Screening for Colorectal Cancer

Part 1: Screening-Tests and Program Design

Ludwig Boltzmann Institut
Health Technology Assessment

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Summary

Significance of colonoscopy in screening for colorectal cancer

Colonoscopy …

Colonoscopy is 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 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.

… final common pathway in all CRC-screening

… invasive, serious complications

… operator-dependent

Effectiveness of screening for CRC

limited evidence base for CRC-screening …

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. A large randomized controlled trial on once only flexible sigmoidoscopy as a first-line test showed a relative risk reduction of 31% for disease-specific CRC-mortality and a reduction of CRC incidence of 23%. Results from three more randomized trials on flexible sigmoidoscopy are expected in the coming years. Two randomized studies on screening with colonoscopy 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.

… RCTs from gFOBT and recently flexible sigmoidoscopy

… more sigmoidoscopy results expected soon

no RCT evidence for colonoscopy

International screening-activities

most screening-activity not population-based …

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 – England, Scotland, Finland and Australia – 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 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.

… but opportunistic with low participation rates

Choice of first-line test

first-line screening test's impact on program participation more important than test sensitivity

When considering first-line screening-tests on which to base an organized program, the test's impact on participation is more important than its test-sensitivity. Program-sensitivity largely depends on participation rates. Recent developments in first-line screening include quantitative iFOBTs. CT-colonoscopy, capsule endoscopy and new molecular tests are not yet viable alternatives for use in population-based mass-screening.

Improving screening-effectiveness

integrated screening – program considering diagnosis – treatment – surveillance

incremental implementation of national program recommended

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-colonoscopies resulting from CRC-screening. Incremental implementation of a national population-based screening-program, with pilot testing and incremental roll-out, should be considered.

Securing comprehensive program-financing

comprehensive and sustainable program funding needs to be secured from the outset

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 and funds for regular program evaluation through an external institution needs to be secured.

Zusammenfassung

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 komplikationsintensiv. 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.

Koloskopie …

… ist Hauptbestandteil jedes Screening-Pfads

...ist invasive Screening-Maßnahme mit häufigen Komplikationen

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%. Eine große randomisierte Studien belegt für einmaliges Screening mit flexibler Sigmoidoskopie eine Senkung der Darmkrebs-spezifischen Sterblichkeit um 31%. Die Inzidenz von CRC ging um 23% zurück. Ergebnisse dreier weiterer randomisierter Studien zu flexibler Sigmoidoskopie werden im Verlauf der nächsten Jahre erwartet. Zwei randomisierte Studien über Screening mit Koloskopie 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.

wenig Evidenz zur Effektivität von Dickdarmkrebs-Screening vorhanden

… 4 RCTs zu gFOBT

… 1 RCT zu Sigmoidskopie (weitere kommen)

… keine RCT zu Koloskopie

Screening-Aktivitäten international

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 und Australien – verfügen über nationale populationsbezogene Programme. Meist erfolgt Screening aber nicht populationsbezogen im Rahmen eines qualitätsgesicherten Programms, sondern opportunistisch und mit niedriger Teilnahmerate. 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, 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.

Screening erfolgt meist nicht populationsbezogen im Rahmen qualitätsgesicherter Programme …

… sondern opportunistisch und mit niedrigen Teilnahmeraten

Auswahl des Screening-Tests:

… Auswirkung auf Programmsensivität über Teilnahmerate wichtiger

… als Einzelsensitivität des Tests

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 Test-Sensitivität. Die Sensitivität des Programms hängt maßgeblich von der TeilnehmerInnenrate ab. Als neue first-line Screening-Tests bieten sich quantitative iFOBTs an. CT-Koloskopie, Kapselendoskopie und neu entwickelte molekulare Test werden in absehbarer Zeit (noch) keine Alternativen für einen breiten Screening-Einsatz sein.

Ansätze zur Steigerung der Effektivität

Screening-Programm soll Vernetzung mit Diagnose, Behandlung und Surveillance sicher stellen

… schrittweise Einführung empfohlen

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, etwa über Pilottestungen und anschließendes schrittweises Ausrollen, überlegenswert.

Komponenten der Programmfinanzierung

ausreichende und nachhaltige Finanzierung für Erfolg des Screening-Programms notwendig

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

1 Introduction

1.1 Rationale for Colorectal Cancer-Screening

Colorectal cancer (CRC) third most common non-skin cancer

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]

protracted pre-malignant stage, early detection raises chance of survival

CRC has a recognizable, protracted pre-malignant stage (adenoma) that is relatively easy to treat. If an adenoma has progressed to carcinoma, it is an average of nearly 7 years before the disease becomes symptomatic.[4] If the disease is detected early, a person's chances of survival are considerably higher than if it is detected at a later stage. That is why screening for CRC has been introduced in various modes of organization in a number of countries.

1.2 Background and structure of this report

Review of secondary literature on CRC-Screening for Swiss cancer league …

The Swiss cancer league[5] 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. The study questions guiding this report are:

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

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?

report focuses on three recent HTAs

After the ensuing methods section on the literature search, the quality of the three major health technology assessments – which are the main sources of information this report focuses on – is appraised. This is done according to the PRISMA-statement on preferred reporting items for systematic reviews and meta-analyses.[6] Chapter 4 (results I) addresses the first study question and condenses the results of the literature review on important facts about

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 www.krebsliga.ch/de/100_jahre_krebsliga/english.cfm

6 The PRISMA statement: Moher (2009)

CRC-screening. Chapter 5 (results II) addresses the second study question. Part of the focus here lies on distilling important questions on CRC-screening and 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.

2 Methods

2.1 Initial literature search and inclusion Dec. 2009

The search was conducted on Dec. 22nd 2009 with the following PICO[7] – 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:

search limited to secondary literature published from 1999-2009

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

Secondary Databases: Medline, EmBase

7 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 Assessment Committee, 2009, United States Preventive Services Task Force, 2008) 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

The abstracts of these 31 articles were reviewed independently by two researchers. Disagreements about inclusion were resolved through discussion and consensus. 18 were excluded on the basis of their abstracts as not relevant for the PICO-question of this report. The remaining 13 articles were included in the analysis for this report. These 13 references are marked with a star (*) in the list of references at the end of this report.

additional unsystematic search on new molecular screening-tests

Due to a special interest in recent developments in the field of molecular screening-tests expressed by the Swiss cancer league, 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 with two stars (**) in the list of references at the end of this report.

Both searches were supplemented with an initial hand search for topic specific primary articles informing on details of issues covered in this report. These references can be found in appendix B together with a brief description.

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 an update search of the literature was conducted on Nov. 12th 2010 adhering to procedure detailed above.

Systematic update search produced 3 relevant articles

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.

The abstracts of these 46 articles were reviewed – this time by the author alone. 43 were excluded on the basis of their abstracts as not relevant for the PICO-question of this report. In the end 3 results from the systematic litera-

ture update search were included in the analysis for this report. These 3 references are marked with three stars (***) 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 tests[8]. This reference addresses the special interest in recent developments in the field of molecular screening-tests expressed by the Swiss cancer league.

In the course of the compilation of the update of the report further topic specific primary and secondary articles informing on details of issues covered in this report were included. To differentiate these articles in the reference list at the end of the document their Pubmed PMID is included. 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.[9]

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

9 Atkin (2010)

3 Appraisal of three core included HTAs

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

The core of this report is based on three recent health technology assessments/ systematic reviews by major health technology assessment or related institutions: Health Council of the Netherlands, United States Preventive Services Task Force and Ontario Health Technology Assessment Committee These three publications are appraised according to the PRISMA-statement on preferred reporting items for systematic reviews and meta-analyses in table 3-1 below.[10]

For a list of other recent relevant health technology assessments see appendix A.

10 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 Assessement 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.[11]

11 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: Important facts about colorectal cancer-screening

4.1 Colorectal cancer

cancer-screening by definition results in over diagnosis …

… degree difficult to quantify for CRC

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.[12] 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.[13]

80% of CRC sporadic

Most CRC-patients (approximately 75-80%) have no close relatives who have previously suffered from this disease. This majority of cases are classified as 'sporadic CRC'.[14]

20% have positive family history

Approximately 20% of patients with CRC have some type of positive family history. 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.[15] 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.[16] 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 %.[17] 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.[18]

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

The remainder of CRC-cases develops in persons who have predisposing inflammatory bowel disease.[19]

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

… 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.[20] 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.[21]

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

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

14 USPSTF Whitlock (2008a) p. 3 and Health Council of the Netherlands (2009) p. 34

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

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

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

18 e.g. Lynch (2009)

19 USPSTF Whitlock (2008a) p. 3

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

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

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.[22]

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.[23]

referral to colonoscopy based on polyp sized

Polyp size < 6mm: 80% of found abnormalities

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

- consensus by most, but not all experts[24]: no referral required
- risk of being malignant in screening-population 0.03-0.2%

Polyp size 6-10 mm: small polyps

no consensus on polyps 6-10mm

- no consensus; necessity and benefit of removing small polyps is not clear[25]
- data from large screening-studies: 3 – 9% are advanced neoplasia (composite outcome: adenocarcinoma/ invasive carcinoma/ CRC and advanced adenoma[26])
  - 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-populations[27]

"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.[28]

polyps > 10mm, consensus: remove

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 CRC[29] (caveat! – data on the reduction of CRC-incidence through colonoscopy and polypectomy rely on weak evidence[30])

22 compare: www.wikipedia.org

23 USPSTF Whitlock (2008)

24 USPSTF Whitlock (2008)

25 USPSTF Whitlock (2008a) p. 4

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

27 USPSTF Whitlock (2008a) p.6

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

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

30 USPSTF Whitlock (2008a) p. 4

clarifying risk associated with smaller polyps important question for future research

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.

sharply rising cost of CRC-treatment

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.[31]

4.3 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

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

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

The optimal outcome measure for screening-trials is all-cause mortality. This endpoint requires very large samples. Of all causes of death, CRC represents very roughly 3%, a small fraction.[32] The best available evidence suggests that the effect size of CRC-screening is a 15% reduction of CRC-mortality.[33] 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.[34] As a result the necessary sample size to give a study sufficient power would have to be 300,000 per group in the case of CRC-screening.[35] Studies of all-cause mortality that are sufficiently large to have the required precision would not be feasible in many situations.[36] 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.[37]

31 Health Council of the Netherlands (2009) p. 51

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

33 Cochrane Systematic Review, Hewitson (2007)

34 Black (2002)

35 Church (2002)

36 Gail (2002)

37 Weiss (2002)

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 to provide adequate power, disease-specific mortality rather than all-cause mortality has been the accepted end point of screening-studies. Still, 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.[38]

attribution problems of cause of death in practice …

… results in tendency to overestimate screening benefit

Data on all-cause mortality has the additional advantage of being reliably and readily available. Disease-specific mortality data are obtained via the less reliable cause-of-death statistics. The most problematic bias in screening-studies is the so called "slippery linkage bias".[39] Screening-activity and cancer treatment can be associated with excess non-cancer mortality (e.g. car accidents after sedation for screening-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.

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

Where studies are too small (number of participants, 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.[40]

4.3.1 Addressing uncertainties about screening-outcome

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

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 evalu-

38 Juffs (2002)

39 Black (2002)

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

ation of such a screening-program because the effectiveness of preventing deaths is likely to be small and results may otherwise remain inconclusive.[41]

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.[42]

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

4.3.2 Evidence required for introduction of new screening-test

What is the situation when new tests emerge, while a screening-test that has been proven to be effective (such as gFOBT[43]) 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.[44]

evaluation of new test requires direct comparison with old test under screening-conditions

impact of new test on participation rate important for screening-program

4.4 Colonoscopy – final common pathway in CRC-screening

In contrast to the situation with most other screen-able diseases, there are several (first-line) screening-tests available for CRC. The methods differ in various ways, including the participation rate and the sensitivity. Colonoscopy is the final common (second-line) pathway of all CRC-screening.

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

41 Malila (2008)

42 Black (2002)

43 Cochrane Systematic Review, Hewitson (2007)

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

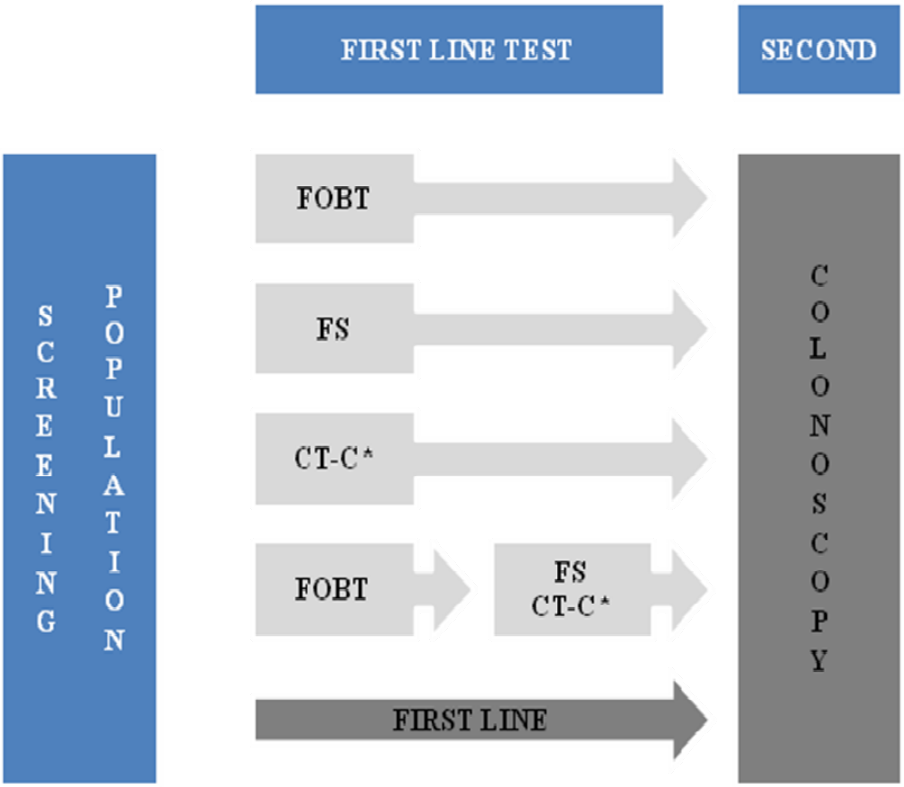

Figure 4.4-1: Colonoscopy as the final common pathway for CRC-screening

**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 4.4-1, Health Council of the Netherlands (2009) p. 13

4.5 Characteristics of Colonoscopy

extensive bowel preparation required

polyps can be removed immediately

colonoscopy at once screening, diagnostic and therapeutic intervention

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. 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, diagnostic and therapeutic intervention. 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 path-

way 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.[45] This is the rationale behind setting upper age limits for CRC-screening.

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.[46] Accuracy is highly dependent on the quality of the bowel preparation and endoscopic examination.[47] Inter-examiner differences in detection of polyps have been shown in population-based studies of screening-colonoscopy.[48] 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.[49] These important missed lesions include adenomas greater than 10 mm in diameter.[50] Both polyp-yield[51] and complication rate[52] 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

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).[53] There is evidence from Germany, Canada and the US that colonoscopy is less effective for right-sided (proximal) CRC than-left sided (distal) cancer.[54] 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.[55] Why would colonoscopy be less effective in preventing death from right-sided (proximal) CRC? 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.[56] Data from the US demonstrate a right-sided (proximal) migration of CRC over the past two decades, which is attributed

colonoscopy worse at detecting right-sided (proximal) lesions

right-sided (proximal) CRC migration observed over the last 20 years

45 e.g. Lieberman (2009)
46 e.g. Lieberman (2009)
47 USPSTF Whitlock (2008)
48 e.g. Barclay (2006)
49 e.g. Barclay (2006)
50 e.g. Lieberman (2006)
51 e.g. Barclay (2006)
52 e.g. Pignone (2000)
53 e.g. Baxter (2009), Brenner (2010)
54 e.g. Baxter (2009)
55 e.g. Brenner (2010)
56 e.g. Baxter (2009)

to a decrease in incidence of left-sided (distal) CRC and an aging population in which right-sided (proximal) lesions are more common.[57]

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-colonoscopies have selected practitioners who were quite experienced and not necessarily representative of community practice. No tandem colonoscopy studies evaluated average-risk populations.[58]

… 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. 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.[59]

4.6 Evidence on CRC-screening tests

no data on all-cause mortality

The evidence base from large trials on the effectiveness of different first-line screening tests for CRC is very limited.

evidence from RCTs for gFOBT: CRC-disease specific mortality RRR 15%, no impact on all-cause mortality …

- guaiac faecal occult blood test or gFOBT – 4 randomized controlled trials (RCTs), disease-specific CRC mortality: relative risk reduction (RRR) 15%, no impact on all-cause mortality[60]. For trial results on gFOBT compare table 4.7-1 below.
- immunochemical faecal occult blood test or iFOBT: 1 RCTs in recruiting phase[61] - results in 10+ years

… no evidence for colonoscopy

- molecular markers: none
- colonoscopy: none, 2 RCTs in recruiting phase[62] – results in 10+ years

57 USPSTF Whitlock (2008a)

58 USPSTF Whitlock (2008a) p. 12

59 Betthauer (2009) p. 301

60 Cochrane Systematic Review, Hewitson (2007)

61 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

62 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

- flexible sigmoidoscopy: a large multicenter RCT in UK[63] showed for disease specific CRC mortality a RRR of 31% and a decline in CRC incidence of 23%. Intermediate results after a shorter follow up from an RCT in Norway[64] showed no influence on CRC mortality [two more trials in Italy[65] and USA[66] to publish results fairly soon, Norwegian study to publish updated results with longer follow-up] - For more detailed trial results on flexible sigmoidoscopy compare table 4.7-5 below.
- CT-colonoscopy: none

… 2 RCTs on sigmoidoscopy so far show RRR 31% and no influence

more sigmoidoscopy RCT results expected …

no evidence on CT-colonoscopy…

"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."[67]

… debate about evidence necessary for introduction of screening

4.7 Characteristics of different CRC-screening tests

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, bienially)	none
Flexible Sigmoid.	23%(UK)[68] none(NO)[69]	27-31%(UK)[70] none(NO)[71]	long (5-10 years)	invasive; enema bowel cleansing
Colonoscopy	Unknown	unknown	long (at least 10 years)	invasive; oral bowel cleansing

*Figures for intention-to-screen analyses observed in randomised trials
Source: Bretthauer (2010) p. 1260

63 UK: once only sigmoidoscopy, Atkin (2010)
64 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)
65 Italy: once only sigmoidoscopy, SCORE, Segnan (2002)
66 USA: sigmoidoscopy every 3-5 years, PLCO, Weissfeld (2005) – results in peer-review process, personal e-mail correspondence with Prof. Weissfeld, Nov. 2010
67 Betthauer (2009) p. 301
68 findings after 11 years of follow-up from the UK: Atkin (2010)
69 preliminary findings from the NORCCAP trial after only seven years of follow-up: Hoff (2009) – NORCCAP will provide an estimate for effectiveness after 10 years of follow-up in 2013
70 findings after 11 years of follow-up from the UK: Atkin (2010)
71 preliminary findings from the NORCCAP trial after only seven years of follow up: Hoff (2009)

no test without drawback: harm, accessibility, low participation

No current CRC-screening tests are without drawbacks, including potential harms, limited accessibility or imperfect acceptability to patients.[72] 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.

FOBTs

FOBT detects blood in stool

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.

1. gFOBT

gFOBT in use for 40 years

not specific to human blood

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 guaiacum officinale (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 low 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.[73] The result is a relatively low participation rate in gFOBT-screening.

low sensitivity …

6 samples necessary → low participation

gFOBT demonstrated effectiveness: RRR 15%

The first efficacy trials (RCTs) conducted in the realm of CRC-screening were based on the guaiac (gFOBT) Haemoccult 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.[74] This makes gFOBT the CRC-screening method with the largest RCT base demonstrating effectiveness. For more information on gFOBT compare table 4.7-1 below.

72 USPSTF Whitlock (2008a) p.6

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

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

2. iFOBT

iFOBT specific for human blood

single faecal sample sufficient → higher participation

analysis of quantitative iFOBTs can be automated

sensitive to degradation of biomarker

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.

iFOBT at equal specificity more sensitive than gFOBT

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.[75] For more information on iFOBT compare table 4.7-2 below.

3. Molecular markers

multitude of tests under development:

large scale validation and optimization for practical screening still outstanding

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, blood or tumor tissue. 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.[76]

3.1 Biomarkers in stool

3.1.1 DNA markers in stool

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.[77]

Innovations emerging …

… much further research needed before possible screening introduction

The technical challenges that compromised first-, second- and third-generation versions of the fecal DNA tests are being addressed. 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, evi-

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

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

New candidates for CRC-screening tests are of particular interest to the initiator of this report. This is the reason for the amount of space allocated to the molecular markers.

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

dence 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.[78]

RNA markers in stool

3.1.2 RNA markers in stool

Faecal RNA has also been investigated as a possible CRC-biomarker.[79]

protein markers in stool

3.1.3 Protein markers in stool

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.[80] One example is the enzyme M2-PK.

3.2 Biomarkers in blood

giving blood sample less inconvenient, biomarker less prone to degeneration

For many people, giving a blood sample is less inconvenient than providing a faecal sample. There is no micro flora which could degrade the biomarker or hamper analysis like in stool. Also sample processing may be easier.[81]

DNA, RNA, protein markers in blood

3.2.1 DNA markers in blood

DNA is not broken down as quickly in blood as in faeces, and blood contains less PCR[82] inhibitory factors.[83] One example is circulating methylated[84] mSEPT9 DNA in plasma.

3.2.2 RNA markers in blood

3.2.3 Protein markers in blood

studies so far have limited sample size, lack external validation

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.[85] The authors conclude that larger prospective studies using study populations representing a screening-population were needed to verify promising results. In addition, future stud-

78 Morrison (CADTH) (2010) p. 3

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

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

81 Hundt (2007)

82 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 thoUSnds 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.

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

84 compare: www.wikipedia.org

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

85 Hundt (2007)

ies should pay increased attention to the potential of detecting not only CRC but precursor lesions, due to their value for CRC-screening.[86]

pilot projects involving adacemia – industry cooperation under way

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. [87] Similar initiatives also involving academia-industry cooperation are under way in other countries.[88]

reasonable to believe that new test will benefit screening in the long run

time frame 10 years

studies can be undertaken in context of existing screening-program

Summing up, it is reasonable to believe that in the long term a screening-program could be enhanced by the use of molecular markers.[89] It is expected to be another 5 years before suitable ones can be identified.[90] 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 5 years. It would not be appropriate to introduce a new screening-test until its superiority to the existing test had been demonstrated in randomized trials. Such studies can be undertaken efficiently in the context of ongoing screening-activities.[91] Furthermore, modelling taking participation rates into account would need to show that the new test was more efficient than existing screening. For more information on molecular markers under development for CRC-screening – including MP-2K and m9SEPT as specific examples – compare table 4.7-3 below.

Methods visualizing the colon

Endoscopic methods

4. Colonoscopy as first-line screening-test

serious adverse events for screening-test in general population

Although colonoscopy is generally safe, it is still 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 even counting hard-to-detect complications (if they occur), such as silent myocardial infarction.[92]

86 Hundt (2007)

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

88 e.g. Germany, compare http://www.innovations-report.de/html/berichte/biowissenschaften_chemie/darmkrebs_erkennen_bevor_entsteht_133139.html accessed March 14th 2010

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

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

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

92 Ransohoff (2009)

colonoscopy complication rates probably underestimated …

… most adverse events not captured by standard reporting

The evidence on complication rates after screening-colonoscopy compared to symptomatic colonoscopy is unconclusive. Some of it suggests that complication rates of screening-colonoscopies are lower than of diagnostic and therapeutic colonoscopies performed in symptomatic patients according to some sources.[93] The argument there is that individuals participating in screening are on average younger and in better health than symptomatic patients. CRC-screening stands out from screening for other diseases.
Recent research finds complications after colonoscopies two to three times higher than previously estimated. Also more complications happen after screening colonoscopy than symptomatic colonoscopy: [94]

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:[95] The overall perforation rate of colonoscopy (higher for colonoscopies with polypectomy than for those without) was 66 per 100.000, the overall mortality rate 6 per 100.000.
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.[96] For more information on colonoscopy as a first-line screening-test compare table 4.7-4 below.

5. Flexible sigmoidoscopy

sigmoidoscopy explores only the distal colon

RCT evidence base evolving …

UK RCT shows … CRC specific mortaliy RRR 31%, CRC incidence minus 23%

preliminary results from Norway RCT show now influence on mortality …

Flexible sigmoidoscopy is a visual examination using an endoscope inserted through the anus into the distal (left-side) portion of the large intestine. There are fewer complications than with colonoscopy. Flexible sigmoidoscopy needs only limited bowel preparation compared to colonoscopy or capsule endoscopy. For flexible sigmoidoscopy an enema is required prior to the examination. Biopsies may be taken during the procedure. A removal of polyps is possible.[97] Inter-examiner differences in the detection of polyps have been shown in population-based studies of screening-flexible sigmoidoscopy.[98] Recently the results of a large multi center randomised controlled trial of once only flexible sigmoidoscopy screening have been published in the UK:[99] After over eleven years of follow-up it finds a decline in disease specific mortality of 31% and a reduction in CRC- incidence of 21%.

93 e.g. Niv (2008)
94 Leffler (2010)
95 Van Heijningen (2010)
96 Baxter (2010)
97 e.g. Atkin (2010)
98 e.g. Barclay (2006)
99 Atkin (2010)

fewer complications than with colonoscopy

"The UK trial 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."[100]

inter-examiner differences in outcome

… evidence may point to longer screening intervals

The previous intermediate results from a Norwegian sigmoidoscopy trial found no influence on disease specific mortality.[101]

…trained nurses as alternatives

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.[102]

Adequately trained nurse practitioners can undertake FS as competently as can gastroenterologists and public acceptance of nurse led flexible sigmoidoscopy is high.[103]

… evidence on population bases screening performance limited

The UK trial[104] provides 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 UK trial excluded people who did not explicitly express their wish to be randomized. NORCCAP[105] is the only study of flexible sigmoidoscopy screening that is truly **population based and will provide an estimate foreffectiveness after 10 years** of follow-up in 2013.[106]

For more information on flexible sigmoidoscopy compare table 4.7-5 below.

6. Capsule Endoscopy

no serious complications

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.[107] 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. The rate of detection of polyps is dependent on the skills of the examiner. Extensive bowel preparation is needed. Biopsy or removal of polyps is not possible.

extensive bowel preparation

polyp detection operator-dependent

not recommended for screeningat this stage

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 cap-

100 Betthauer (2010) p. 1260

101 preliminary findings from the NORCCAP trial after only seven years of follow-up: Hoff (2009) – NORCCAP will provide an estimate for effectiveness after 10 years of follow-up in 2013

102 Betthauer (2010) p. 1260

103 Atkin (2010)

104 Atkin (2010

105 Hoff (2009)

106 Bretthauer (2010)

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

sule endoscopy cannot be recommended [for cancer screening] at this time. [108]

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- or MRI-scanning

Colonography or "virtual colonoscopy" involves examination of the entire large intestine by means of CT- or MRI-scanning, 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. 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.[109] Complications tend not to be serious. In the case of CT-colonography exposure to ionized radiation is a problem

polyp yield reader-dependent

exposure to radioactive radiation

extra-colonic findings problematic

Extra-colonic findings during CT-colonography are an issue. Evaluation of images generated during CT-colonography also involves findings of structures outside the colon itself. This might be an advantage, in the case of serious, treatable disorders, but it can also be a disadvantage. Among the target group for population-screening, the chance that a serious, treatable disease will be found is quite small. Moreover, screening may reveal disorders such as an aneurysm of the aorta, for which the usefulness of early detection is by no means a foregone conclusion. What is clear, however, is that the reporting of extra-colonic abnormalities can double the number of referrals for diagnosis.[110] 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.[111] For more information on CT-colonography as a first-line CRC-screening test compare table 4.7-7 below.

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.[112]

108 Betthauer (2009) p. 300

109 USPSTF Whitlock (2008)

110Health Council of the Netherlands (2009), p. 68

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

112 USPSTF Whitlock (2008)

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	4 RCTs 1975-2002 follow-up: 8-18 years 320,000 participants disease-specific CRC-mortality: RRR 11-18% no impact on all-cause mortality found	low around 50% 47-50% in NL trials		limited HCII test-sensitivity: CRC 13-38% HCII biennial program sensitivity: CRC 50-60%	CRC 99% PPV for advanced neoplasia: 50%	• laborious and user unfriendly: two samples each on three consecutive stools necessary ➔ 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 ➔ dietary measures necessary before test ➔ medication use can influence test (vitamin c, aspirin etc.) • color change unstable, has to be visually assessed ➔ reader dependence COMPLICATIONS • gFOBT: no studies exist[113], 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
HCII … hemoccult II test
iFOBT … immunochemical FOBT
ITA … Italy
mm … millimeters
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), adopted with specifically cited inputs

113 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	little data available on regularly repeated iFOBT-screening 1 study found CRC-mortality: RRR 32% (because of cluster randomization methodically problematic) numerous observational studies	60-62% in NL trials	35/1,000 assuming participation rate of 60% and referral threshold of 75ng/ml	higher than gFOBT estimates show variability within each test, possibly because of different collection methods, reference standards[114] depending on referral threshold and specific test test-sensitivity: CRC 55-90%	lower than gFOBT depending on referral threshold and specific test PPV for advanced neoplasia: 33%	• more false positives than gFOBT • for screening-participants more user friendly sampling, more reliable, more hygienic than gFOBT ➔ positive impact on participation • iFOBT detects more early CRCs and advanced adenomas, which involve less bleeding than later stage CRC, than gFOBT ➔ 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 ➔ adjusting threshold enables screening to be more focused and cost-effective ➔ automated testing (reader independent, cheaper) • no data available concerning an optimum referral threshold to C ➔ test characteristics of screening dependent on it: the lower the threshold ➔ 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 • 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) COMPLICATIONS • iFOBT: no studies exist[115], 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), adopted with specifically cited inputs

114 USPSTF Whitlock (2008)

115 USPSTF Whitlock (2008)

Table 4.7-3: Detailed characteristics of molecular markers as CRC-screening test

Test	Evidence on effectiveness	Expected participation rate	Number of resulting co-lono-scopies	Sensitivity of test	Specificity of test	Information
3. Molecular markers	numerous candidate biomarkers development of practical tests ongoing large-scale validation studies required thereafter					biomarkers: DNA, RNA, proteins in faeces, blood or tumor tissue • clinical accuracy data on faecal DNA tests is still too limited to support population-screening[116] • mismatch between available clinical studies on faecal DNA tests and commercially available tests[117] • biomarkers do not yet constitute a realistic alternative to FOBT • progress is being made with development of numerous candidate biomarkers[118] • development of practical tests will require the involvement of companies capable of marketing the tests • further development work will focus exclusively on markers over which intellectual property rights have been secured
3.1.3 **faecal M2-PK (enzyme)**	evidence on detecting precursors to CRC scant and controversial[119] one large study among 1,082 screening-participants in Germany [120] one study prospectively comparing office-based iFOBT and M2-PK in 600 subjects above average risks[121]			cut-off 4U/ml advanced adenomas: 22%[122] other adenomas: 23%[123] CRC and large adenomas >10mm: 72,4%[124]	cut-off 4U/ ml 82%[125] CRC and large adenomas >10mm: 73,8%[126]	• 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 C[127] • poor performance characteristics demonstrated do not certify further use as a screening-tool in CRC and large adenomas[128]

116 USPSTF Whitlock (2008a)
117 USPSTF Whitlock (2008a)
118 e.g. Morrison (CADTH) (2010)
119 Haug (2008)
120 Haug (2008)
121 Shastri (2008)
122 Haug (2008)
123 Haug (2008)
124 Shastri (2008)
125 Haug (2008)
126 Shastri (2008)
127 Haug (2008)

3.2.1 **methylated SEPT9 DNA in blood plasma**	no data available on detecting precursors to CRC no data available on detecting CRC in screening-population test for detection of precursor lesions (large adenomas etc.) under development					• small producer affiliated study deals with biomarker for detection of invasive colorectal adenocarcinoma only, not detection of precursor lesions[129] o study undertaken in non-screening population[130] o study with screening-population underway[131] • development of test for precursor lesions under way, that would shed light on possible future benefit as CRC-screening test[132]

Abbreviations: see table 4.7-1 above

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

128 Shastri (2008) p. 1502

129 deVos (2009)

130 deVos (2009)

131 deVos (2009) p. 1345

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

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

Test	Evidence on effectiveness	Expected participation rate	Number of resulting colono-scopies	Sensitivity of test	Specificity of test	Information
4. Colonoscopy C	limited data available on the effect of C-screening on CRC-incidence and mortality no evidence yet available from RCTs: results from two[133] RCTsl expected in about 10+ years NNScope* CRC or advanced adenomas: 13 NNScope* CRC: 125	unknown initial data 20-40% NL-CoCoS-trial anticipates 20-25%	250/1,000 (assuming participation rate of 25%)	C is (imperfect) reference standard insufficient evidence to provide precise estimates in community settings[134] CRC: >97% adenomas >10mm: 90-98% adenomas 6-9mm: 87% miss rates for adenomas >10mm possibly higher than CT-C[135]		• risk of serious complications including death • serious harms from community C are about 10 times more common than with FS[136] • screening-yield is heavily dependent on the endoscopist • participation in C-screening significantly lower than in iFOBT-screening ➔ 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 CRC[137] • tumors in the right (proximal) colon are harder to detect for C those in the left (distal) colon o anatomic "blind spots" o incomplete bowel preparation o 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 more[138] • considerable C-capacity required COMPLICATIONS of screening-colonoscopy • procedure related hospital visits 950/ 100.000[139] • serious complications from C in asymptomatic populations 310/

133 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

134 USPSTF Whitlock (2008)

135 USPSTF Whitlock (2008a)

136 USPSTF Whitlock (2008)

137 USPSTF Whitlock (2008)

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

139 Leffler (2010)

						100,000[140] o perforation: 56/ 100,000[141] and 66/ 100,000[142] and 50 - 10/ 100,000[143] o bleeding: 120/ 100,000[144] and 60 - 20/100,000[145] • death: most screening-studies indicate no fatal outcomes of screening-C o death from colonoscopy for symptomatic patients: 4/ 100,000 ▪ patients older than screening-population ▪ more co-morbidities ▪ more intestinal problems o overall death from colonoscopy: 6/ 100,000[146] • from bowel preparation[147] • from sedation, not systematically documented and linked to intervention[148] COMPLICATIONS of follow-up C after positive first-line screening-test are higher than for screening-C • 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 CRC or advanced adenomas. In the case of CRC alone, the figure is 125 – see Health Council of the Netherlands (2009)

Abbreviations: see table 4.7-1 above

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

140 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).

141 USPSTF Whitlock (2008a)

142 Van Heijningen (2010)

143 Health Council of the Netherlands (2009)

144 USPSTF Whitlock (2008a)

145 Health Council of the Netherlands (2009)

146 Van Heijningen (2010)

147 e.g. Heher (2008)

148 Lieberman (2009)

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	Results from large multicentre RCT in UK[149], intention to treat analysis[150]: CRC incidence minus 23% CRC mortality minus 31% Number needed to screen to prevent • one CRC diagnosis: 191 • one CRC death: 489 first results from NOR showed no stat. sign. reduction in CRC-mortality[151] with publication of results from RCT in USA[152] [in the near future[153]] and RCT in ITA[154] [later] community performance of FS-screening will become even clearer[155] from NL trial: NNScope* CRC • 625 invitations • 207 FS • 18 C NNScope* advanced adenomas • 48 invitations • 16 FS • 1-2 C	10-40% about 35% RCT UK[156] 32% in Rotterdam trial	18/1,000[157] on top of 350 FS assuming 35% participation rate under population based screening conditions 27/1,000 on top of 327 FSs assuming participation rate of 32%	little data available concerning sensitivity in population-screening based on C-studies in average risk population (over-estimation): CRC: 58-75% advanced neoplasia: 72-86%		• serious harms from community FS are about 10 times less common than with C[158] • estimates for harms from FS have much wider confidence intervals[159] • 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 high[160] • FS takes only about five minutes, a lot less than colonoscopy • 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 • procedure takes approx. 7 minutes • limited bowel preparation – less extensive than for C o enema 120-150ml, possibly self-administered o 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 ➔ 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) • no data currently available regarding the effectiveness of FS-screening as a means of reducing CRC-mortality COMPLICATIONS • FS serious complications: 34/100,000 (CI 6-190)[161] o FS perforation: 4.6/ 100,000[162] and 2-3/100,000[163] • FS from limited bowel preparation • follow up-colonoscopy, see table 4.7-5

149 55- 64 yrs old, once only sigmoidoscopy, median follow up 11.2 years, Atkin (2010)

150 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

151 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.

152 sigmoidoscopy every 3-5 years, PLCO trial: Weissfeld (2005)

153 personal e-mail correspondence with Prof. Weissfeld, Nov. 2010

154 once only sigmoidoscopy, SCORE trial: Segnan (2002)

155 USPSTF Whitlock (2008)

* ... 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), adopted with specifically cited inputs

156 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%.

157 High referral threshold to colonoscopy in UK RCT, only 5% referred to colonoscopy with 4% entering surveillance program Atkin (2010), referral thresholds lower in NORCCAP and PLCO trials, resulting in 3 to 4 times higher rates of follow up colonoscopies (with the added consequences on the rate of referral to surveillance regimes.

158 USPSTF Whitlock (2008)

159 USPSTF Whitlock (2008)

160 Atkin (2010)

161 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).

162 USPSTF Whitlock (2008a)

163 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 colono-scopies	Sensitivity of test	Specificity of test	Information
6. Capsule endoscopy CE	small, producer sponsored studies only	no data available		CRC 74%[164] 76%[165] adenomas >6mm 64%[166] 68%[167] adenomas >10mm: 64 %	Adenomas >6mm 82%[168]	• CE has been widely used to analyze pathologies of the small intestine for several years[169] • current price of a capsule approx. € 950.-[170] • need for extensive bowel preparation, more extensive than for colonoscopy or CT-colonography • within the upcoming 7 years, improvements are 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 o remedy: use of capsules with delayed activation, reduced energy consumption, increased battery capacity COMPLICATIONS • CE: from bowel preparation • follow up-colonoscopy, see table 4.7-5
New developments in endoscopy						• 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 o high-definition endoscopes o auto fluorescence narrow-band imaging

Abbreviations: see table 4.7-1 above

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

164 producer supported study on 320 patients, Van Gossum (2009), sensitivity probably overestimated compare Bretthauer (2009)

165 Meta analysis of 8 studies with data on 837 patients, Spada (2010)

166 Van Gossum (2009)

167 Spada (2010)

168 Spada (2010)

169 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

170 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[171] advanced neoplasia: 97% less sensitive for small adenomas detection of adenomas >10mm possibly higher than C[172]	limited evidence on performance in population screening-programs estimates are somewhat uncertain[173] for large polyps: >95% PPV advanced adenomas: 41% (referral threshold 6mm) 52-67% (referral threshold 10mm)	• almost identical sensitivity for CRC-cancer and polyps >10mm as C o possibly more sensitive for larger lesions than C, less so for smaller lesions[174] • screening-yield is heavily dependent on radiologist • variety of technologies used[175] o varying slice thickness o single/multi detector scanner o 2D/ 3D/ 3D fly-through o oral contrast ▪ radiation dosage expected to decline with future progress in CT-technology: o lower radiation exposer for CRC-screenees o low radiation dosage reduces image quality outside the colon and is expected to significantly reduce the number of referrals[176] • less unpleasant for subject 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 – as opposed to much more common peduncu-lated (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 → 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. COMPLICATIONS • CT-C radiation • CT-C issue of extra-colonic findings unresolved • CT-C from limited bowel preparation • CT-C as yet no perforation reported in limited use as a screening-method • follow up-colonoscopy, see table 4.7-5

171 USPSTF Whitlock (2008)

172 USPSTF Whitlock (2008a)

173 USPSTF Whitlock (2008)

Abbreviations: see table 4.7-1 above
Source: information from Health Council of the Netherlands (2009), adopted with specifically cited inputs

174 USPSTF Whitlock (2008)
175 USPSTF Whitlock (2008a)
176Health Council of the Netherlands (2009), p. 68

4.8 CRC-screening activities worldwide

European Union

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

Finland, England and Scotland are currently working on the phased introduction of nationwide population-based screening-programs.[177] 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 EU[178]. 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. In almost every case, member states opted for gFOBT-screening. Italy selected iFOBT-screening 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) use colonoscopy while Italy uses flexible sigmoidoscopy.

Ireland to indtroduce iFOBT population based screening program from 2012

In Ireland a national colorectal cancer screening programme for men and women aged 55 to 74 is scheduled for introduction in January 2012. The program will be based on IFOBT as first line test every two years. Procurement of IFOBT kits will be completed by mid 2011. Screening colonoscopies after referrals will take place at contracted units in hospitals.[179] 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.[180]

EU guidelines for colorectal cancer screening in preparation

Comprehensive guidelines for quality assurance of colorectal cancer screening which are suitable for implementation throughout the 27 EU Member States are currently being developed in a project which is 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

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

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

179 www.cancerscreening.ie und www.cancerscreening.ie/publications/ImplementingColorectalProgramme.pdf

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

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.[181]

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.[182] 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.

Australia, Canada phase in population-based screening

Colonoscopy main screening-test in US

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 have well organized, nationwide, population-based screening-programs.

only little well organized, nationwide, population-based screening

4.9 Current CRC-screening recommendations by selected institutions

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. 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 results of local pilot programs into account.[183] The United States Preventive Services Task Force addresses the heterogeneous US-healthcare system where only the Veterans Administration runs a CRC-screening program.

institutions take different perspectives for recommendations

science-base for CRC-screening rapidly evolving

"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."[184]

181 Lecture Lawrence von Karsa, IARC
www.transatlantic-symposium.de/abstracts/lawrence-von-karsa/index.php
182 USPSTF Whitlock (2008a) p. 7
183 Health Council of the Netherlands (2009)
184 Imperiale (2010)

Screening for CRC has a rapidly evolving science base, such that guidance may be expected to change as additional research becomes available.[185] This may for instance be happening in regards to flexible sigmoidoscopy screening after the recent publications of a large randomised controlled trial in the UK[186]:

"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."[187]

Table 4.9-1: Selected CRC-screening recommendations

Institution	Date	Recommendation	Comment
Health Council of the Netherlands NL	2009	• 55-75 years • iFOBT 75 ng/ml • every 2 years	•
USPSTF US	2008	• 50-75 years • FOBT **or** • flexible sigmoidoscopy **or** • colonoscopy	• first USPSTF recommendation for CRC-screening in 1996 • current recommendations based on update of 2002 systematic review • previous USPSTF recommendations from 2002 do not give suggest upper limit of screening-age
OHTAC CAN	2009	• from 50 years • FOBT • every 2 years	•
EPAGE II international	2008	• from 50 years • colonoscopy	•

Abbreviations: CAN … Canada
EPAGE II… European Panel on the Appropriateness of Gastrointestinal Endoscopy, www.epage.ch
FOBT … faecal occult blood test
iFOBT … immunochemical faecal occult blood test
OHTAC … Ontario Health Technology Advisory Committee
ng/ml … nanogram per millilitre
NL … Netherlands
US … United States of America
USPSTF … United States Preventive Services Task Force

Source: Health Council of the Netherlands (2009), USPSTF (2008), OHTAC (2009), EPAGE II see Arditi (2008)

185 USPSTF Whitlock (2008a)
186 Atkin (2010)
187 Betthauer (2010) p. 1260

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

Criteria

Netherlands have program focus

- simplicity
- acceptance
- performance/ test characteristics
- safety

Recommendation for CRC-screening in NL

iFOBT75

- 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

every 2 years

- followed by colonoscopy in case of positive test result in outpatient clinic under sedation and with the aid of pain management

age 55-75

- targeted group: women and men aged 55-75
  - (referral to screening thereafter to be decided individually with GP)

Anticipated results from modelling

NNT: 785 iFOBTs, 40 colonoscopies

- Number needed to treat (life saved from CRC)
  - 785 people would need to complete iFOBTs
  - 40 follow-up colonoscopies

EUR 2,200.- per life year gained

- 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)

Table 4.10-1: 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
$iFOBT_{75}$ … 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: Important questions to ask about CRC-screening and program design

5.1 Why is screening different?

screening addresses healthy general population

Screening for disease is not a logical extension of ordinary medical practice. The ethical position is quite 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.[188]

balance of benefits and harms required

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

Early detection must have a positive net health benefit. Only a minority of people undergoing screening stands 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%[189] The lifetime mortality rate in the US is 2.4% for women and 3.3% for men.[190] 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.[191] 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.[192]

screening-program must meet high quality standards

screening-program must be well organized and managed

operator-dependent tests require quality focus

Given potential harms and observed variability in test accuracy, emphasis on quality standards für implementation of any operator-dependent CRC-screening test appears prudent.[193]

188 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

189 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)

190 USPSTF Whitlock (2008a)

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

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

193 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 issues still need to be dealt with when establishing an organized program:

5.2.1 Effectiveness of CRC-screening

evidence on effectiveness of CRC-screening limited

- ??? 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 once only flexible sigmoidoscopy
  - none for colonoscopy (expected in 10+ years), CT-colonography, capsule endoscopy, molecular test
- ??? evidence from screening-setting in clinical practice very limited[194], including on complications[195]- there is evidence that complications might have been underestimated[196]

optimal referral thresholds from first-line test to colonoscopy unknown

- Norway's NORCCAP is the only study (on flexible sigmoidoscopy) that is truly population based and will provide an estimate after 10 years of follow up in 2013[197]

5.2.2 Parameters relevant for CRC-screening

optimal screening-interval unknown

- ??? 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 on flexible sigmoidoscopy[198]
  - ? CT- colonography to colonoscopy

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

- ??? optimal screening-interval
  - ? iFOBT – 1 year?, 2 years?, more?
  - ? flexible sigmoidoscopy – 5 years?, more?[199]
  - ? colonoscopy[200] – 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

194 e.g. Lieberman (2009), Brenner (2010)
195 e.g. Lieberman (2009), Betthauer (2010)
196 E.g. Leffler (2010)
197 Hoff (2009)
198 USPSTF Whitlock (2008a)
199 Bretthauer (2010)
200 e.g. Brenner (2010)

longer, as subjects with negative findings at endoscopy are at very low risk for at least 20 more years[201]

- ??? iFOBT
  - ? optimal test of the many available iFOBTs[202]
  - ? optimal number of stool samples to take[203]

- ??? colonoscopy
  - there is evidence of much lower yields of proximal/ right-sided vs. distal/ left-sided CRC
    - ? causality of this difference not fully understood[204]
    - ? repercussions for decision between colonoscopy and flexible sigmoidoscopy unaddressed[205]

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

  - ? hygiene standards and adverse events (e.g. double washing of endoscopic equipment and infectious disease transmission)
- ??? screening-program level
  - general
    - ? influence divergent rates of adenoma detection might have on screening-goal of prevention of CRC unclear[206]
      - does focus on detection rate (including small adenomas) make sense?
      - there is relatively small clinical benefit of detecting and removing very small polyps[207]

influence of adenoma detection on CRC unclear

    - recommendation for screen-detected larger adenomas >10mm is clear: removal; but optimal screening-regime for dealing with smaller adenomas unclear
      - ? 6-10mm
      - ? < 6mm?

optimal screening-guideline for detected adenomas < 10mm unclear

    - ? optimal surveillance regime

optimal surveillance regime unclear

    - screening may induce lifestyle changes that might negatively affect benefit, e.g.
      - ? impact of negative polyp test on tobacco use[208]
      - ? impact of negative polyp test on dietary habits (obesity)[209]

influence of screening on lifestyle changes unclear

201 e.g. Brenner (2008)
202 e.g. Lieberman (2009)
203 e.g. Hundt (2009), Lieberman (2009)
204 e.g. Baxter (2009), Brenner (2010)
205 e.g. Baxter (2010)
206 e.g. Baxter (2010)
207 e.g. Barclay (2006)
208 e.g. Levin (2002)
209 e.g. Levin (2002)

best management of iFOBT home-testing unclear

optimal financial incentives for screening-colonoscopy unclear

optimal quality indicators for screening-colonoscopy unknown

program quality and participation rate more important than choice of first-line screening-test

- 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 important
    - dating of samples by participants does not work well
    - storage/ temperature exposure of sample before arrival at analysis not easily controllable
      - e.g. Australia (and potentially Canada) send out iFOBTs only in cooler months of the year[210]
  - ? colonoscopy
    - formulation of program-aim aligned financial incentives for examiners[211]
      - remuneration per screening-colonoscopy?
        - caveat: incentive to perform screening-colonoscopy rapidly
      - remuneration linked to yield (adenoma detected and removed)?
        - caveat: if this really contributes to aim of screening-program 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 (withdrawal time?, …)[212]

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

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

212 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 screening

Informed consent of screening-participants

- significance attached to ensuring that participation decisions can be made freely increases[213]
  - ➔ non-participation must not entail negative consequences for individuals, neither in relationship with their health insurance provider, nor with their physician[214]

no negative consequences for non-participants

- 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 test[215]
- 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 reasons[216]
  - decision-making about screening involves complex risk assessment
  - many people overestimate the benefit of screening
  - screening-providers are inclined to stress benefits and trivialize drawbacks[217]
- 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

information from program and provider independent institution

e.g. Nordic Cochrane Centre

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

214 OHTAC (2009) p. 4

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

216 National Health Committee (2003) p. 2

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

by who?
- e.g. Nordic Cochrane Centre, Copenhagen, Denmark[218]
- e.g. University of Hamburg, Fachwissenschaft Gesundheit, Germany[219]

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

choice of first-line screening test valued

- Is choice valued in itself?
  - YES: 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 colonoscopy[220]
  - possible options for choice in CRC-screening
    - FOBT or colonoscopy
    - FOBT or flexible sigmoidoscopy
  - if the results of flexible sigmoidoscopy-screening trials in England and Italy (expected later in 2010) confirm the expected mortality reductions, consideration could be given to investigating the feasibility of combining flexible sigmoidoscopy-screening with FOBT-screening and offering the choice between the two methods[221]
- 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 screening[222]

218 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

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

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

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

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

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

- 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"[223]
- 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 interval[224]

impact of screening test on participation important

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

5.3.4 Program guidelines

- 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

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

5.3.5 Quality

- 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 standard[225]
  - 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 colonoscopic polypectomy
    - ➔ the biggest risk factor for adenoma patients in relation to the development of CRC is incomplete adenoma removal[226]

quality of colonoscopy is key

223 Imperiale (2010) p. 1642

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

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

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

quality of endoscopist determines yield and complication rate

- 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

successful screening requires adequate follow-up care

- 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

quality assurance in colonoscopy …

- 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

… and down the treatment line

  - installation of reliable system to gather data on unintended consequences of screening activity (i.e. hospital stays after screening endoscopies)[227]

standardized data protocol and documentation

  - 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 evaluated[228]
    - ➔ 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
    - iFOB-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)

227 e.g. Leffler (2010)

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

5.3.6 Surveillance

- design of surveillance[229] 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 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 capacity[230]
    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

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

current surveillance regime too strict for screening-context

surveillance colonoscopy has worst benefit-harms trade-off

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 <u>not</u>: "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 and colonoscopy capacity – would be test-independent[231]

critical program evaluation also from independent outside institution

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

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

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

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

5.3.8 International and research focus

program to learn from and to inform international best practice

- program culture focusing on international best-practice
  - transparency
  - sharing knowledge
  - investing in partnership
  - learning from each other
  - (research) leadership

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

- enable program to generate new scientific evidence

… before

  - before introduction of program: setting up of smaller pilot projects generating specific national data needed for conceptualization of nationwide screening-program
    - e.g. NL[232]

… during

  - 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, these 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 randomization of the target population at the implementation phase[233]

… after

  - 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 program[234]

… roll-out of screening-program

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
  - population centers below the Canton-level
  - individual Cantons
  - all of Switzerland

232 Health Council of the Netherlands (2009)

233 e.g. Malila (2008)

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

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

6 Conclusion: Take-home message from review of literature in a nutshell

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

integration of screening, diagnosis, treatment and surveillance fosters quality

focus should be put on training and continued education of endoscopists

➔ CRC-screening is not simply about choosing the right initial test for screening

➔ effective CRC-screening is about establishing of 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 participation has a greater influence than the sensitivity of the screening-test[235]

- particularly in the context of a population-based screening-program for slowly developing abnormalities (e.g. for CRC), regular participation is likely to be more important than high test sensitivity[236]
  - ➔ study of determinants of participation rate warranted to inform program design[237]

- 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

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

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

237 e.g. Holden (2010)

7 References

(*) … 13 results from systematic literature search on Dec. 22nd 2009, see chapter 2.1

(**) … 3 results from unsystematic additional literature search on new molecular screening-tests, see chapter 2.1

(***) … 3 results from systematic literature update search on Nov. 12th 2010, see chapter 2.2

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8 Appendices

8.1 Appendix A: Systematic health technology reviews from major HTA-institutions

	Institution	Titel/ PubMed citation	Remark (in German)
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	Umfassende Behandlung der Fragestellungen zu organisiertem populationsbezogenem CRC-Screening, de facto Systematic Review
2.	**US Preventive Services Task Force**	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.PMID: 18838716	United States Preventive Services Task Force: Empfehlung
3.		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.PMID: 18838718	United States Preventive Services Task Force: Systematic Review
4.	**USPSTF**	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: gesamter Review im Umfang von 220 Seiten
5.	**US Preventive Services Task Force**	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.PMID: 18838717	United States Preventive Services Task Force: Modellierung
6.	**USPSTF**	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: Modellierung - gesamter Report im Umfang von 65 Seiten
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 Zusammenstellung (Umfang 270 Seiten) der sechs unten folgenden Reports

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 Zusammenfassung des Reviews
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. *Feca*l 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.	**CANADA HTA**	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) Kapselendoskopie
17.		Ho C, Jacobs P, Sandha G, Noorani HZ, Skidmore B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectivenes [Technology report no 60]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2006	Canadian Agency for Drugs and Technologies in Health (CADTH) Durchführung flexible Sigmoidoskopie durch Nicht-ÄrztInnen
18.	**Danish 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 Kapselendoskopie Englische Zusammenfassung des in dänischer Sprache verfassten Reports

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 Zur Bedeutung der Teilnahmerate Englische Zusammenfassung des in dänischer Sprache verfassten Reports
20.	**NHS UK**	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.	**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 Filliettaz S, Juillerat P, Gonvers JJ; EPAGE II Study Group. Endoscopy. 2009 Mar;41(3):200-8. Epub 2009 Mar 11. Review.PMID: 19280531	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 Filliettaz 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.PMID: 19280532	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 Coloretal Cancer; American Cancer Society. Am Fam Physician. 2008 Apr 1;77(7):995-1002.PMID: 18441865	U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society Consensus Guidelines
24.	**Private Institute for Clinical 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 Colonography

8.2 Appendix B: Primary literature from hand search deemed relevant

Article	Topic / question addressed (in German)
BAXTER 2009	Komplikationen von Koloskopie
BAXTER 2010	Editorial zu Effectiveness von Koloskopie Anlass: Studie über unterschiedliche Entdeckungsraten im linken (distalen) und rechten (proximalen) Kolon (BRENNER JNCI 2010)
BRENNER 2010	Studie über unterschiedliche Entdeckungsraten im linken (distalen) und rechten (proximalen) Kolon bei Koloskopie
BRENNER 2008	Wirft generell zu beachtende Fragestellungen beim Screening auf.
BRETTHAUSER 2009	Kapselendoskopie
EKELUND 2006	Kritische Fragen zu Evidenz für Screening
ELIAKIM 2006	Kapselendoskopie
ELIAKIM 2009	Kapselendoskopie
GUTIERREZ-IBARLUZEA 2008	Überblick über Screening-Aktivitäten in Europa
HAKAMA 2005	Artikel, auf den EKELUND Acta Oncologica 2006 kritisch antwortet
HAKAMA response to EKELUND 2006	Antwort auf EKELUND Acta Oncologica 2006
HEHER 2008	Nebenwirkung von oraler Koloskopievorbereitung
HOFF 2009	Sigmoidoskopie Screening
LANSDORP-VOGELAAR 2008	Wirft aus der Warte einer Koloskopie-Screening Befürworterin generell zu beachtende Fragestellungen auf.
MALILA 2008	Finnländisches Beispiel des Einbindens von Forschungsfragen in laufendes Screening-Programm
MALILA 2007	Follow-up nach 25 Jahren von finnischer Population, an FOBT Screening teilnahm
NIV 2008	Meta-Analyse israelischer Autoren
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
VAN GOSSUM 2009	Kapselendoskopie
WILKINS 2009	Meta-Analyse von Screening durch AllgemeinärztInnen