reason of increasing the power of a study, two step recruiting processes are used in screening studies. The first step could be a questionnaire asking about general willingness to participate in screening if offered, like, for example, in two large recent studies on flexible sigmoidoscopy screening that included only such individuals.⁵⁵ Apart from the general problem of self-selection bias of recruited subjects (subjects may show a different risk profile compared with the general population)⁵⁶, self selection in screening trials on the basis of the important parameter of “willingness to participate in screening” will inflate the important parameter of participation rate above the levels realistic for population based screening. Such studies provide es-

weaker surrogate end point: detection rates ...

... translation of higher detection of advanced adenomas into decreased mortality not straightforward ...

... again results in tendency to overestimate screening benefit

introduction of screening-program suggested as ideal setting for evidence generation through experimental designs

establishing net-effect of screening often exceeds limits of medical science

screening studies ideally recruit directly from population registry ...

... results only then generalizable to average risk population

⁵² Health Council of the Netherlands (2009) p. 32

⁵³ Malila (2008)

⁵⁴ Black (2002)

⁵⁵ Atkin (2010), Segnan (2011)

⁵⁶ Segnan (2011)

estimates of the efficacy of screening, but the effectiveness of screening in the general population remains uncertain.⁵⁷

Intention-to-screen vs. per-protocol analysis of screening trials

**intention-to-screen
analysis represents
public health
perspective on screening**

The equivalent of intention-to-treat analysis in clinical trials is intention-to-screen analysis in screening trials. Non compliance in the screening group is thereby taken into account: non participation in screening, non participation in follow-up colonoscopy in case of positive first-line screening test, non participation in one or more subsequent screening round(s). Supposing a positive effect of screening on disease specific mortality and cancer incidence, intention-to-screen analysis will result in weaker effects on relative risk, since the non participants in screening are included. The results of intention-to-screen analysis are relevant for public health decision makers, since non participation of screening is a fact of life. Per-protocol analysis of screening trials provides estimates of risk reductions for those individuals who attend screening. This information is relevant for an individual member of the general population at average risk who contemplates if or if not to attend screening. An example of the different results of intention-to-screen (public health perspective) and per-protocol analysis (perspective of the individual contemplating screening) from meta-analysis of the four gFOBT screening trials is: 16% reduction of CRC-mortality in intention-to-screen analysis, 25% reduction of CRC-mortality for those individuals who attended at least one round of screening.⁵⁸

**results of intention-to-
screen analysis in
gFOBT screening: CRC-
mortality RRR 16% vs.
25% in per-protocol
analysis, representing
perspective of individual**

Evidence required for introduction of new screening-test

**evaluation of new test
less demanding:
... direct comparison
with old test**

What is the situation when new tests emerge, while a screening-test that has been proven to be effective (such as gFOBT⁵⁹) is already available? Guidelines for such situations have been drawn up on the basis of systematic reviews of the literature together with a consensus approach involving experts. Studies to determine whether a new test is as good as or better than existing ones do not need to use disease-specific mortality as an end point again, provided that randomized screening-trials have demonstrated that the existing test reduces disease-specific mortality. The evaluation must involve a direct comparison of the old and new tests on the basis of 'intention to screen', a comparison in terms of uptake and yield, the evaluation must be conducted among the general population and followed by a cost-effectiveness analysis.⁶⁰

**... under screening-
conditions (intention-
to-screen-analysis)**

**impact of new test on
participation rate
important**

⁵⁷ Bretthauer (2011)

⁵⁸ compare Bretthauer (2011)

⁵⁹ Cochrane Systematic Review, Hewitson (2007)

⁶⁰ Health Council of the Netherlands (2009) p. 28

4.4 Colonoscopy in CRC-screening

In contrast to the situation with most other screen-able diseases, there are several (first-line) screening-tests available for CRC: FOBTs, flexible sigmoidoscopy and colonoscopy, to name the strategies recommended by the USPSTF. The methods differ in various ways. Very important is their impact on participation and as a result program sensitivity/ specificity. Colonoscopy is the final common (second-line) test of all CRC-screening strategies. Figure 4.4-1 illustrates the central role of colonoscopy in CRC-screening.

several first-line tests exist – colonoscopy as final common screening-pathway

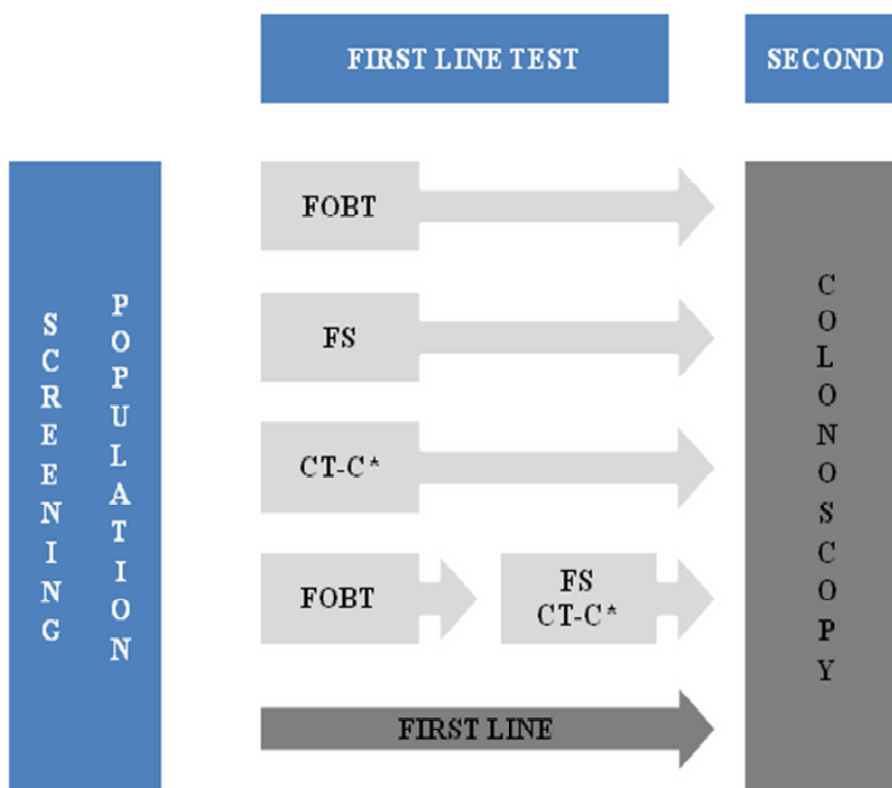


Figure 4.4-1: Colonoscopy as the final common pathway for CRC-screening

**in practice CT-colonography is presently not recommended by any mayor health-technology-assessment institution or medical society as a first-line test for population-based CRC-screening*

Abbreviations: CT-C ... computed tomography colonography

FOBT ... faecal occult blood test

FS ... flexible sigmoidoscopy

Source: adapted from figure 1, Health Council of the Netherlands (2009) p. 13

4.5 Evidence on CRC-screening tests

<p>no data on all-cause mortality</p> <p>dynamic evidence base</p>	<p>The evidence base from large trials on the effectiveness of different first-line screening tests for CRC is limited. There is no evidence on the effect of CRC-screening on all-cause mortality. So far gFOBT and FS have been proven to reduce CRC-mortality in screening-trials. Confidence interval values of gFOBT and FS effects overlap, so the superiority of one test over the other cannot be determined.⁶¹ No head-to-head trials comparing FOBT and FS have been conducted⁶², nor are any ongoing. First evidence on iFOBT and C is another decade away.</p>
<p>evidence from RCTs for gFOBT: CRC-disease specific mortality RRR 15%, no impact on all-cause mortality ...</p>	<ul style="list-style-type: none"> ✿ guaiac faecal occult blood test or gFOBT: 4 randomized controlled trials (RCTs). Three trials used repetitive multiple screening rounds, either annually or bi-annually, one trial offered two rounds of screening only with a two year interval, three trials were population based, one trial enrolled subjects only after they had agreed to participate in screening. Participation was between 53-78%, 78% in the trial enrolling subjects only after agreeing to participate in screening.⁶³ Disease-specific CRC mortality: relative risk reduction (RRR) 15%, no impact on all-cause mortality⁶⁴. For trial results on gFOBT compare table 4.7-1 below.
<p>... no evidence for colonoscopy</p>	<ul style="list-style-type: none"> ✿ immunochemical faecal occult blood test or iFOBT: none⁶⁵. 1 Spanish RCT comparing C and biennial iFOBT completed first round of screening⁶⁶ - results expected in 2021, 1 US-RCT comparing C and iFOBT in recruiting phase – results expected in 2025⁶⁷ ✿ biomarkers other than blood markers: none

⁶¹ Bretthauer (2011)

⁶² Bretthauer (2011)

⁶³ Bretthauer (2011)

⁶⁴ Compared to no screening in an intention-to-screen analysis, taking into account non-compliance in the screening group. A 25% risk reduction was observed for those individuals who attended at least one screening round (RR 0.75, 95% CI 0.66-0.84), compare Bretthauer (2011) and Cochrane Systematic Review, Hewitson (2007).

⁶⁵ One RCT from Jiashan County, China, published in 2003 with only one round of iFOBT-screening is difficult to interpret, compare Bretthauer (2011).

⁶⁶ Barcelona, Spain, COLONPREV-study: Colorectal cancer screening in average-risk population: immunochemical fecal occult blood test versus colonoscopy, ten years of follow-up. Results at completion of baseline screening published in Quintero (2012), population-based participation rate iFOBT 34.2%, C 24.6%.

Trial registered at www.ClinicalTrials.gov with registration no: NCT00906997

⁶⁷ US, Department of Veterans Affairs, CONFIRM-study. Colorectal cancer screening in average risk Veterans Affairs population: annual quantitative immunochemical fecal occult blood testing versus colonoscopy, enrolment of 50,000 planned, ten years of follow-up.

Trial registered at www.ClinicalTrials.gov with registration no: NCT01239082

- ✿ colonoscopy: none.⁶⁸ 1 RCT⁶⁹ completed first round of screening, 2 RCTs⁷⁰ in recruiting phase, – results in 10+ years
- ✿ flexible sigmoidoscopy: 3 non population based RCTs, two once only, one two FS rounds, reported participation rates of 71%, 58%, 86% and disease-specific RRR of 33%, (statistically not significant) 22%, 26% and no impact on all-cause mortality. For more detailed trial results on flexible sigmoidoscopy compare table 4.7-5 below.
- ✿ CT-colonoscopy: none. 1 Spanish RCT comparing C and biennial iFOBT completed first round of screening⁷¹ - results expected in 2021, 1 US-RCT comparing C and iFOBT in recruiting phase – results expected in 2025⁷²

... 3 RCTs on sigmoidoscopy so far show CRC-mortality RRR 22-31% (1 not stat. sign.)

no evidence on CT-colonoscopy for another decade ...

“Randomized trials have been a long-standing requirement for the introduction of new drugs to the market. It is difficult to understand why the standard of evidence should be lower for diagnostic tools or screening tests.”⁷³

... debate about evidence necessary for introduction of screening

⁶⁸ Church (2011) cites a nested case-control analysis of colonoscopy utilization and CRC outcomes in Canada by Baxter (2009) as estimating a rather similar effect of colonoscopy screening on CRC mortality as of screening with flexible sigmoidoscopy and gFOBT.

⁶⁹ Barcelona, Spain, COLONPREV-study: Colorectal cancer screening in average-risk population: immunochemical fecal occult blood test versus colonoscopy, ten years of follow-up. Results at completion of baseline screening published in Quintero (2012).

⁷⁰ Nordic countries, the Netherlands and Poland, NordICC-study. Once only colonoscopy.

Trial is registered at www.ClinicalTrials.gov with registration no: NCT0088379

US, Department of Veterans Affairs, CONFIRM-study. Colorectal cancer screening in average risk Veterans Affairs population: annual quantitative immunochemical fecal occult blood testing versus colonoscopy, enrolment of 50,000 planned, ten years of follow-up.

Trial registered at www.ClinicalTrials.gov with registration no: NCT01239082

⁷¹ Barcelona, Spain, COLONPREV-study: Colorectal cancer screening in average-risk population: immunochemical fecal occult blood test versus colonoscopy, ten years of follow-up. Results at completion of baseline screening published in Quintero (2012), population-based participation rate iFOBT 34.2%, C 24.6%.

Trial registered at www.ClinicalTrials.gov with registration no: NCT00906997

⁷² US, Department of Veterans Affairs, CONFIRM-study. Colorectal cancer screening in average risk Veterans Affairs population: annual quantitative immunochemical fecal occult blood testing versus colonoscopy, enrolment of 50,000 planned, ten years of follow-up.

Trial registered at www.ClinicalTrials.gov with registration no: NCT01239082

⁷³ Betthauer (2009) p. 301

4.6 Characteristics of Colonoscopy in CRC-screening

central role of colonoscopy in CRC-screening

Because of the central role of colonoscopy in CRC-screening its characteristics are elaborated on first. Characteristics of other screening tests and overview tables of all screening tests' characteristics can be found in chapter 4.7.

extensive bowel preparation required

In colonoscopy, a video-endoscope is used to examine the entire length of the colon. Extensive bowel preparation is required. Colonoscopy is often performed with the subject under conscious sedation. Depending on the regionally established clinical practice, operator preference and setting (private practice, hospital) colonoscopy is also performed without sedation. In France, for example, most colonoscopies are performed under full sedation, requiring the presence of an anaesthesiologist.⁷⁴ Colonoscopy is considered the (imperfect) reference standard for detecting CRC and adenomas. Where technically possible, polyps are removed immediately (polypectomy). If this is not possible, biopsies are taken. All retrieved lesions are evaluated histologically. In this respect colonoscopy stands out in potentially being at once a screening (optical inspection), diagnostic (biopsy) and therapeutic intervention (polypectomy) covering the entire colon. Flexible sigmoidoscopy only covers the left (distal) colon with these functions. Some screening-programs use colonoscopy as a first-line screening-method. With all screening-methods, if any abnormalities are detected, the patient is referred for colonoscopy. Colonoscopy is the final common pathway of all CRC-screening. With advancing age and coexisting conditions the risk associated with colonoscopy increases. At the same time the benefit diminishes because of shorter life expectancy.⁷⁵ This is the rationale behind setting upper age limits for CRC-screening.⁷⁶

polyps can be removed immediately

colonoscopy at once screening, diagnostic and therapeutic intervention

risks of colonoscopy increase with age

Two aspects limit colonoscopy as a perfect gold standard for CRC and adenoma detection. Endoscopic methods are operator and technology dependent.⁷⁷ Accuracy is highly dependent on the quality of the bowel preparation and endoscopic examination.⁷⁸ Inter-examiner differences in detection of polyps have been shown in population-based studies of screening-colonoscopy.⁷⁹ The examiners' skill and care in examining the colon (completeness of colonoscopy, withdrawal time) vary greatly. Repeated colonoscopy or colonography by means of computed tomography performed in close succession to colonoscopy can identify neoplastic lesions that were not detected during the initial procedure.⁸⁰ These important missed lesions include adenomas greater than 10 mm in diameter.⁸¹ Both polyp-yield⁸² and complication rate⁸³ vary by a factor of up to ten between examiners.

colonoscopy operator and technology dependent

inter-examiner differences in detection and complication 1:10

colonoscopy misses lesions including cancer

⁷⁴ Hassan (2011)

⁷⁵ e.g. Lieberman (2009)

⁷⁶ Health Council of the Netherlands (2009), USPSTF Whitlock (2008a)

⁷⁷ e.g. Lieberman (2009)

⁷⁸ USPSTF Whitlock (2008)

⁷⁹ e.g. Barclay (2006)

⁸⁰ e.g. Barclay (2006)

⁸¹ e.g. Lieberman (2006)

⁸² e.g. Barclay (2006)

⁸³ e.g. Pignone (2000)

CRC-screening stands out from screening for other diseases. Although colonoscopy is generally safe, it is an invasive procedure with a 0.2% rate of serious complications — ten times higher than for any other commonly used cancer screening test. Repeated examinations over time may incur a substantial cumulative rate of complications, not counting hard-to-detect complications (if they occur), such as silent myocardial infarction.⁸⁴ Complications of colonoscopy increase with age and have declined overall⁸⁵, perhaps due to an increased focus on quality and because of developments in endoscopic technology. No other screening-test – e.g. PAP for cervical cancer and mammography for breast-cancer – has comparable rates to colonoscopy of serious adverse complications, including death, through the testing itself. In this sense colonoscopy is unprecedented for a screening-test recommended for use in the general population.⁸⁶

The evidence on complication rates after screening-colonoscopy compared to symptomatic colonoscopy is inconclusive and evolving. On the one hand some of it suggests that complication rates of screening-colonoscopy are lower than of diagnostic and therapeutic colonoscopies performed in symptomatic patients.⁸⁷ The argument here would be that individuals participating in screening are on average younger and in better health than symptomatic patients. On the other hand recent research finds complications after colonoscopies two to three times higher than previously estimated, and more complications happening after screening colonoscopy than after symptomatic colonoscopy.⁸⁸ Risks of complications reported in organized screening programs are lower than those reported for general practice colonoscopies.⁸⁹

Procedure related hospital visits within 14 days of the procedure occurred in 0.84% of colonoscopies and in 0.95% of screening colonoscopies. Most events were not captured by standard reporting. The complication rate might in reality be higher since only complications treated at the studied hospital were recorded and not in neighbouring ones. The most common complications were abdominal pain (47%), gastrointestinal bleedings (12%) and chest pain (11%). The cost of unexpected hospital visits post endoscopy may be significant and should be taken into account in screening and surveillance programs. Also strategies for automating adverse event reporting should be developed.

A systematic review of perforation and mortality of colonoscopy found no differences in complication rates between screened populations versus patient populations:⁹⁰ The overall perforation rate of colonoscopy (higher for colonoscopies with polypectomy than for those without) was 66 per 100,000 and the overall mortality rate 6 per 100,000.

For more information on colonoscopy as a first-line screening-test compare table 4.7-4 below.

serious adverse events for screening-test in general population

complications increase with age ...

... have generally declined overall

colonoscopy complication rates probably underestimated ...

... most adverse events not captured by standard reporting

evidence on complications from screening-colonoscopy in population based settings lacking

⁸⁴ Ransohoff (2009)

⁸⁵ Zauber (2010)

⁸⁶ Baxter (2010)

⁸⁷ e.g. Niv (2008)

⁸⁸ Leffler (2010)

⁸⁹ Zauber (2010)

⁹⁰ Van Heijningen (2010)

colonoscopy worse at detecting right-sided (proximal) lesions
right-sided (proximal) CRC migration observed over the last 20 years

Though evidence on the magnitude of overall protection from CRC according to anatomical site through colonoscopy performed in the community setting is sparse, the association of colonoscopy with fewer deaths from CRC is primarily limited to deaths from cancer developing in the left side of the colon (distal cancer).⁹¹ There is evidence from Germany, Canada and the US that colonoscopy is less effective for right-sided (proximal) CRC than for left-sided (distal) CRC.⁹² There is evidence that the prevalence of left-sided (distal) but not of right-sided (proximal) advanced adenomas is reduced within a 10-year period after colonoscopy.⁹³ Why would colonoscopy be less effective in preventing death from right-sided (proximal) CRC? The evidence base on which to answer this question is still evolving, possible reasons are: First, some supposedly “complete” colonoscopies in practice do not actually evaluate the entire right (proximal) colon all the way to the cecum. Second, bowel preparation may be worse in the right (proximal) colon. Finally, right-sided (proximal) and left-sided (distal) colonic neoplasia may differ biologically. Right-sided (proximal) colonic adenomas are less often pedunculated and are occasionally flat, which makes them harder to identify and remove. The histology and molecular features of right-sided (proximal) cancer may differ, implying predominant genetic pathways of carcinogenesis, which may influence the effectiveness of early detection. Differences in tumor biology may limit the potential to prevent right-sided (proximal) CRC-death with current endoscopic technology.⁹⁴ Data from the US demonstrate a right-sided (proximal) migration of CRC over the past two decades, which is attributed to a decrease in incidence of left-sided (distal) CRC and an aging population in which right-sided (proximal) lesions are more common.⁹⁵

little evidence to estimate sensitivity and specificity of screening-colonoscopy ...

Estimating the sensitivity and specificity for screening-colonoscopy in a real life environment from the available evidence is even more challenging than for diagnostic colonoscopy, where the data situation is better. Most available studies for screening-colonoscopy have selected practitioners who were quite experienced and not necessarily representative of community practice. No tandem colonoscopy studies evaluated average-risk populations.⁹⁶

... overly optimistic claims about benefits unwarranted

Randomized trials studying the effect of colonoscopy on the incidence of or the mortality due to colorectal cancer have not been conducted. Two are underway, though, comparing colonoscopy and iFOBT as first-line screening tests. Results are expected in a decade. Recommended guidelines are based on statistical prediction models and case-control studies. Recent estimates suggest that colonoscopy has a lower effect on mortality associated with colorectal cancer than previously thought, and researchers have warned that overly optimistic claims about its benefits have been used to sell colonoscopy to the general public.⁹⁷

⁹¹ e.g. Baxter (2009), Brenner (2010)

⁹² e.g. Baxter (2009)

⁹³ e.g. Brenner (2010)

⁹⁴ e.g. Baxter (2009)

⁹⁵ USPSTF Whitlock (2008a)

⁹⁶ USPSTF Whitlock (2008a) p. 12

⁹⁷ Betthauer (2009) p. 301

4.7 Characteristics of different CRC-screening tests

No current CRC-screening tests are without drawbacks, including potential harms, limited accessibility or imperfect acceptability to patients.⁹⁸ The different CRC-screening tests are briefly described below. Details about their characteristics can be found in tables 4.7-1 to 4.7-7 thereafter. The different screening tests are numbered to facilitate finding the corresponding additional evidence in these tables. A first broad overview is given in the following table 4.7-1.

no test without drawback: harm, accessibility, low participation

Table 4.7-1: Characteristics of commonly used CRC-screening tests

Test	CRC incidence reduction [†]	CRC mortality reduction [†]	Screening interval	Invasiveness and preparedness
gFOBT ^{**}	none	15%	short (annually, biennially)	none
Flexible Sigmoid. ^{***}	18%, 21%, 23%	22% (not stat. sign.), 26%, 31%	long (5-10 years, once only)	invasive; less extensive enema bowel cleansing
Colonoscopy	Unknown	unknown	long (at least 10 years)	invasive; more extensive oral bowel cleansing

** Figures for intention-to-screen analyses observed in randomised trials*

*** low-sensitivity Hemocult II, newer gFOBTs, i.e. Hemocult SENSA, more sensitive*

**** 2 once-only RCTs, 1 two sigmoidoscopy screening rounds RCT with 3-5 year interval*

Source: updated from Bretthauer (2010) p. 1260

A qualitative overview of the relative merits of the different screening tests was compiled by the Health Council of the Netherlands, compare table 4.11-1.

⁹⁸ USPSTF Whitlock (2008a) p.6

Tests using biomarkers

Blood: FOBTs

<p>FOBT detects blood in stool ...</p> <p>... FOBTs are not specific to CRC-related bleeding</p>	<p>Both guaiac or gFOBT and immunochemical or iFOBT are based on the principle of detecting blood traces in faeces, hence the name faecal occult blood test FOBT. FOBTs are nonspecific tests for gastrointestinal bleeding. Causes relevant for CRC-screening are bleeding of CRC and of CRC-precursor lesions. Bleeding may also result from erosion of ulcers and inflammatory bowel disease. In these cases FOBTs screening for CRC would yield false positive results in CRC-screening.⁹⁹</p>
<p>wide variety of FOBTs available ...</p> <p>... many lacking evidence on characteristics</p>	<p>A wide variety of FOBTs from different manufacturers is available. Most countries do not require medical diagnostic tools to prove clinical efficacy before entering the market. This is why many FOBTs lack evidence on test performance, storage and transport durability.¹⁰⁰</p>
<p><i>1. gFOBT</i></p>	
<p>gFOBT in use for 40 years</p>	<p>This test method has been used for around 40 years. Most chemical FOBTs make use of guaiac gum, which is extracted from the hardwood tree <i>guaiacum officinale</i> (gFOBT). Guaiac oxidizes when in contact with hydrogen peroxide, resulting in an unstable color change which has to be visually assessed by a person. This reaction is catalyzed by haem, a component of haemoglobin common to all species. The test is not specific for human blood and can generate false positive and false negative results due to peroxidase reactions (and their inhibitors) in food products, such as red meat. gFOBTs lower sensitivity means that two samples must be collected from each of three consecutive stools, six samples in total. This renders gFOB-testing laborious for the screening-participant and not particularly user-friendly.¹⁰¹</p>
<p>not specific to human blood</p>	<p>The result is a relatively lower participation rate in gFOBT-screening than in iFOBT-screening.</p>
<p>old gFOBTs: lower sensitivity ...</p>	
<p>6 samples necessary → lower participation</p>	
<p>gFOBT demonstrated effectiveness: RRR 15%</p>	<p>The first efficacy trials (RCTs) conducted in the realm of CRC-screening were based on the guaiac (gFOBT) Haemocult II test. Four RCTs with a total of 320,000 participants were conducted between 1995 and 2002 with follow-up of 8-18 years, showing a relative risk reduction in CRC-specific mortality of 15 % while no impact on all-cause mortality was found.¹⁰² This makes gFOBT the CRC-screening method with the largest RCT base demonstrating effectiveness. Newer, more sensitive gFOBTs have been developed. For more information on gFOBT as a first line CRC-screening test compare table 4.7-1 below.</p>
<p>newer, more sensitive gFOBTs are available</p>	

⁹⁹ Bretthauer (2011)

¹⁰⁰ Bretthauer (2011)

¹⁰¹ Health Council of the Netherlands (2009) p. 43

¹⁰² RCTs in Gothenberg, SWE; Funen, DK; Nottingham, UK; Minnesota, US; Cochrane Systematic Review, Hewitson (2007)

2. iFOBT

More recently a test method has been developed, which involves the immunological analysis of faecal samples for occult blood (iFOBT). These tests are specific for human blood. The subject only has to provide a single faecal sample, positively affecting participation rate. Analysis of quantitative iFOB-testing can be automated, thus increasing quality control and reducing cost. There is micro flora in stool that can degrade the biomarker or hamper analysis. This problem becomes more pronounced the longer it takes for the stool sample to be analyzed and the higher the temperature the sample is exposed to during that time. Special precautions need to be taken to optimize the test-process in practice from stool-sampling at home to analysis in a laboratory.

The participation rate in iFOBT CRC-screening can be expected to be higher than in gFOBT CRC-screening.¹⁰³ In terms of sensitivity, the benefit of iFOBT relative to gFOBT lies primarily in the detection of early CRCs and advanced adenomas, which involve less bleeding than later stage CRC. This means that iFOBT-screening can be expected to have a greater effect on cancer incidence and mortality than gFOBT-screening. At equal specificity, iFOBT is more sensitive than gFOBT.¹⁰⁴ For more information on iFOBT as a first line CRC-screening test compare table 4.7-2 below.

3. Test using other biomarkers than blood

The basis of CRC is a disturbance of the biological processes in the intestinal epithelial cells, particularly resulting from (generally non-hereditary) changes in the way that certain oncogenes and tumor suppressor genes function. This disturbance is accompanied by changes in the molecular structure or quantity of substances such as DNA, RNA and protein. By means of laboratory tests, it is possible to measure molecules of these substances – referred to in this context as ‘biomarkers’ – in samples of stool (see 3.1) or blood (see 3.2). Research in this field is aimed at the identification and large-scale validation of biomarkers with better test characteristics, and optimization of the relevant test methodologies.¹⁰⁵ For more information on test using other biomarkers than blood compare table 4.7-3 below.

3.1 Other biomarkers in stool

3.1.1 DNA markers in stool

When faeces pass a tumor during progression through the bowel, tumor cells or cell remnants are entrained. The excreted faeces therefore contain tumor DNA, which can be detected by testing.¹⁰⁶

iFOBT specific for human blood

automation in test reading possible

single faecal sample sufficient → higher participation than with gFOBT

multitude of tests under development:

large scale validation and optimization for practical use in screening necessary

DNA markers in stool

¹⁰³ e.g. a recent study from the New Mexico Veterans Affairs Health Care System: 61.4% vs. 50.5%; Hoffman (2010)

¹⁰⁴ Health Council of the Netherlands (2009) p. 47

¹⁰⁵ Health Council of the Netherlands (2009) p. 73

New candidates for CRC-screening tests are of particular interest to the Swiss Cancer League (Krebsliga Schweiz). This is the reason for the relatively large amount of space allocated to the molecular markers in spite of their at this stage not being recommended for population based CRC-screening.

¹⁰⁶ Health Council of the Netherlands (2009) p. 74

<p>innovations emerging ...</p> <p>... further research and development needed before possible screening introduction</p>	<p>Technical challenges of the fecal DNA tests are being addressed in ongoing research and development. Refinements in recent laboratory methodologies, additional improvements of panel biomarkers that maximize sensitivity and specificity for both advanced adenomas and cancer, and cost modifications are emerging. If DNA fecal testing can improve compliance and reduce unnecessary diagnostic follow-up compared with FOBT's, cost savings may be realized. In addition, the demonstration of mortality benefit in clinical trials, evidence to assess the sensitivity and specificity of fecal DNA tests, and verification of optimal screening intervals are necessary before fecal DNA testing can be used as a CRC detection tool in average risk screening populations.¹⁰⁷</p>
<p>RNA markers in stool</p>	<p><i>3.1.2 RNA markers in stool</i></p> <p>Faecal RNA has also been investigated as a possible CRC-biomarker.¹⁰⁸</p>
<p>other protein markers in stool</p>	<p><i>3.1.3 other protein markers in stool</i></p> <p>iFOBT is in fact a test for the presence of a protein (globin) in stool. Using the same principle, it should be possible to test for tumor-specific proteins.¹⁰⁹ One example is the enzyme M2-PK, compare table 4.7-3.1.3.</p>
<p>giving blood sample less inconvenient, biomarker in blood less prone to degeneration</p>	<p><i>3.2 Biomarkers in blood</i></p> <p>For many people giving a blood sample is less inconvenient than providing a faecal sample. Another advantage is that in blood there is no micro flora which could degrade the biomarker or hamper analysis like in stool. Also sample processing may be easier.¹¹⁰</p>
<p>DNA, RNA, protein markers in blood</p>	<p><i>3.2.1 DNA markers in blood</i></p> <p>DNA is not broken down as quickly in blood as in faeces, and blood contains less PCR¹¹¹ inhibitory factors.¹¹² One example is circulating methylated¹¹³ mSEPT9 DNA in plasma, compare table 4.7-3.2.1</p>

¹⁰⁷ Morrison (CADTH) (2010) p. 3

¹⁰⁸ Health Council of the Netherlands (2009) p. 74

¹⁰⁹ Health Council of the Netherlands (2009) p. 75

¹¹⁰ Hundt (2007)

¹¹¹ compare: www.wikipedia.org

Polymerase chain reaction (PCR) is a technique to amplify a single or few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications. These include the diagnosis of hereditary diseases and the detection and diagnosis of infectious diseases.

¹¹² Health Council of the Netherlands (2009) p. 75

¹¹³ compare: www.wikipedia.org

DNA-methylation, a modification of DNA (as opposed to a genetic mutation) contributes to epigenetic inheritance.

3.2.2 RNA markers in blood

3.2.3 Protein markers in blood

A systematic review of blood markers for early detection of CRC found the evidence thus far restricted to single studies with limited sample size and without further external validation.¹¹⁴ The authors conclude that larger prospective studies using study populations representing a screening-population were needed to verify promising results. In addition, future studies should pay increased attention to the potential of detecting not only CRC but precursor lesions, due to their value for CRC-screening.¹¹⁵

One of the pilot projects set up in preparation for the decision whether – and if, how – to initiate a population-based screening-program in the Netherlands aims to develop molecular screening-tests and molecular diagnostics for customized therapy. The main thrust of the approach is to translate recent discoveries about the molecular biology of CRC into new laboratory tests and new applications for diagnostic imaging. Existing biomarker tests are validated in a screening-population.¹¹⁶ Similar initiatives also involving academia-industry cooperation are under way in other countries.¹¹⁷

Summing up, it is reasonable to believe that in more distant future a screening-program could be enhanced by the use of molecular markers.¹¹⁸ It is expected to be another few years before suitable ones can be identified.¹¹⁹ Then it will be necessary to conduct research in unselected populations to establish whether biomarker-based screening-offers any advantages over the existing methods. This will take at least another few years. It would not be appropriate to introduce a new screening-test until its superiority to the existing test will have been demonstrated in randomized trials. Such studies can be undertaken efficiently in the context of ongoing screening-activities.¹²⁰ Furthermore, modelling taking participation rates into account would need to show that the new test was more efficient than existing screening.

studies so far have limited sample size, lack external validation

pilot projects involving academia – industry cooperation under way

reasonable to believe that new test will benefit CRC-screening ...

... time frame at least a few years

... studies can be undertaken in context of existing screening-program

Methods visualizing the colon

Endoscopic methods

4. Colonoscopy as first-line screening-test

For characteristics of colonoscopy as a CRC-screening test compare 4.6 above. For more information on colonoscopy as a first-line screening-test compare table 4.7-4 below.

114 Hundt (2007)

115 Hundt (2007)

116 Health Council of the Netherlands (2009) p. 25

117 e.g. Germany, compare <http://www.innovations-re->

[port.de/html/berichte/biowissenschaften_chemie/darmkrebs_erkennen_bevor_entsteht_133139.html](http://www.innovations-re-port.de/html/berichte/biowissenschaften_chemie/darmkrebs_erkennen_bevor_entsteht_133139.html)

accessed March 14th 2010

118 Health Council of the Netherlands (2009) p. 76

119 Health Council of the Netherlands (2009) p. 81

120 Health Council of the Netherlands (2009) p. 76

5. Flexible sigmoidoscopy

Flexible sigmoidoscopy explores only the distal colon ...

strong evidence base from recent RCTs...

usually performed without sedation

inter examiner differences in polyp-detection

3 RCTs show ...

... CRC specific mortality RRR 22-31% (one stat. not significant)

... CRC incidence RRR 18-23%

different referral thresholds to colonoscopy yield very different screening-induced rates of colonoscopy

Flexible sigmoidoscopy is a visual examination using an endoscope inserted through the anus into the distal (left-side) portion of the large intestine. The use of flexible sigmoidoscopy in CRC-screening is based on the observation that a majority of adenomas and cancers are located in the distal colon, within reach of flexible sigmoidoscopy.¹²¹ There are fewer complications than with colonoscopy. Flexible sigmoidoscopy needs only limited bowel preparation – an enema prior to the examination – compared to colonoscopy or capsule endoscopy. Flexible sigmoidoscopy is usually performed without sedation.¹²² Biopsies may be taken during the procedure. A removal of polyps is possible.¹²³ Inter-examiner differences in the detection of polyps have been shown in population-based studies of screening-flexible sigmoidoscopy.¹²⁴ These can be considerable.¹²⁵ Before an effect of flexible sigmoidoscopy screening can be expected in screening trials, a follow-up period of at least 10 years is required.¹²⁶

Recently the results of two large multi center randomised controlled trial of once only flexible sigmoidoscopy screening following a very similar protocol (UK, Italy)¹²⁷ and one on screening with two rounds of flexible sigmoidoscopy (US)¹²⁸ were published.¹²⁹ With a non-population based attendance rate¹³⁰ of 71% the UK-trial finds a decline in disease specific mortality of 31% (11.2 years of follow-up) and a reduction in CRC- incidence of 23% (11.2 years of follow-up). With a non-population based attendance rate¹³¹ of 58.3% the Italian trial finds a decline in disease specific mortality of 22% (11.4 years of follow up, statistically not significant) and a reduction in CRC-incidence of 18% (10.5 years of follow-up).¹³² The lower referral threshold to total colonoscopy than in the UK trial adopted in the Italian trial¹³³ (resulting in higher rates of colonoscopy) was not efficient in identifying subjects at high risk for proximal neoplasia.¹³⁴ With a non-population based attendance rate of 83.5% for the initial flexible sigmoidoscopy and 54.0% for the second round of flexible sigmoidoscopy screening either 3 or 5

¹²¹ Bretthauer (2011)

¹²² Bretthauer (2011)

¹²³ e.g. Atkin (2010)

¹²⁴ e.g. Barclay (2006)

¹²⁵ Bretthauer (2011)

¹²⁶ Bretthauer (2011)

¹²⁷ UK-NHS-Trial Atkin (2010), ITA-SCORE-Trial Segnan (2011)

¹²⁸ US-PLCO-Trial Schoen (2012)

¹²⁹ Results reported here based on intention-to-screen analysis.

¹³⁰ Subjects were recruited only after affirmatively answering a questionnaire about their willingness to participate in CRC-screening if offered.

¹³¹ Subjects were recruited only after affirmatively answering a questionnaire about their willingness to participate in CRC-screening if offered.

¹³² UK and Italian trials both not population based, since subjects were recruited only after affirmatively answering a questionnaire about their willingness to participate in CRC-screening if offered. Protocol followed almost identical, flexible sigmoidoscopies performed in hospital settings, Italian trial had lower threshold for referral to colonoscopy.

¹³³ Referral threshold to total colonoscopy in UK trial: large distal polyps \geq 10mm, smaller advanced adenomas $<$ 10mm; referral threshold in Italian trial: small advanced adenoma \leq 5mm and any distal polyp $>$ 5mm; Segnan (2011)

¹³⁴ Segnan (2011)

years later¹³⁵, the US-trial finds a decline in disease specific mortality of 26% (11.9 years of follow-up) and a reduction in CRC-incidence of 21% (11.9 years of follow-up). The threshold for referral to total colonoscopy in the US-trial was even lower than in the Italian trial, resulting in the highest number of colonoscopies performed.¹³⁶

Colorectal cancer screening guidelines usually recommend flexible sigmoidoscopy with a five year screening interval. Summing up the evidence from both the UK and the Italian trial Segnan et al. don't expect a substantial increase in the protective effect of screening by repeating flexible sigmoidoscopy before 10 years. They infer that flexible sigmoidoscopy screening may not need to be repeated.¹³⁷

Adequately trained nurse practitioners can (and did in the UK and US-trials) undertake flexible sigmoidoscopy as competently as can gastroenterologists and public acceptance of nurse led flexible sigmoidoscopy is high.¹³⁸

The UK, Italian and US trials provide valid and robust evidence for the efficacy of flexible sigmoidoscopy screening. The effectiveness of such screening in the general population is still uncertain, however, because the trials did not recruit directly from the general population. NORCCAP¹³⁹ is the only study of flexible sigmoidoscopy screening that is truly population based and will provide an estimate of effectiveness after 10 years of follow-up in 2013.¹⁴⁰

For more information on flexible sigmoidoscopy as a first-line CRC-screening test compare table 4.7-5 below.

6. Capsule Endoscopy

Capsule endoscopy is a technique in which the subject swallows a capsule that takes photographs at regular intervals while it travels through the large bowel.¹⁴¹ These images are transferred wirelessly to an external receiver, which is worn by the individual being examined. After 24 hours, the data accumulated by the receiver is downloaded and the images are examined on a monitor. At the end of the examination period the capsule is ejected from the body with the faeces. Extensive bowel preparation is needed. Biopsy or removal of polyps is not possible. The rate of detection of polyps is dependent on the skills of the examiner.

“With the capsule’s relatively low sensitivity for the detection of colorectal lesions, its requirement for more extensive bowel-cleansing regimens as compared with colonoscopy and CT colonography, and its high cost, colon capsule endoscopy cannot be recommended [for cancer screening] at this time.”¹⁴²

... evidence may point to longer screening intervals for FS or even once-only FS

...trained nurses as alternatives

FS now has robust evidence base for use in CRC-screening

...trained nurses as alternatives

no serious complications

extensive bowel preparation necessary

polyp detection operator-dependent

not recommended for screening at this stage

¹³⁵ 86.6% underwent at least one flexible sigmoidoscopic screening, 50.9% underwent two screenings, 80.5% of participants with positive finding followed suggestion to undergo further diagnosis within a year (95.6% of these colonoscopy), Schoen (2012)

¹³⁶ 5% UK-trial, 8.4% Italian trial, 21.9% US trial; Schoen (2012)

¹³⁷ Segnan (2011)

¹³⁸ Atkin (2010)

¹³⁹ Hoff (2009)

¹⁴⁰ Bretthauer (2010); For preliminary findings of NORCCAP-trial after only seven years of follow-up compare Hoff (2009).

¹⁴¹ Health Council of the Netherlands (2009) p. 65

For more information on capsule endoscopy as a first-line CRC-screening test compare table 4.7-6 below.

Virtual endoscopic methods

7. Colonography

examination by means of CT-scanning	Colonography or “virtual colonoscopy” involves examination of the entire large intestine by means of CT-scanning ¹⁴³ , preferably after limited bowel preparation (1-day low-fiber diet, oral contrast agent for the uniform staining of stool residue and moisture). To achieve colonic distension carbon dioxide is delivered via a rectal catheter. Examinations are performed in both supine and prone position. Biopsy or removal of polyps is not possible. Formal standards for performing CT-colonography are lacking. ¹⁴⁴ The challenges of adequately ensuring high-quality CT-colonography readings are illustrated by reports that half of the radiologists did not pass the initial certifying examination after 1.5 days of training or experience with more than 500 cases. ¹⁴⁵ Complications tend not to be serious. In the case of CT-colonography exposure to ionized radiation is a largely unexplored problem
polyp yield reader-dependent	
exposure to radioactive radiation	
extra-colonic findings problematic	Extra-colonic findings during CT-colonography are also an issue. Evaluation of images generated during CT-colonography also involves findings of structures outside the colon itself. In the case of serious, treatable disorders this might be an advantage. Among the target group for population-screening, the chance that a serious, treatable disease will be found is quite small, though. Extra-colonic findings can also be a disadvantage: Screening may reveal disorders such as an aneurysm of the aorta, for which the usefulness of early detection is not a foregone conclusion. What is clear, however, is that the reporting of extra-colonic abnormalities can double the number of referrals for diagnosis. ¹⁴⁶ The use of low radiation dosage reduces image quality outside the colon and is expected to significantly reduce the number of referrals due to extra-colonic findings after screening with CT-colonography. ¹⁴⁷
emphasis on quality standards for operator-dependent tests	Given potential harms and observed variability in test accuracy, emphasis on quality standards für implementation of any operator-dependent CRC-screening test appears prudent. ¹⁴⁸
CT-C estimated to be less burdensome than C, actual experience the opposite	A RCT from the Netherlands found that people invited to screening via CT-colonography perceived the procedure (ahead of it) as less burdensome than colonoscopy. After actually having undergone the procedure, CT-colonography screenees perceived it as having been more burdensome than colonoscopy screenees. Intended participation in a future round of screening was comparable. ¹⁴⁹

¹⁴² Betthauer (2009) p. 300

¹⁴³ also MRI-scanning is possible

¹⁴⁴ Pox (2010)

¹⁴⁵ USPSTF Whitlock (2008)

¹⁴⁶Health Council of the Netherlands (2009), p. 68

¹⁴⁷ Health Council of the Netherlands (2009), p. 68

¹⁴⁸ USPSTF Whitlock (2008)

¹⁴⁹ de Wijckerslooth (2011)

Another RCT from the Netherlands found attendance rates for CT-colonography screening to be higher than those for colonoscopy screening (34% vs. 22%).¹⁵⁰

Large prospective multi-center trials are warranted to collect data on CT-colonography as a candidate for first-line screening test in the average risk population.¹⁵¹ For more information on CT-colonography as a first-line CRC-screening test compare table 4.7-7 below.

attendance rates of CT-C screening may be higher than for C-screening

¹⁵⁰ Stoop (2012)

¹⁵¹ Kaufman (2010)

Table 4.7-1: Detailed characteristics of gFOBT as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
1. gFOBT	<p>4 RCTs with traditional lower-sensitivity gFOBT</p> <p>1975-2002</p> <p>follow-up: 8-18 years</p> <p>320,000 participants</p> <p>disease-specific CRC-mortality: RRR 11-18%</p> <p>no impact on all-cause mortality found</p>	<p>lower than iFOBT</p> <p>around 50%</p> <p>47-50% in NL trials</p>	<p>n.a.</p> <p>lower-sensitivity gFOBT has smallest number of resulting C of all screening strategies</p>	<p>limited</p> <p>HCII test-sensitivity: CRC 13-38%</p> <p>HCII biennial program sensitivity: CRC 50-60%</p> <p>(today higher-sensitivity gFOBTs available, e.g. Hemoccult SENSE)</p>	<p>CRC 99%</p> <p>PPV for advanced neoplasia: 50%</p>	<ul style="list-style-type: none"> laborious and user unfriendly: two samples each on three consecutive stools necessary, six altogether <ul style="list-style-type: none"> ➔ negative impact on participation test is not specific for human blood and can generate false positive and false negative results due to peroxidase reactions (and their inhibitors) in food products, such as red meat <ul style="list-style-type: none"> ➔ dietary measures necessary before test ➔ medication use can influence test (vitamin c, aspirin etc.) color change unstable, has to be visually assessed <ul style="list-style-type: none"> ➔ reader dependence <p>COMPLICATIONS</p> <ul style="list-style-type: none"> gFOBT: no studies exist¹⁵², assumption: none follow up-colonoscopy, see Table 4.7-4

Abbreviations: C ... colonoscopy
 CE ... capsule endoscopy
 CI ... confidence interval
 CRC ... colorectal cancer
 CT-C ... computed tomography-colonography
 DNA ... deoxyribonucleic acid
 FOBT ... faecal occult blood test
 FS ... flexible sigmoidoscopy
 gFOBT ... guaiac faecal occult blood test

CE ... capsule endoscopy
 HCII ... Hemoccult II: low sensitivity gFOBT
 iFOBT ... immunochemical FOBT
 ITA ... Italy
 mm ... millimeters
 n.a. ... not available
 NL ... Netherlands
 NL-CoCoS ... Population screening for colorectal cancer by colonoscopy or CT-colonography in the Netherlands
 NNScope ... number needed to scope

NordICC ... The Nordic-European Initiative on Colorectal Cancer
 PPV ... positive predictive value, percentage of true positives among test positives
 RCT ... randomized controlled trial
 RNA ... ribonucleic acid
 RRR ... relative risk reduction
 UK ... United Kingdom

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

152 USPSTF Whitlock (2008)

Table 4.7-2: Detailed characteristics of iFOBT as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
2. iFOBT	<p>little data available on regularly repeated iFOBT-screening</p> <p>1 study found CRC-mortality: RRR 32% (because of cluster randomization methodically problematic)</p> <p>numerous observational studies</p>	60-62% in NL trials	<p>35/1,000</p> <p>assuming participation rate of 60% and referral threshold of 75ng/ml</p>	<p>higher than gFOBT</p> <p>estimates show variability within each test, possibly because of different collection methods, reference standards¹⁵³</p> <p>depending on specific test and referral threshold (of quantitative iFOBTs) set in program</p> <p>test-sensitivity: CRC 55-90%</p>	<p>lower than gFOBT</p> <p>depending on specific test and referral threshold (of quantitative iFOBT) set in program</p> <p>PPV for advanced neoplasia: 33%</p>	<ul style="list-style-type: none"> more false positives than gFOBT for screening-participants more user friendly sampling, more reliable, more hygienic than gFOBT <ul style="list-style-type: none"> → positive impact on participation iFOBT detects more early CRCs and advanced adenomas, which involve less bleeding than later stage CRC, than gFOBT <ul style="list-style-type: none"> → iFOBT-screening can be expected to have a greater effect on cancer incidence and mortality at equal specificity, iFOBT is more sensitive than gFOBT some iFOBTs are quantitative in nature <ul style="list-style-type: none"> → adjusting threshold enables screening to be more focused and cost-effective → automated testing (reader independent, cheaper) little data available concerning an optimum referral threshold to C¹⁵⁴ → test characteristics of screening dependent on it: the lower the threshold <ul style="list-style-type: none"> → the higher the sensitivity → the higher the number of participants who have to be referred to C → the higher the number of false positives (i.e. the lower the specificity) no convincing evidence to suggest that iFOBT-screening is less effective in detecting proximal tumors as opposed to distal tumors (like FS for obvious reasons but also C) no clear evidence of adverse risk selection (in which fewer individuals from high-risk groups participate) as is the case with cervical-cancer screening iFOBT yields better participation rates, detection rates and is significantly more cost effective than gFOBT-screening (NL trials) <p>COMPLICATIONS</p> <ul style="list-style-type: none"> iFOBT: no studies exist¹⁵⁵, assumption: none follow up-colonoscopy, see Table 4.7-4

Abbreviations: see table 4.7-1 above

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

¹⁵³ USPSTF Whitlock (2008)

¹⁵⁴ for study on referral threshold from the Netherlands compare Wilschut (2011)

¹⁵⁵ USPSTF Whitlock (2008)

Table 4.7-3: Detailed characteristics of bio-markers other than blood as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colono-scopies	Sensitivity of test	Specificity of test	Information
3. Bio-markers other than blood	<p>numerous candidate biomarkers</p> <p>development of practical tests ongoing</p> <p>large-scale validation studies for use in CRC-screening required thereafter</p>					<p>biomarkers: DNA, RNA, proteins in faeces or blood</p> <ul style="list-style-type: none"> clinical accuracy data on faecal DNA tests is still too limited to support population-screening¹⁵⁶ biomarkers do not yet constitute a realistic alternative to FOBT mismatch between small number of available clinical studies on faecal DNA tests and larger number of commercially available tests¹⁵⁷ progress is being made with development of numerous candidate biomarkers¹⁵⁸ development of practical tests will require the involvement of companies capable of marketing the tests development work by companies focuses exclusively on markers over which intellectual property rights have been secured
3.1.3 faecal M2-PK (enzyme)	<p>evidence on detecting precursors to CRC scant and controversial¹⁵⁹</p> <p>one larger study among 1,082 screening-participants in Germany: Haug (2008)</p> <p>one study prospectively comparing office-based iFOBT and M2-PK in 600 subjects above average risk: Shastri (2008)</p>			<p>cut-off 4U/ml</p> <p>Haug (2008) advanced adenomas: 22%</p> <p>other adenomas: 23%</p> <p>Shastri (2008) CRC and large adenomas >10mm: 72,4%</p>	<p>cut-off 4U/ ml</p> <p>Haug (2008) 82%</p> <p>Shastri (2008) CRC and large adenomas >10mm: 73,8%</p>	<ul style="list-style-type: none"> tumor M2-PK is an isoform of the glycolytic enzyme PK, which is over expressed in proliferating cells such as tumor cells test has been proposed for early detection of CRC test has only very limited potential to distinguish between people bearing precursors to CRC and people with no finding at C¹⁶⁰ poor performance characteristics demonstrated do not certify further use as a screening-tool in CRC and large adenomas¹⁶¹

¹⁵⁶ USPSTF Whitlock (2008a)

¹⁵⁷ USPSTF Whitlock (2008a)

¹⁵⁸ e.g. Morrison (CADTH) (2010)

¹⁵⁹ Haug (2008)

¹⁶⁰ Haug (2008)

¹⁶¹ Shastri (2008) p. 1502

Results part I: Facts about colorectal cancer-screening

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
3.2.1 methyiated SEPT9 DNA in blood plasma	deVos (2009) single, small producer affiliated study on test for detection of invasive colorectal adenocarcinoma only (not for detection of precursor lesions)					<ul style="list-style-type: none"> • study undertaken in non-screening population • study with screening-population underway • development of test for precursor lesions, that would shed light on possible future benefit as CRC-screening test, is under way¹⁶²

Abbreviations: see table 4.7-1 above

Source: design of table from Health Council of the Netherlands (2009), input from 2009 hand search for studies on molecular tests

Table 4.7-4: Detailed characteristics of colonoscopy as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
4. Colonoscopy C	<p>limited data available on the effect of C-screening on CRC-incidence and mortality</p> <p>no evidence yet available from RCTs: results from two¹⁶³ RCTs expected in about 10+ years</p> <p>NNScope* either CRC or advanced adenomas: 13</p> <p>NNScope* CRC: 125</p>	<p>unknown</p> <p>initial data 20-40%</p> <p>NL-CoCoS-trial anticipates 20-25%</p>	<p>250/1,000 (assuming participation rate of 25%)</p>	<p>C is (imperfect) reference standard</p> <p>insufficient evidence to provide precise estimates in community settings¹⁶⁴</p> <p>CRC: >97%</p> <p>adenomas >10mm: 90-98%</p>		<ul style="list-style-type: none"> • small risk of serious complications including death • serious harms from community C are about 10 times more common than with FS¹⁶⁶ • screening-yield is heavily dependent on the endoscopist • participation in C-screening significantly lower than in iFOBT-screening <ul style="list-style-type: none"> ➔ program detection rate lower with difference increasing in subsequent screening-rounds • unpleasant screening-method due to its invasive nature • extensive bowel preparation necessary at home on preceding day: drinking of 2 liters of laxative solution • participants in screening have to reserve 2 days for entire procedure (bowel preparation, aftercare) • C itself takes approx. 20 minutes • most sensitive existing test for detecting advanced neoplasia (imperfect reference standard) • C misses some polyps and may also miss CRC¹⁶⁷

¹⁶² compare http://www.innovations-report.de/html/berichte/biowissenschaften_chemie/darmkrebs_erkennen_bevor_entsteht_133139.html accessed March 14th 2010

¹⁶³ Barcelona, Spain: Colorectal Cancer Screening in Average-Risk Population: Immunochemical Fecal Occult Blood Testing Versus Colonoscopy Trial registered at www.ClinicalTrials.gov with registration no: NCT00906997

once only colonoscopy, NordICC is a multicentre, randomised trial in Nordic countries, the Netherlands and Poland

Trial is registered at www.ClinicalTrials.gov with registration no: NCT0088379

¹⁶⁴ USPSTF Whitlock (2008)

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
				adenomas 6-9mm: 87% miss rates for adenomas >10mm possibly higher than CT-C ¹⁶⁵		<ul style="list-style-type: none"> • tumors in the right (proximal) colon are harder to detect for C those in the left (distal) colon <ul style="list-style-type: none"> ○ different nature of right (proximal) and left sided (distal) tumors; sessile (flat) abnormalities, that are more difficult to detect, are more frequent in the proximal colon – as opposed to much more common and easier to detect pedunculated (spherical) polyps ○ anatomic “blind spots” ○ incomplete bowel preparation ○ incomplete C • if needed, polypectomy or biopsy possible during same screening-procedure • evidence for timing of C-screening is limited, suggesting re-screening would be needed once every 10 years, or up to 20 years and more¹⁶⁸, possibly once-only triage screening also an option to consider¹⁶⁹ • considerable C-capacity required <p>COMPLICATIONS of screening-colonoscopy with evolving evidence base</p> <ul style="list-style-type: none"> • procedure related hospital visits 950/100,000¹⁷⁰ • serious complications from C in asymptomatic populations 310/100,000¹⁷¹ <ul style="list-style-type: none"> ○ perforation: 56/100,000¹⁷² and 66/100,000¹⁷³ and 50 - 10/100,000¹⁷⁴ ○ bleeding: 120/100,000¹⁷⁵ and 60 - 20/100,000¹⁷⁶

¹⁶⁵ USPSTF Whitlock (2008a)

¹⁶⁶ USPSTF Whitlock (2008)

¹⁶⁷ USPSTF Whitlock (2008)

¹⁶⁸ e.g. Brenner (2008), Brenner (2010)

¹⁶⁹ Bretthauer (2012)

¹⁷⁰ Leffler (2010)

¹⁷¹ USPSTF Whitlock (2008a) – Serious complications were defined as adverse events requiring hospital admission, including perforation, major bleeding, diverticulitis, severe abdominal pain, cardiovascular events, and deaths attributable to colonoscopy (p. 24).

¹⁷² USPSTF Whitlock (2008a)

¹⁷³ Van Heijningen (2010)

¹⁷⁴ Health Council of the Netherlands (2009)

¹⁷⁵ USPSTF Whitlock (2008a)

¹⁷⁶ Health Council of the Netherlands (2009)

¹⁷⁷ Van Heijningen (2010)

¹⁷⁸ e.g. Heher (2008)

¹⁷⁹ Lieberman (2009)

Results part I: Facts about colorectal cancer-screening

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
						<ul style="list-style-type: none"> • death: most screening-studies indicate no fatal outcomes of screening-C <ul style="list-style-type: none"> ◦ death from colonoscopy for symptomatic patients: 4/ 100,000 <ul style="list-style-type: none"> ▪ patients older than screening-population ▪ more co-morbidities ▪ more intestinal problems ◦ overall death from colonoscopy: 6/ 100,000¹⁷⁷ • from bowel preparation¹⁷⁸ • from sedation, not systematically documented and linked to intervention¹⁷⁹ <p>COMPLICATIONS of follow-up C after positive first-line screening-test are higher than for screening-C</p> <ul style="list-style-type: none"> • perforation: 100/ 100,000 • bleeding: 140/100,000

**... On the basis of prevalence figures from the Netherlands: for every 13 people who undergo colonoscopy in the context of screening, just one will be found to have either CRC or advanced adenomas. For every 125 people who undergo colonoscopy in the context of screening just one will be found to have CRC – see Health Council of the Netherlands (2009)*

Abbreviations: see table 4.7-1 above

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

Table 4.7-5: Detailed characteristics of flexible sigmoidoscopy as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
5. Flexible sigmoidoscopy FS	<p>results from three large non-population based RCTs¹⁸⁰, intention to treat analysis¹⁸¹:</p> <ul style="list-style-type: none"> Atkin (2010) CRC mortality minus 31% Atkin (2010) CRC incidence minus 23% Segnan (2011) CRC mortality minus 22% Segnan (2011) CRC incidence minus 22% (statistically NOT significant) Schoen (2012) CRC incidence minus 18% Schoen (2012) CRC mortality minus 26% Schoen (2012) CRC incidence minus 21% <p>results from population based trial expected in 2013¹⁸²</p> <p>from NL trial:</p> <p>NNScope* CRC</p> <ul style="list-style-type: none"> 625 invitations 207 FS 18 C <p>NNScope* advanced adenomas</p> <ul style="list-style-type: none"> 48 invitations 16 FS 1-2 C 	<p>10-40%</p> <p>Atkin (2010) 71%¹⁸³</p> <p>Segnan (2011) 58.3%¹⁸⁴</p> <p>Schoen (2012) 86,6%¹⁸⁵</p> <p>more realistic: 32% in Rotterdam trial</p>	<p>Atkin (2010)¹⁸⁶ 50/1000</p> <p>more realistic: 18/1,000</p> <p>on top of 350 FS assuming 35% participation rate under population based screening conditions</p> <p>Segnan (2011)¹⁸⁷ 84/1000</p> <p>Schoen (2012)¹⁸⁸ 219/1000</p> <p>27/1,000</p> <p>on top of 327 FSs</p> <p>assuming participation rate of 32%</p>	<p>little data available concerning sensitivity in population-screening</p> <p>based on C-studies in average risk population (over-estimation):</p> <p>CRC: 58-75%</p> <p>advanced neoplasia: 72-86%</p>		<ul style="list-style-type: none"> serious harms from community FS are about 10 times less common than with C¹⁸⁹ estimates for harms from FS have much wider confidence intervals¹⁹⁰ screening-yield is heavily dependent on the endoscopist adequately trained nurse practitioners can undertake FS as competently as can gastroenterologists and public acceptance of nurse led flexible sigmoidoscopy is high¹⁹¹ FS takes only about 5-7 minutes, less than colonoscopy (20 mins.) uptake significantly lower than for iFOBT-screening (NL trial) uptake would need to be significantly higher than projected 30% (NL trial) to render FS an effective screening-method roughly equally sensitive for CRC as single iFOBT significantly more sensitive for advanced adenomas not clear whether screening needs to be repeated every 5 or 10 years limited bowel preparation – less extensive than for C <ul style="list-style-type: none"> enema 120-150ml, possibly self-administered 9-20% of participants have to make new appointment due to inadequate preparation no data available concerning an optimum referral threshold to C → test characteristics of screening dependent on it: the lower the threshold <ul style="list-style-type: none"> → the higher the sensitivity → the higher the number of participants who have to be referred → the higher the number of false positives (i.e. the lower the specificity) <p>COMPLICATIONS</p> <ul style="list-style-type: none"> FS serious complications: 34/100,000 (CI 6-190)¹⁹² <ul style="list-style-type: none"> FS perforation: 4.6/ 100,000¹⁹³ and 2-3/100,000¹⁹⁴ FS from limited bowel preparation follow up-colonoscopy, see table 4.7-5

¹⁸⁰ 2 RCTs once-only sigmoidoscopy; 1 two rounds of sigmoidoscopy screening, 3-5 years apart

¹⁸¹ Intention-to-treat analysis: all participants allotted to the screening group, including those who decided not undergo screening as opposed to per-protocol analysis, only participants actually screened

¹⁸² once only sigmoidoscopy, NORCCAP trial, preliminary results after only 7 years of follow up: Hoff (2009) – NORCCAP is the only study of flexible sigmoidoscopy screening that is truly population based and will provide an estimate for effectiveness after 10 years of follow-up in 2013.

** ... On the basis of prevalence figures from the Netherlands: for one person to be found to have CRC or advanced adenomas 16 will need to undergo flexible sigmoidoscopy and 1-2 follow-up colonoscopy, In the case of CRC alone, the figures are 207 and 18 – Health Council of the Netherlands (2009)*

Abbreviations: see table 4.7-1 above

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

¹⁸³ This figure is an estimate of the participation in a population based screening based on Atkin (2010). This UK RCT was designed to have high power to examine the efficacy of FS (incidence and mortality of CRC). It was not designed to determine realistic participation rates in FS based population based screening. The RCT therefore had a pre-selected population. Participants in RCT were only enrolled after answering “Yes” to the question if they would participate in FS screening if invited. This meant that the compliance rate in the trial was (much) higher than would be expected in population based screening. Of the invited 71% participated in FS screening. But 47% of the potential screening population were excluded from being invited. Assuming that the excluded would not have participated in the screening the participation rate in a population based screening might be estimated to be a little above 35%.

¹⁸⁴ same problem as Atkin (2010)

¹⁸⁵ not population-based, unrealistic

¹⁸⁶ Referral threshold to total colonoscopy: large distal polyps ≥ 10 mm, smaller advanced adenomas < 10 mm; Segnan (2011)

¹⁸⁷ unrealistic participations rate, lower threshold for colonoscopy than Atkin (2010): small advanced adenoma ≤ 5 mm and any distal polyp > 5 mm; Segnan (2011)

¹⁸⁸ unrealistic participations rate, lower threshold for colonoscopy still than Segnan (2011): detection of any polyp or mass ; Schoen (2012)

¹⁸⁹ USPSTF Whitlock (2008)

¹⁹⁰ USPSTF Whitlock (2008)

¹⁹¹ Atkin (2010)

¹⁹² USPSTF Whitlock (2008a) – Serious complications were defined – in analogy to colonoscopy – as adverse events requiring hospital admission, including perforation, major bleeding, diverticulitis, severe abdominal complaints, myocardial infarction, syncope, and deaths attributable to flexible sigmoidoscopy (p. 26).

¹⁹³ USPSTF Whitlock (2008a)

¹⁹⁴ Health Council of the Netherlands (2009)

Table 4.7-6: Detailed characteristics of capsule endoscopy as CRC-screening test and new developments in endoscopy

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
6. Capsule endoscopy CE	small, producer sponsored studies only	no data available		Spada (2010) ¹⁹⁵ CRC: 76% adenomas >6mm: 68% Van Gossum (2009) ¹⁹⁶ CRC: 74% adenomas >6mm: 64% adenomas >10mm: 64 %	Adenomas >6mm 82% ¹⁹⁷	<ul style="list-style-type: none"> CE has been widely used to analyze pathologies of the small intestine for several years¹⁹⁸ current price of a capsule approx. € 950.-¹⁹⁹ need for extensive bowel preparation, more extensive than for colonoscopy or CT-colonography in the coming years, improvements may be expected to make CE suitable for use as a method of CRC-screening randomized studies, involving comparisons with existing screening-methods, will then have to be carried out to determine whether CE can actually improve the efficacy or efficiency of screening battery life limits the use of this technique as a screening-method for CRC <ul style="list-style-type: none"> remedy: use of capsules with delayed activation, reduced energy consumption, increased battery capacity <p>COMPLICATIONS</p> <ul style="list-style-type: none"> CE: from bowel preparation follow up-colonoscopy, see table 4.7-5
New developments in endoscopy						<ul style="list-style-type: none"> more adenomas can be detected using chromoscopy (colonoscopy in which the intestinal wall is stained) this technique is very time consuming and does not appear to be suitable for use as a general screening-method same is true of <ul style="list-style-type: none"> high-definition endoscopes auto fluorescence narrow-band imaging

Abbreviations: see table 4.7-1 above

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

¹⁹⁵ Meta analysis of 8 studies with data on 837 patients

¹⁹⁶ producer supported study on 320 patients, sensitivity probably overestimated compare Bretthauer (2009)

¹⁹⁷ Spada (2010)

¹⁹⁸ Capsule endoscopy has become part of the reimbursement basket for Germany's social health insurance to investigate unclear bleeding in the small intestine in November 2010. See Gemeinsamer Bundesausschuss, www.g-ba.de

¹⁹⁹ Bretthauer (2009)

Table 4.7-7: Detailed characteristics of CT-colonography as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colonoscopies	Sensitivity of test	Specificity of test	Information
7. Computed-Tomography colonography CT-C	no evidence from randomized trials that CT-C reduces CRC-incidence and CRC-mortality	Unknown	20/1,000 assuming a participation rate of 35% and a polyp referral threshold of 10mm referral threshold of 6mm approx. doubles number of Cs	limited evidence on performance in population screening-programs variability between readers limits ability to provide precise estimates ²⁰⁰ advanced neoplasia: 97% less sensitive for small adenomas detection of adenomas >10mm possibly higher than C ²⁰¹	limited evidence on performance in population screening-programs estimates are somewhat uncertain ²⁰² for large polyps: >95% PPV advanced adenomas: 41% (referral threshold 6mm) 52-67% (referral threshold 10mm)	<ul style="list-style-type: none"> almost identical sensitivity for CRC-cancer and polyps >10mm as C <ul style="list-style-type: none"> possibly more sensitive for larger lesions than C, less so for smaller lesions²⁰³ screening-yield is heavily dependent on radiologist variety of technologies used²⁰⁴ <ul style="list-style-type: none"> varying slice thickness single/multi detector scanner 2D/ 3D/ 3D fly-through oral contrast radiation dosage expected to decline with future progress in CT-technology: <ul style="list-style-type: none"> lower radiation exposure for CRC-screenees low radiation dosage reduces image quality outside the colon and is expected to significantly reduce the number of referrals from extracolonic findings²⁰⁵ subjects expect CT-C to be less unpleasant than C clear preference for CT-C in studies of subjects' experience clear preference for CT-C in people who have undergone both CT-C and C may be superior to C for detecting proximal CRC sessile (flat) abnormalities, which are more common in the proximal colon – as opposed to much more common pedunculated (spherical) polyps – are difficult to detect less likely to have serious complications than C limited bowel preparation – less than for C no agreement on best referral threshold to C – usually ≥ 6 mm → test characteristics of screening dependent on it: the lower the threshold <ul style="list-style-type: none"> → the higher the sensitivity → the higher the number of participants who have to be referred to C → the higher the number of false positives (i.e. the lower the specificity) examination takes about 15 mins., reading about 10 mins. <p>COMPLICATIONS</p> <ul style="list-style-type: none"> CT-C radiation CT-C issue of extra-colonic findings unresolved CT-C from limited bowel preparation follow up-colonoscopy, see table 4.7-5

²⁰⁰ USPSTF Whitlock (2008)

²⁰¹ USPSTF Whitlock (2008a)

²⁰² USPSTF Whitlock (2008)

²⁰³ USPSTF Whitlock (2008)

Abbreviations: see table 4.7-1 above

Source: information from Health Council of the Netherlands (2009), adapted with specifically cited inputs

²⁰⁴ USPSTF Whitlock (2008a)

²⁰⁵ Health Council of the Netherlands (2009), p. 68

4.8 CRC-screening activities worldwide

European Union

Finland, England and Scotland are currently working on the phased introduction of nationwide population-based screening-programs.²⁰⁶ Nationwide population-based programs are at the preparatory stage in 5 other countries, while France, Spain, Italy and Sweden already have population screening-programs in place at regional level. Italy has a national body for the evaluation of its 72 regional screening-programs for CRC. In total, the population-based programs that are either in preparation or already under way cover 43 % of the target population in the EU²⁰⁷. Many countries have a variety of obstacles to a nationwide population-based program, such as a decentralized health care services and public-health policy determination. For example, Germany, Austria and the Czech Republic have established non-population-based programs. Screening in those countries is carried out on an individual basis (27% of the target group). This is referred to as opportunistic screening. The participation rates involved are low. 8 of the 27 member states have yet to start preparing screening-programs of their own. In 2007, 12 million people actually underwent screening for CRC. On the basis of a biennial screening, this represents 18% of the target group. Most of the countries with a national screening program use gFOBT.²⁰⁸ CRC-screening with iFOBT is on the rise, though. Italy selected iFOBT-screening, so did Ireland and the Netherlands and the UK is considering a switch to that system in the near future. The primary screening-test in Poland is colonoscopy. In 6 countries, endoscopic screening is used in combination with – or as an alternative to – FOBT-screening. 5 of these states (including Germany, Austria) use colonoscopy while Italy uses flexible sigmoidoscopy.

In Ireland a national colorectal cancer screening programme started inviting 60-69 year old men and women for biennial iFOBT based CRC-screening in 2012. The choice of screening test was based on cost-effectiveness analysis.²⁰⁹ Eventually the program is set to include the age range from 55 to 74. Screening colonoscopies after referrals will take place at contracted units in hospitals.²¹⁰ In advance of the decision to organise a population based screening program the Irish government commissioned a thorough analysis of screening options and important issues to be considered. These HTA documents can be downloaded on the internet.²¹¹

Finland, England, Scotland phase in population-based screening

43% of target population in EU have access to some sort of screening

opportunistic screening with low participation rate

gFOBT most common test

Ireland begins population based biennial iFOBT screening program

²⁰⁶ For this section compare Health Council of the Netherlands (2009) p. 21

²⁰⁷ For the situation in the EU compare also e.g. Gutierrez-Ibarluzea (2008)

²⁰⁸ Wilschut (2011)

²⁰⁹ Sharp (2012)

²¹⁰ www.cancerscreening.ie und

www.cancerscreening.ie/publications/ImplementingColorectalProgramme.pdf

²¹¹

www.hiqa.ie/news_releases/090617_HTA_colorectal_cancer_screening_programme.asp

**Australia, Canada phase
in population-based
screening**

**Colonoscopy main
screening-test in US**

**only few well organized,
nationwide, population-
based screening
programs**

Outside the EU

Countries like Australia and 3 of the 10 Canadian provinces have commenced the phased introduction of population-screening based on gFOBT, iFOBT or flexible sigmoidoscopy. In the US, Japan and Taiwan, screening takes place on an individual basis. Colonoscopy is the most widely used technique in the US. In 2002, 14 million colonoscopies were carried out in the US, approximately 40% of which involved primary screening. Colonoscopy utilization for screening has increased recently, and use of flexible sigmoidoscopy decreased, due largely to the decision in 2001 to cover screening-colonoscopy for patients on Medicare, and similar decisions by private pay insurers.²¹² Over 20% of colonoscopies in the US were performed as part of the surveillance of high-risk groups. Japanese citizens who are over 40 years of age and who have health insurance cover have been offered iFOBT-screening since 1992. Only 17% of the target group made use of this facility in 2002. There is no provision for the evaluation of the screening-program.

The sum total of current programs throughout the world represents a considerable amount of screening-activity. Many such programs have been under way for many years, as in Japan, Italy and Germany. Nevertheless, only a few countries like the UK and soon Ireland and the Netherlands have organized, nationwide, population-based screening-programs.

4.9 Current CRC-screening recommendations by selected institutions

EU guidelines for colorectal cancer screening

**EU publishes first
edition of guidelines for
quality assurance in
CRC-screening**

Comprehensive guidelines for quality assurance of colorectal cancer screening which are suitable for implementation throughout the 27 EU Member States were developed in a project coordinated by International Agency for Research on Cancer IARC and co-funded by the EU Health Programme. The most fundamental principle being that screening should be implemented in the context of an organized, population-based programme following comprehensive quality assurance guidelines. Adequate attention needs to be paid to planning and training, identification and information of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation.²¹³

**institutions take
different perspectives
motivating their
recommendations**

When analyzing CRC-screening recommendations, the different respective health system background, stakeholder pressures and target audience for the screening-recommendations should be born in mind. Recommendations from different organizations also vary because the rationale behind the recommendations differs (prevention of cancer, early detection of cancer, unequivocal advice to clinicians, ...)²¹⁴. The Health Council of the Netherlands for instance, got the specific task from the minister of health to formulate recommendations for a national screening-program that should take the re-

²¹² USPSTF Whitlock (2008a) p. 7

²¹³ For the "European guidelines for quality assurance in colorectal cancer screening and diagnosis.-First edition" compare Segnan (2010).

²¹⁴ Zauber (2010)

sults of local pilot programs into account.²¹⁵ The United States Preventive Services Task Force addresses the heterogeneous US-healthcare system where only the Veterans Administration runs a CRC-screening program. Compare table 4.9-1 for CRC-screening recommendations by the three independent HTA/ Review-Institutions the core of this report relies on.

Table 4.9-1: CRC-screening recommendations from three independent institutions

Institution	Date	Recommendation	Comment
Health Council of the Netherlands NL	2009	<ul style="list-style-type: none"> • 55-75 years • iFOBT 75 ng/ml • every 2 years 	-
United States Preventive Services Task Force USPSTF US	2008	<ul style="list-style-type: none"> • 50-75 years • FOBT or • flexible sigmoidoscopy or • colonoscopy 	<ul style="list-style-type: none"> • first USPSTF recommendation for CRC-screening in 1996 • current recommendations based on update of 2002 systematic review • previous USPSTF recommendations from 2002 do not suggest upper limit of screening-age
Ontario Health Technology Advisory Committee OHTAC CAN	2009	<ul style="list-style-type: none"> • from 50 years • FOBT • every 2 years 	-

Abbreviations: CRC ... colorectalcarcinoma
 FOBT ... faecal occult blood test
 iFOBT ... immunochemical faecal occult blood test
 ng/ml ... nanogram per millilitre

Source: Health Council of the Netherlands (2009), USPSTF (2008), OHTAC (2009)

The production of guidelines is generally not a straight-forward process:

“Although the term *evidence-based* may suggest that guidelines simply emerge from evidence, guidelines making is a human process, like creating and operating a judicial system is a human process, requiring structure and process to make it function properly. In other words, it is inherently a political process and should be managed as such.”²¹⁶

production of guidelines evidence based ...
... as well as political process

Screening for CRC has a rapidly evolving science base, such that guidance may be expected to change as additional research becomes available.²¹⁷ This may for instance be happening in regards to flexible sigmoidoscopy screening after the recent publications of three large randomised controlled trials²¹⁸:

science-base for CRC-screening rapidly evolving

“Colorectal cancer screening guidelines usually recommend flexible sigmoidoscopy with a five year screening interval. In light of the UK trial, longer screening intervals should be recommended.”²¹⁹

215 Health Council of the Netherlands (2009)
 216 Imperiale (2010)
 217 USPSTF Whitlock (2008a)
 218following quote refers to UK-trial: Atkin (2010)
 219 Betthauer (2010) p. 1260

4.10 Cost-effectiveness analysis of CRC-screening

LBI-HTA published separate report of cost-effectiveness of CRC-Screening

For a review of cost-effectiveness analyses of alternative CRC-screening options and an introduction to important program-cost drivers in CRC-screening compare part two of this report series.²²⁰

4.11 Detailed CRC-screening program recommendations, the example of the Netherlands

After evaluating the merits and drawbacks of possible CRC-screening strategies – compare table 4.11-1 below – the Health Council of the Netherlands made the following recommendations for a population based CRC-screening program in the Netherlands.

Netherlands have program focus

Criteria

- ✿ simplicity
- ✿ acceptance
- ✿ performance/ test characteristics
- ✿ safety

iFOBT75

Recommendation for CRC-screening in NL

- ✿ immunochemical Faecal Occult Blood Test (iFOBT), a self test
 - ✿ product: OC-sensor
 - ✿ single faecal sample
 - ✿ threshold 75 ng/ml (provisional recommendation due to lack of colonoscopy capacity in NL today)
 - ✿ every 2 years
- ✿ followed by colonoscopy in case of positive test result in outpatient clinic under sedation and with the aid of pain management
- ✿ targeted group: women and men aged 55-75
 - ✿ (referral to screening after the age of 75 to be decided individually with GP)

every 2 years

age 55-75

Anticipated results from modelling

NNT: 785 iFOBTs, 40 follow-up colonoscopies

- ✿ number needed to treat for one CRC-death prevented
- ✿ 785 people would need to complete iFOBTs
- ✿ 40 follow-up colonoscopies

²²⁰ Patera N., Radlberger P., Schumacher I., Zechmeister I. Screening for Colorectal Cancer. Part 2: Health economic evaluations and aspects of screening-costs. HTA project report. 2012; 41b. available at <http://eprints.hta.lbg.ac.at>

- ✿ cost-effectiveness: EUR 2,200.- per life year gained (assuming participation rate of 60% derived from iFOBT-pilot trials conducted in the run up to the decision of introducing a national CRC-screening program in NL)

EUR 2,200.- per life year gained

Table 4.11-1: Health Council of the Netherlands: relative merit of six screening-methods

	gFOBT	iFOBT ₇₅	Molecular markers	Colonoscopy	Flexible Sigmoido-scopy	CT – colonography
Attendance	+	++	?	?	-	?
Evidence	++	+	+/-	+/-	+/-	+/-
Test performance	+/-	++	+	++	++/-	++
Less burdensome	+	++	+			+/-
Less risk	++	++	++		+	+
Cost-effective	+	++	?	+?	+?	?
Less colonoscopy capacity needs	++	+	?			

Abbreviations: CT... computed tomography

gFOBT... guaiac faecal occult blood test

iFOBT₇₅... immunochemical faecal occult blood test – threshold 75 nanograms per millilitre

Source: adapted from table 5, Health Council of the Netherlands (2009) p. 80

5 Results part II: Questions to ask about CRC-screening and program design

5.1 Why is screening different from ordinary medical practice?

Screening for disease is not a logical extension of ordinary medical practice. The ethical position is different. Screening involves an unsolicited offer to in principle healthy persons. These exceptional characteristics mean that screening is justified only if it is demonstrably advantageous. Proof of principle alone – i.e. reduction of all-cause or disease-specific mortality through CRC-screening – is not enough for the introduction of screening: balancing of downsides with benefits is necessary.²²¹

Early detection must have a positive net health benefit. Only a minority of people undergoing screening stand to benefit directly from participation. In the case of CRC-screening, although CRC is a common cancer, the lifetime risk for an individual is actually quite low, 5%²²² The lifetime mortality rate in the US is 2.4% for women and 3.3% for men.²²³ Of these, even if attendance of CRC-screening was 100%, not all would benefit from it since some cancers would not be detected earlier and for other cancers early detection through screening does not prolongue life. So more than 95% of people have no benefit from CRC-screening but are still exposed to the potential harms of it. Even if CRC-screening was to completely eliminate CRC-cancer (which it does not), it is still necessary to carefully weigh up the pros and cons of any such program.²²⁴ As a cautious starting premise, it is by no means implausible that the desirable effects of a given form of screening will be outweighed by the undesirable effects: false positive results, false negative results, over-diagnosis, overtreatment etc.. As a consequence it is very important that the design of a screening-program meets high quality standards, maximizes desirable effects and minimizes undesirable effects. Because a screening-program is made up of numerous diverse constituent activities, professional organization and effective management are vital.²²⁵

Given potential harms and observed variability in test accuracy, emphasis on quality standards für implementation of any operator-dependent CRC-screening test appears prudent.²²⁶

screening addresses healthy general population

balance of benefits and harms required

over 95% of participants don't profit from CRC - screening but are still exposed to potential harms

screening-program must meet high quality standards

screening-program must be well organized and managed

operator-dependent tests require quality focus

²²¹ e.g. Health Council of the Netherlands (2009), Raffle (2009), Saul H. Interview with Michael Baum: Shooting sacred cows. *Cancer Futures* 2003;2:273-8

²²² e.g. Baxter (2010); US CRC-lifetime risk males 5.9% (lifetime mortality rate 2.4%), females 5.4% (lifetime mortality rate 3.3%) - USPSTF Whitlock (2008a)

²²³ USPSTF Whitlock (2008a)

²²⁴ Health Council of the Netherlands (2009) p. 33

²²⁵ Health Council of the Netherlands (2009) p. 107

²²⁶ USPSTF Whitlock (2008)

5.2 What is NOT known about CRC-screening?

uncertainties about CRC-screening need to be addressed in program

At this point in time reliable evidence is lacking in some areas giving rise to uncertainties and open questions about CRC-screening. These areas of uncertainty still need to be dealt with when establishing an organized program:

5.2.1 Natural course of CRC

some question about natural course of CRC unclear

- ✱ one of the most uncertain assumptions is that all CRC arises from adenomas²²⁷
- ✱ frequency and malignant potential of hyperplastic and flat polyps in populations/ true underlying population prevalence of adenomas is uncertain²²⁸

5.2.2 Effectiveness of CRC-screening

evidence on effectiveness of CRC-screening limited

truly population based screening studies are rare ...

... two are underway, one for FS, one comparing C and iFOBT

multitude of FOBTs with uncertain characteristics available

- ✱ ??? no high-grade evidence (randomized controlled trials) for impact of any form of CRC-screening on all-cause mortality
- ✱ ??? no high-grade evidence for reduction of disease-specific mortality other than for CRC-screening with gFOBT and flexible sigmoidoscopy
 - ✱ none for colonoscopy (expected in 10+ years), CT-colonography, capsule endoscopy, other biomarker tests
- ✱ ??? evidence from screening-settings very limited²²⁹, including on complications²³⁰- there is evidence that complications might have been underestimated²³¹; Norway's NORCCAP is the only study on flexible sigmoidoscopy that is truly population based and will provide an estimate of screening impact after 10 years of follow up in 2013.²³² Spain's COLONPREV is the only truly population based study on iFOBT and colonoscopy, results are expected in a decade.²³³
- ✱ ??? even for gFOBT, which has been extensively investigated, a lack of certainty about true performance characteristics – particularly for newer versions of the test – remains. For iFOBT numerous test are available with heterogeneous performance characteristics.²³⁴

²²⁷ Wilschut (2011)

²²⁸ Sharp (2012)

²²⁹ e.g. Lieberman (2009), Brenner (2010)

²³⁰ e.g. Lieberman (2009), Betthauer (2010)

²³¹ e.g. Leffler (2010)

²³² Hoff (2009)

²³³ Quintero (2012)

²³⁴ Sharp (2012)

5.2.3 Optimal setting of relevant CRC-screening parameters

- ✿ ??? optimal referral threshold (number of polyps, size of polyps)
 - ✿ ? iFOBT to colonoscopy
 - ✿ ? flexible sigmoidoscopy to colonoscopy
 - appropriate polyp size threshold for referral to colonoscopy is not well-established, thus colonoscopy referral often follows detection of any lesion by flexible sigmoidoscopy²³⁵
 - ✿ ? CT- colonography to colonoscopy
- ✿ ??? optimal screening-interval
 - ✿ ? iFOBT – 1 year?, 2 years?, more?
 - ✿ ? flexible sigmoidoscopy – possibly once only?²³⁶, 5 years?, 10 years?²³⁷
 - ✿ ? colonoscopy²³⁸ – once only as a triage-test?²³⁹ 10 years?, up to 20 years?, more?
 - recent evidence from epidemiological studies suggests that intervals for screening with colonoscopy might be extended to 20 years or even longer, as subjects with negative findings at endoscopy are at very low risk for at least 20 more years²⁴⁰
 - the concept of using colonoscopy as a triage screening test offered at the age of 60 and used to classify persons as having low risk of CRC (no adenomas detected) or high risk (adenomas detected, particularly advanced ones), with no further screening for the low risk group has been suggested²⁴¹
- ✿ ??? iFOBT
 - ✿ ? optimal test of the many available iFOBTs²⁴²
 - ✿ ? optimal number of stool samples to take²⁴³
- ✿ ??? colonoscopy
 - ✿ there is some evidence of much lower yields of proximal/ right-sided vs. distal/ left-sided CRC, research is ongoing
 - ? causality of this difference not fully understood²⁴⁴
 - ? repercussions for decision between colo-

optimal referral thresholds from first-line test to colonoscopy unknown

optimal screening-interval unknown ...

... recent evidence may point to longer intervals for FS and also C

if iFOBT chosen as first-line: optimal iFOBT and number of stool samples unknown

causality of colonoscopy's lower yield of proximal/ right-sided CRC unclear

²³⁵ USPSTF Whitlock (2008a)

²³⁶ Segnan (2011)

²³⁷ Bretthauer (2010)

²³⁸ e.g. Brenner (2010)

²³⁹ Bretthauer (2012)

²⁴⁰ e.g. Brenner (2008)

²⁴¹ Bretthauer (2012)

²⁴² e.g. Lieberman (2009)

²⁴³ e.g. Hundt (2009), Lieberman (2009)

²⁴⁴ e.g. Baxter (2009), Brenner (2010)

- scopy and flexible sigmoidoscopy unad-dressed²⁴⁵
 - ☼ ? hygiene standards and adverse events (e.g. double wash-ing of endoscopic equipment and infectious disease trans-mission)
- ☼ ??? screening-program level
 - ☼ general
 - ? influence divergent rates of adenoma detection might have on screening-goal of prevention of CRC unclear²⁴⁶
 - does focus on detection rate (including detection of small adenomas) make sense? unknown share of adenomas that never become malignant are included as screening-benefit.
 - there is relatively small clinical benefit of detecting and removing very small polyps²⁴⁷
 - recommendation for screen-detected larger ade-nomas >10mm is clear: removal; but optimal screening-regime for dealing with smaller ade-nomas unclear
 - ? 6-10mm
 - ? < 6mm?
 - ? optimal surveillance regime
 - screening may induce lifestyle changes that might negatively affect benefit, e.g.
 - ? impact of negative polyp test on tobacco use²⁴⁸
 - ? impact of negative polyp test on dietary habits (obesity)²⁴⁹
- ☼ test-specific program organization issues
 - ? iFOBT: management of interval between faecal sampling at individual's home and analysis at lab
 - faecal samples used for iFOBT prone to denaturation: their quality is very impor-tant
 - dating of samples by participants does not work well
 - storage/ temperature exposure of sample before arrival at analysis not easily con-trollable
 - e.g. Australia (and potentially Canada) send out iFOBTs only in cooler months of the year²⁵⁰

influence of adenoma detection on CRC unclear

optimal screening-guideline for detected adenomas < 10mm unclear

optimal surveillance regime unclear

influence of screening on lifestyle changes unclear

best management of iFOBT home-testing unclear

²⁴⁵ e.g. Baxter (2010)

²⁴⁶ e.g. Baxter (2010)

²⁴⁷ e.g. Barclay (2006)

²⁴⁸ e.g. Levin (2002)

²⁴⁹ e.g. Levin (2002)

²⁵⁰ Health Council of the Netherlands (2009) p. 114

- ? colonoscopy
 - formulation of program-aim aligned financial incentives for examiners difficult²⁵¹
 - remuneration per screening-colonoscopy?
 - caveat: incentive to perform screening-colonoscopy rapidly
 - remuneration linked to yield (adenoma detected and removed)?
 - caveat: if high adenoma detection rate really contributes to aim of screening-program (reduced all-cause mortality) is unknown
 - setting of colonoscopy remuneration relative to remuneration for flexible sigmoidoscopy?
 - formulation of quality indicators for monitoring that are meaningful in terms of achieving program aim (documentation?, examiner experience?, withdrawal time of endoscope during which colon is examined?, completion rate?, hygiene standards?, yield? ...) ²⁵²

optimal financial incentives for screening-colonoscopy unclear

optimal quality indicators for screening-colonoscopy debated

²⁵¹ e.g. Barclay (2006), Gupta (2007), Lieberman (2009)

²⁵² e.g. Barclay (2006)

5.3 Essentials to keep in mind when designing a population based CRC-screening program

5.3.1 Program design

Installation of screening-program structure with view to

- assuring quality
- sustainability

informed consent to take part in screening

Informed consent of screening-participants: inherent conflict of interest: high participation rate crucial for program success

no negative consequences for non-participants

- significance attached to ensuring that participation decisions can be made freely increases²⁵³
 - non-participation must not entail negative consequences for individuals, neither in relationship with their health insurance provider, nor with their physician²⁵⁴
- ensuring that participation can be based on informed choice is vital for screening-program's legitimacy
 - e.g.: FOBT testing
 - test itself entirely safe
 - positive test result implies referral for colonoscopy
 - potential participants must therefore be made aware of the albeit small risk of serious complications associated with colonoscopy before they decide whether to have the initial "harmless" FOBT test²⁵⁵
- informed choice is not easy to achieve
 - screening is a complex process not generally well understood by professionals and the public for a range of reasons²⁵⁶
 - decision-making about screening involves complex risk assessment
 - many people overestimate the benefit of screening
 - screening-providers are inclined to stress benefits and trivialize drawbacks²⁵⁷
- information to be given by program and provider independent institution
 - why?
 - (high) participation rate determines success of screening-program → program organizers biased
 - participation rate determines provider income → operator/ examiner/ reader biased

decision to participate in CRC-screening or not involves complex assessment of risks

information from program and provider independent institution

²⁵³ Health Council of the Netherlands (2009) p. 99

²⁵⁴ OHTAC (2009) p. 4

²⁵⁵ Health Council of the Netherlands (2009) p. 101

²⁵⁶ National Health Committee (2003) p. 2

²⁵⁷ Health Council of the Netherlands (2009) p. 101

by who?

- e.g. Nordic Cochrane Centre, Copenhagen, Denmark²⁵⁸
- e.g. University of Hamburg, Fachwissenschaft Gesundheit, Germany²⁵⁹

independent information: e.g. Nordic Cochrane Centre

“The decision to undergo screening should be a personal one. The aim of the medical community is simply to provide the individual with unbiased, informative and comprehensive information and comprehensive information about the advantages and disadvantages of screening.”²⁶⁰

5.3.2 Offering potential participants a choice of first-line screening-test

- Is choice valued in itself?
 - YES: e.g. one attitude survey conducted among colonoscopy-naive individuals showed that, ONCE they had been fully informed about the techniques in question, most people preferred FOBT-screening to colonoscopy²⁶¹
 - possible options for choice in CRC-screening
 - FOBT or colonoscopy
 - FOBT or flexible sigmoidoscopy
 - consideration could be given to investigating the feasibility of combining flexible sigmoidoscopy-screening with FOBT-screening and offering the choice between the two methods²⁶²
- Is choice a tool to increase participation?
 - NO: currently no data available to support that implementing a multi-option program would result in higher participation or increase the effectiveness of screening²⁶³

choice of first-line screening test valued

²⁵⁸ download for breast cancer screening in English:

www.cochrane.dk/screening/index-en.htm or in German:

<http://www.cochrane.dk/screening/index-de.htm> , accessed March 14th, 2010

²⁵⁹ download for CRC-screening in German: http://www.gesundheit.uni-hamburg.de/cgi-bin/newsite/index.php?page=page_46 , accessed March 14th, 2010

²⁶⁰ Brethauer (2011) p. 96

²⁶¹ Health Council of the Netherlands (2009) p. 62

²⁶² Health Council of the Netherlands (2009) p. 81

²⁶³ Health Council of the Netherlands (2009) p. 93

5.3.3 Selection of screening-test(s) to use in population based program

impact of screening test on participation most important

program sensitivity measured in real-world context not test sensitivity matters from public health point of view

- expected influence of a test/ choice of tests on participation rate central for program's decision
“The best test is the one that the patient will accept’ was often stated by experts”²⁶⁴
- program test characteristics (incorporating participation rate) matter from a public health point of view – single test characteristics are of only theoretical interest
- evidence of test characteristics in real-world setting/ screening-context relevant, not evidence from artificial trial setting/ symptomatic-test setting
- the greater the sensitivity of a test (e.g. colonoscopy) for gradually developing abnormalities (e.g. CRC), the less advantage there is in having a shorter test interval²⁶⁵

5.3.4 Program guidelines

integrated guidelines over entire process of screening, diagnosis, treatment and surveillance

- development of integrated (multidisciplinary) guidelines covering the entire chain from screening to diagnosis, treatment, follow-up and surveillance as evidence-based backbone of population based screening-program

5.3.5 Quality

quality of colonoscopy is key

- if the potential benefit of screening is to be realized, steps must be taken to ensure that the quality of colonoscopy examinations is of an appropriate standard²⁶⁶
 - all screening-designs, independent of initial test (gFOBT, iFOBT, flexible sigmoidoscopy), ultimately rely on colonoscopy for effectiveness
 - if an adenoma is detected, the most important issue is that the abnormality will be fully removed during polypectomy
 - ➔ the biggest risk factor for adenoma patients in relation to the development of CRC is incomplete adenoma removal²⁶⁷

²⁶⁴ Imperiale (2010) p. 1642

²⁶⁵ Health Council of the Netherlands (2009) p. 95

²⁶⁶ Health Council of the Netherlands (2009) p. 118

²⁶⁷ Health Council of the Netherlands (2009) p. 119

- quality of endoscopists (training, continued education and experience) determines screening-yield and rate of adverse events
 - roles of different health professions in screening-program (capabilities, legal requirements, ...) – e.g. nurse endoscopists
- provision of necessary quantity of qualified human resources for screening
- CRC beyond screening: professional staff and facilities for diagnosis and treatment need to be sufficiently well developed to cope with the volume of referrals that a national screening-program would generate
 - ➔ screening is only desirable once the necessary follow-up care capacity has been built up
- Process of Quality Assurance
 - accreditation for endoscopists
 - experience
 - continued education
 - meeting of process parameters, e.g.
 - proof of full colonoscopy (image of cecum)
 - withdrawal time
 - adenoma detection rate
 - complication rate
- installation of reliable system to gather data on unintended consequences of screening activity (i.e. hospital stays after screening endoscopies)²⁶⁸
- quality assurance is more difficult but still essential in those areas, the screening-program does not have direct management or funding control over
 - depending on local health care system: diagnostics, treatment, surveillance ...
- follow procedural and data protocol including standardized, uniform documentation of detected abnormalities (essential for evaluation)
- pathology diagnoses will be the primary outcome on which the program is evaluated²⁶⁹
 - ➔ quality assurance in the domain of pathology is key
- special considerations according to chosen screening-test: e.g. in the case of iFOBt-based screening
 - iFOBt-testing is automated and its quality is easy to control
 - focus of quality assurance therefore not on the screening-test itself but on
 - organization of sample transport from participants to lab
 - follow-up testing and examination (colonoscopy, histopathology)

quality of endoscopist determines yield and complication rate

successful screening requires adequate follow-up care

quality assurance in colonoscopy ...

... and down the treatment line

standardized data protocol and documentation

²⁶⁸ e.g. Leffler (2010)

²⁶⁹ Health Council of the Netherlands (2009) p. 126

5.3.6 Surveillance

unmanaged screening-program may lead to explosion in number of surveillance-colonoscopies

current surveillance regime needs to be adapted to screen-detected adenomas

surveillance colonoscopy has worst benefit-harms trade-off

- design of surveillance²⁷⁰ thresholds has mayor impact on number of colonoscopies resulting from screening → unmanaged program may easily lead to explosion in number of surveillance colonoscopies
- existing CRC-surveillance regimes practiced the world over today are problematic
 - population-based screening-program calls for reformulation: underlying guidelines were intended for normal clinical practice rather than for screen-detected adenomas
 - current guidelines are stricter than supported by scientific evidence
 - (already strict) guidelines interpreted even stricter in actual practice → too many patients are undergoing surveillance colonoscopies
- elements of colonoscopy capacity²⁷¹
 1. screening
 2. diagnosis, polypectomy (polyp removal)
 3. surveillance (25-40 % today, present level increasingly seen as excessive, danger of further increase through unmanaged screening-program)
 - of the above, surveillance colonoscopy has
 - lowest yield
 - worst benefit-harms trade-off
- benefit of screening of people with family history of CRC under 55 unclear ²⁷²
 4. screening
 5. diagnosis, polypectomy (polyp removal)
 6. surveillance (25-40 % today, present level increasingly seen as excessive, danger of further increase through unmanaged screening-program)
 - of the above, surveillance colonoscopy has
 - lowest yield
 - worst benefit-harms trade-off

²⁷⁰ Health Council of the Netherlands (2009) p. 120; for examples on surveillance guidelines by EPAGE II compare Arditì (2009); for American Cancer Society and US Multi-Society Task Force on Colorectal Cancer recommendations compare Brooks (2008)

²⁷¹ Health Council of the Netherlands (2009) p. 120

²⁷² IQWiG (2012)

5.3.7 Flexibility

- culture of flexibility independent of initial program setup desirable
- mission statement: “Our screening-program focuses on the maximum benefit for the population.”
 - ongoing critical evaluation by program itself and through independent (outside/ foreign) institution
 - openness to new (scientific or evidence) developments
 - mission statement not: “Our screening-program conducts the best possible screening with the chosen test X.” as this would result in locking-in of initial decisions
- a new test could be introduced within the existing infrastructure of the operational program, since various key elements of a CRC-program – such as a call/recall system, a system for documentation and quality assurance as well as colonoscopy capacity – would be test-independent²⁷³

critical program evaluation also from independent outside institution

program should be open to incorporating rapidly evolving science-base of CRC-screening

5.3.8 International and research focus

- program culture focusing on international best-practice
 - transparency
 - sharing knowledge
 - investing in partnership
 - learning from each other
 - (research) leadership
- enable program to generate new scientific evidence
 - before introduction of program: setting up of smaller pilot projects generating specific national data needed for conceptualization of nationwide screening-program
 - e.g. NL²⁷⁴
 - during roll-out: due to small effect sizes involved in screening-studies: randomized trials on screening-effectiveness need large number of participants and long follow-up to establish effectiveness of preventing deaths, especially set up trials are expensive → in absence of trials the results of screening may remain inconclusive
 - roll-out of screening-program offers possibility for experimental design to gather evidence on effectiveness of screening at small additional cost
 - every population based public health program for CRC-screening using any primary test modality should be launched with ran-

program to both learn from and inform international best practice

(small) pilot projects in context of screening-program to generate new scientific evidence...

... before,

... during,

... after

... roll-out of screening-program

²⁷³ Health Council of the Netherlands (2009) p. 81

²⁷⁴ Health Council of the Netherlands (2009)

- dominization of the target population at the implementation phase²⁷⁵
 - after introduction of program: program evaluation and introduction of pilots within the larger screening-program
 - e.g. design of program should enable trials of potentially preferable test methods performed as flanking studies within the context of the operational program²⁷⁶
 - public funding of research necessary

“The UK trial [on flexible sigmoidoscopy in CRC-Screening]²⁷⁷ illustrates the value of long term publicly funded medical research. The study was designed in the early 1990s, and the main results are available almost 20 years later. Many people argue that medicine is developing so rapidly that a trial of this duration would be outdated by the time the results are available. This landmark study shows that this is a false assumption. It is important that large funding organizations like the UK National Health System, the European Union, and others support long term clinical trials that tackle important health problems beyond the often short term scope of industry funded medical research.”²⁷⁸

5.3.9 Consideration of phased/staged introduction

staged introduction of screening-program offers advantages

- roll-out of CRC-screening program is complex
- ‘teething problems’ during initial stage of newly established program more easily addressed with phased introduction
- first stages of introduction can provide necessary data for calibrating national program
- roll-out options Switzerland
 - local
 - regional
 - national

5.3.10 Program financing

sustainable and comprehensive financing of program necessary to achieve screening-goals

- well managed screening needs resources for program overhead
 - call/recall system
 - training, continued education and program-accreditation of examiners
 - data/ IT system
 - quality assurance
 - from the outset, budgetary provision should also be made for

²⁷⁵ e.g. Malila (2008)

²⁷⁶ Health Council of the Netherlands (2009) p. 82

²⁷⁷ Atkin (2010)

²⁷⁸ Betthauer (2010) p. 1260

- monetary provisions for independent information of participants
- program-internal monitoring of ongoing screening-activities
- regular program evaluation from independent (outside/foreign) institution
- reference system
- promotion of knowledge and innovation-oriented scientific research, necessary to keep the screening-program up to date

**screening overhead
expensive ...**

**... achieving high
participation rate
possibly, too**

6 Conclusion

- program design (quality) and participation rate matter
- choice of screening-test is of secondary importance²⁷⁹

- CRC-screening is not simply about choosing the right initial test for screening
- effective CRC-screening is about establishing a quality assured screening-program integrating diagnosis, treatment and surveillance
 - emphasis on quality focused human resource development of endoscopists
- uptake is the primary determinant of effectiveness for a screening-program
- level of regular participation and the resulting effective program-sensitivity has a greater influence than the sensitivity of a single performance of a screening-test²⁸⁰ particularly in the context of a population-based screening-program for slowly developing abnormalities (e.g. for CRC)²⁸¹
 - study of determinants of participation rate warranted to inform program design²⁸²
- quality of screening-program (narrower realm of screening plus integration of diagnosis – treatment – surveillance) affects desired outcome of mortality reduction and minimization of negative repercussions on screened population

integration of screening, diagnosis, treatment and surveillance fosters quality

focus should be put on training and continued education of endoscopists

²⁷⁹ „In the end, a test can only provide benefit if it is actually done.”, Church (2011)
“Patient preferences for screening tests should be identified and respected – in this case the best test is the one that gets done.”, Inadomi (2012)
“The role of adherence is key to understanding which CRC tests provide higher life years gained at reasonable resource use and cost.”, Zauber (2010)

²⁸⁰ Health Council of the Netherlands (2009) p. 99

²⁸¹ Health Council of the Netherlands (2009) p. 95

²⁸² e.g. Holden (2010)

7 References

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8 Appendices

8.1 Appendix A: Systematic health technology reviews on CRC-screening issues from major HTA-institutions

	Institution	Titel	Remark
1.	Health Council of the Netherlands	Health Council of the Netherlands. A national colorectal cancer screening programme. The Hague: Health Council of the Netherlands, 2009; publication no. 2009/13E	Comprehensive analysis of questions around the establishment of a population based CRC-screening program in the Netherlands, contains systematic review of the literature
2.	US Preventive Services	Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. U.S. Preventive Services Task Force. Ann Intern Med. 2008 Nov 4;149(9):627-37. Epub 2008 Oct 6.	United States Preventive Services Task Force recommendation
3.	Task Force	Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008 Nov 4;149(9):638-58. Epub 2008 Oct 6. Review.	United States Preventive Services Task Force: systematic review published in journal
4.		Whitlock, EP, Lin J, Liles E, Beil T, Fu R, O'Connor E, Thompson RN, Cardenas T. Screening for Colorectal Cancer: An Updated Systematic Review. Evidence Synthesis No. 65, Part 1. AHRQ Publication No. 08-05124-EF-1. Rockville, Maryland, Agency for Healthcare Research and Quality, October 2008	United States Preventive Services Task Force: full systematic review
5.	US Preventive Services	Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Ann Intern Med. 2008 Nov 4;149(9):659-69. Epub 2008 Oct 6.	United States Preventive Services Task Force: modelling for economic evaluation of alternative CRC-screening strategies published in journal
6.	Task Force	Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating Test Strategies for Colorectal Cancer Screening—Age to Begin, Age to Stop, and Timing of Screening Intervals: A Decision Analysis of Colorectal Cancer Screening for the U.S. Preventive Services Task Force from the Cancer Intervention and Surveillance Modeling Network (CISNET). Evidence Synthesis No. 65, Part 2. AHRQ Publication No. 08-05124-EF-2. Rockville, Maryland, Agency for Healthcare Research and Quality, March 2009.	United States Preventive Services Task Force: full economic evaluation
7.	Ontario HTA	Medical Advisory Secretariat. Screening methods for early detection of colorectal cancers and polyps. Ontario Health Technology Assessment Series 2009;9(6-11).	Ontario Health Technology Assessment Summary and compilation of six reports below
8.		Medical Advisory Secretariat. Screening methods for early detection of colorectal cancers and polyps: summary of evidence-based analyses. Ontario Health Technology Assessment Series 2009;9(6).	Ontario Health Technology Assessment

9.	Ontario HTA	Medical Advisory Secretariat. Computed tomographic (CT) colonography for colorectal cancer screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(7).	Ontario Health Technology Assessment Review - CT-Colonography
10.		Medical Advisory Secretariat. Magnetic resonance (MR) colonography for colorectal cancer screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(8).	Ontario Health Technology Assessment Review – MR-Colonography
11.		Medical Advisory Secretariat. Capsule Endoscopy for Colorectal Cancer Screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(9).	Ontario Health Technology Assessment Review - Capsule Endoscopy
12.		Medical Advisory Secretariat. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(10).	Ontario Health Technology Assessment Review - Fecal Occult Blood Test
13.		Medical Advisory Secretariat. Flexible sigmoidoscopy for colorectal cancer screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9 (11).	Ontario Health Technology Assessment Review – Flexible Sigmoidoscopy
14.	Canada HTA	Mujoomdar M, Cimon K, Spry C. <i>Fecal</i> Immunochemical Tests for Colorectal Cancer Screening: A Systematic Review of Accuracy and Compliance. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009	Canadian Agency for Drugs and Technologies in Health (CADTH) Review – Immunochemical Tests plus compliance
15.		Ho C, Heitman S, Membe SK, Morrison A, Moulton K, Manns B, Au F, Reed M, Hilsden R. Computed tomographic colonography for colorectal cancer screening in an average risk population: Systematic review and economic evaluation. [Technology report number 114]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008	Canadian Agency for Drugs and Technologies in Health (CADTH) Review – CT-Colonography
16.		Tran K. Capsule colonoscopy: PillCam® Colon [Issues in emerging health technologies issue 106]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007	Canadian Agency for Drugs and Technologies in Health (CADTH) Capsule Endoscopy
17.		Ho C, Jacobs P, Sandha G, Noorani HZ, Skidmore B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectiveness [Technology report no 60]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2006	Canadian Agency for Drugs and Technologies in Health (CADTH) Non physician flexible sigmoidoscopy examiners
18.	Denmark HTA	Christensen, LA; Dahlerup, JF; Poulsen, PB; Thranholm L Capsule endoscopies of the small intestine – a Health Technology Assessment Copenhagen: National Board of Health, Danish Centre for Health Technology Assessment, 2007 Danish Health Technology Assessment – Projects funded by Dacehta 2007; 7 (1)	Danish Centre for Health Technology Assessment Capsule Endoscopy English summary of report in Danish
19.	Danish HTA	National Board of Health, Monitoring & Health Technology Assessment Screening for colorectal cancer: The significance of participation rates – A Health Technology Assessment Copenhagen: Danish National Board of Health, Monitoring & Health Technology Assessment, 2008 Health Technology Assessment 2008; 10(1)	Danish Centre for Health Technology Assessment On the importance of participation rates English summary of report in Danish

20.	UK NHS	Tappenden P, Eggington S, Nixon R, Chilcott J, Sakai H, Karnon J. Colorectal cancer screening options appraisal. Cost-effectiveness, cost-utility and resource impact of alternative screening options for colorectal cancer. Report to the English Bowel Cancer Screening Working Group. University of Sheffield, 2004	Bericht für NHS Bowel Cancer Screening Programme Colorectal cancer screening options appraisal
21.	Europe EPAGE II	Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Arditi C, Peytremann-Bridevaux I, Burnand B, Eckardt VF, Bytzer P, Agréus L, Dubois RW, Vader JP, Froehlich F, Pittet V, Schusselé Fillietaz S, Juillerat P, Gonvers JJ; EPAGE II Study Group. Endoscopy. 2009 Mar;41(3):200-8. Epub 2009 Mar 11. Review.	European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE II) Review von Guidelines, Systematic Reviews und Primärliteratur
22.		Appropriateness of colonoscopy in Europe (EPAGE II). Surveillance after polypectomy and after resection of colorectal cancer. Arditi C, Gonvers JJ, Burnand B, Minoli G, Oertli D, Lacaine F, Dubois RW, Vader JP, Schusselé Fillietaz S, Peytremann-Bridevaux I, Pittet V, Juillerat P, Froehlich F; EPAGE II Study Group. Endoscopy. 2009 Mar;41(3):209-17. Epub 2009 Mar 11. Review.	European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE II) Guidelines für Surveillance
23.	US Multi Society Task Force	Colonoscopy surveillance after polypectomy and colorectal cancer resection. Brooks DD, Winawer SJ, Rex DK, Zauber AG, Kahi CJ, Smith RA, Levin B, Wender R; U.S. Multi-Society Task Force on Colorectal Cancer; American Cancer Society. Am Fam Physician. 2008 Apr 1;77(7):995-1002.	U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society Consensus Guidelines
24.	US Institute for Clinical and Economic Review	Scherer R, Knudsen A, Pearson SD CT Colonography for colorectal cancer screening – Final appraisal document. Institute for Clinical and Economic Review ICER, 2008	Institute for Clinical and Economic Review ICER (private) Colonography

8.2 Appendix B: 13 primary literature references from hand search 2009 not cited in report

Article	Topic / question addressed (in German)
BAXTER 2010	Editorial zu Effectiveness von Koloskopie Anlass: Studie über unterschiedliche Entdeckungsraten im linken (distalen) und rechten (proximalen) Kolon (BRENNER JNCI 2010)
EKELUND 2006	Kritische Fragen zu Evidenz für Screening
ELIAKIM 2006	Kapselendoskopie
ELIAKIM 2009	Kapselendoskopie
HAKAMA 2005	Artikel, auf den EKELUND Acta Oncologica 2006 kritisch antwortet
HAKAMA response to EKELUND 2006	Antwort auf EKELUND Acta Oncologica 2006
MALILA 2007	Follow-up nach 25 Jahren von finnischer Population, an FOBT Screening teilnahm
PINEDA 2008	Darmvorbereitung vor operativem Eingriff – Meta-Analyse und Systematic Review
RAMOS 2008	Review zum Einfluss von Zeitpunkt von Diagnose und Therapie auf Staging von kolorektal Krebs
SCHOOFS 2006	Kapselendoskopie
SIEG 2009	Kapselendoskopie
VAN DEN BROEK 2009	Review eines alternativen Koloskopieverfahrens: narrow band imaging
VAN GILS 2009	Review zu Annahmen über Teilnahmeraten in der ökonomischen Evaluation von Screening