EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

STOOL DNA TESTING FOR EARLY DETECTION OF COLORECTAL CANCER

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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Five individual patients were interviewed during the assessment. This input was used as additional information for assessing the relevance of potential ethical and social aspects and for answering research questions related to patient aspects.

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All authors, co-authors, dedicated reviewers, external experts and patients involved in the production of this assessment have declared that they have no conflicts of interest in relation to the technology and comparator assessed according to the EUnetHTA declaration of interest and confidentiality undertaking (DOICU) statement form.

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LIST OF ABBREVIATIONS

5-FU/FA	5-fluorouracil/folinic acid
ACTB	Gene encoding β-actin
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
APL	Advanced precancerous lesions
BMP3	Bone Morphogenetic Protein 3
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CEA	Serum carcinoembryonic antigen
CIMP	CpG island methylator phenotype
COL	Benefit–harm modeling strategy: colonoscopy (age 50–74 years; screening interval, 10 years)
ColoAlert	Benefit–harm modeling strategy: stool DNA-based screening with ColoAlert® (age 50–74 years; screening interval, 3 years)
Cologuard	Benefit–harm modeling strategy: stool DNA-based screening with Cologuard® (age 50–74 years; screening interval, 3 years)
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
CTC	Computed tomography colonography
CTFPHC	Canadian Task Force on Preventive Health Care
CUR	'Health problem and current use of technology' domain
DEFACTUM	Social & Health Services and Labour Market
DNA	Deoxyribonucleic acid
DOICU	Declaration of interest and confidentiality undertaking
DRE	Digital rectal examination
EFF	'Clinical effectiveness' domain
EMVI	Extramural venous invasion
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
ETH	'Ethical analysis' domain
EU	European Union
FDA	US Food and Drug Administration
FIT	Fecal immunochemical test; Benefit–harm modeling strategy (age 50–74 years; screening interval, biennial)
FLOX	5-Fluorouracil + leucovorin + oxaliplatin
FOLFIRI	Folinic acid + 5-fluorouracil + irinotecan
FOLFOX	Folinic acid + fluorouracil + oxaliplatin
FOLFOXIRI	Leucovorin + 5-fluorouracil + oxaliplatin + irinotecan

FP	Fluoropyrimidine
gFOBT	Guaiac (based) fecal occult blood test
GOEG	Gesundheit Österreich GmbH
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HNPCC	Hereditary nonpolyposis colorectal cancer
hDNA	Human DNA
HTA	Health Technology Assessment
i.v.	Intravenous
IBD	Irritable bowel disease
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
iFOBT	Immunochemical (based) fecal occult blood test
IHBR	Incremental harm–benefit ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVD	*In vitro* diagnostics
JAZMP	Javna Agencija Republike Slovenije za Zdravila in Medicinske Pripomočke
KRAS	Kirsten rat sarcoma 2 viral oncogene homologue
LARC	Long-acting reversible contraceptives
LBI-HTA	Ludwig Boltzmann Institute for HTA
LEG	'Legal aspects' domain
LV	Leucovorin
LY	Life year
LYG	Life years gained
M2-PK	Pyruvate Kinase Isoenzyme Type M2
mCRC	Metastatic colorectal cancer
MeSH	Medical subject headings
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NDRG4	N-Myc Downstream Regulated Gene 4
NICE	National Institute for Health and Care Excellence
NIJZ	Nacionalni Inštitut za Javno Zdravje
NNH	Number needed to harm
NNS	Number needed to screen
NPV	Negative predictive value
No Screening	Benefit–harm modeling strategy: no screening
ORG	'Organisational aspects' domain

Osteba	Basque Office for HTA
PET	Positron emission tomography
PFS	Progression-free survival
PICO	Population–intervention–comparison–outcomes
PPV	Positive predictive value
QoL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
QuARTS	Quantitative Allele-specific Real-time Target and Signal Amplification
RRs	Higher response rates
SAF	'Safety' domain
SMDM	Society for Medical Decision Making
SOC	'Patient and social aspects' domain
TEC	'Description and technical characteristics' domain
TEM	Transanal endoscopic microsurgery
TME	Tumor immune microenvironment
TNM	Tumor–node–metastases
UICC	Union for International Cancer Control
UK	United Kingdom
UMIT	Private University of Health Sciences, Medical Informatics and Technology
USA	United States of America
USPSTF	US Preventive Services Task Force
WHO	World Health Organization
WGO	World Gastroenterology Organization
WP	Work Package
XELOX	Oxaliplatin + capecitabine

SUMMARY OF RELATIVE EFFECTIVENESS OF STOOL DNA TESTING FOR EARLY DETECTION OF COLORECTAL CANCER

Scope

The scope can be found here: Scope.

Introduction

Description of technology and comparators

Deoxyribonucleic acid (DNA) stool testing for the early detection of colorectal cancer (CRC) is a non-invasive technology that supplements the established stool tests [e.g. fecal immunochemical test (FIT) or guaiac (based) fecal occult blood test (gFOBT)] for CRC detection with the stool-based analysis of tumor DNA (B0001).

The currently CE-marked stool DNA tests in Europe are ColoAlert® (PharmGenomics) and Cologuard® (Exact Sciences). However, only ColoAlert® is sold on the European market. Both technologies are solely to be used for screening as well as prevention purposes in public health (B0001, A0020). The expected benefit of DNA stool testing is having a non-invasive screening test that is superior to gFOBT and FIT in terms of test accuracy and comparable in terms of patient compliance and can replace those tests in the screening pathway (B0002).

Given that stool DNA tests are non-invasive systems (ColoAlert®, Cologuard® as well as FIT and gFOBT), they do not require any bystander or healthcare provider interaction. Access to a toilet is necessary to collect a stool sample (B0008). For the evaluation, the samples have to be sent to a laboratory for further analysis. According to PharmGenomics, the ColoAlert® lab technology is only suitable for use by lab personnel with an appropriate academic and/or technical degree and at least 3 years of experience with polymerase chain reaction who have also attended and successfully completed PharmGenomics onsite training. For each lab system, 8 m² of lab space is needed. A separate room for the DNA extraction process is further recommended. For the use of the technology, thermocycler capillary pipettes, tips and laboratory gloves are required [1] (B0008).

The following cut-off points for stool DNA tests are established for the early detection of CRC: for Cologuard®, quantitative measurements of each marker [aberrantly methylated Bone Morphogenetic Protein 3 (*BMP3*) and N-Myc Downstream Regulated Gene 4 (*NDRG4*) promoter regions, mutant Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (*KRAS*), β-actin (*ACTB*) and FIT] were incorporated into a validated, prespecified logistic-regression algorithm, with a value of 183 or more indicating a positive multitarget stool DNA test result [2]. ColoAlert® comprises four markers: KRAS and B-Raf Proto-Oncogene, Serine/Threonine (*BRAF*) mutations, quantification of human (h)DNA and FIT. FIT is interpreted according to the manufacturer's specifications. For hDNA quantification, the positive test result cut-off concentration, as currently recommended by the manufacturer (written information from December 2018), is >1 ng hDNA per µL of total DNA extracted. The combined DNA stool assay is considered to be positive if at least one of the four markers is positive and considered to be negative if none of the four testing systems are positive (B0018).

Health problem

Development of CRC is a multistage process by which healthy normal colonocytes in colonic epithelium slowly develop into benign polyps or adenomas following genetic transformation. Over time, the further accumulation of genetic abnormalities (gene mutations, gene amplifications, etc.) and epigenetic alterations (aberrant DNA methylation, chromatin modifications, etc.) result in some polyps enlarging, eventually becoming severely dysplastic and later transforming into invasive malignancy (A0002). The estimated time interval for development from normal mucosa to adenoma to invasive adenocarcinoma is 5–10 years (A0004). Advanced adenomas are lesions ≥1 cm in size or that have high-grade dysplasia or villous elements, and have high prevalence in cancer, whereas nonadvanced adenomas have a low prevalence of cancer and a long adenoma–cancer sequence (A0004). Symptoms are common and prominent during late-stage CRC, are less common and less obvious during early stages of the disease. Common symptoms include abdominal pain, rectal bleeding, altered bowel habits and involuntary weight loss. They depend on the location and size

of the cancer, and the presence of metastases (A0002). CRC rarely results in symptoms before it has reached an advanced stage. Therefore, many patients are diagnosed when the tumor is no longer localized. Survival largely depends on tumor stage at the time of diagnosis, reaching a 5-year survival of up to 90% for localized disease, but only 10% for CRC with distant metastases (A0004).

CRC ranks third among the most commonly diagnosed cancers worldwide, affecting ~1.23 million patients each year and resulting in ~600,000 deaths annually. In developed countries, it is the second cause of cancer-related death in men and the third cause in women. CRC is also a leading cause of cancer-related deaths in Europe. In the European Union (EU), the highest incidence of CRC was reported in Germany, with 58,047 new cases for both genders and all age groups, followed by Italy, with 49,327 new cases, United Kingdom (UK) and France with just above 47,000 new cases in 2018. Most deaths were reported in Germany (27,334), followed by Italy (20,172) and UK (20,957). In Austria, the incidence amounted to 4421 and mortality to 2276, whereas, in Slovenia, the related numbers were 1987 (incidence) and 740 (mortality) (A0006).

The high incidence and associated mortality, the natural history of CRC with slow progression from a premalignant polyp to cancer, and the common lack of symptoms or presence of nonspecific symptoms, especially during the early stages of the disease, render CRC suitable for population screening. CRC screening aims to detect early-stage CRCs and precancerous lesions in asymptomatic individuals without a previous history of cancer or precancerous lesions and without a familial history of CRC; such screening would reduce the CRC incidence and mortality through the detection and removal of precancerous lesions. Methods commonly used for CRC screening include stool-based tests to detect the presence of blood or biomarkers in stool (gFOBT, FIT and multitarget-stool DNA test) and endoscopic tests, with direct optical examination of the rectum and colon [colonoscopy, computed tomographic (CT) colonography (CTC) and sigmoidoscopy] (A0024).

In general, the CRC-screening target population includes asymptomatic individuals of both genders who are at average risk and aged 50–74. Recommendations from the American Cancer Society extended the age interval to 45–85 years (qualified recommendation), but strong recommendation for regular CRC screening is only given to adults aged 50 years or older. High-risk individuals should follow high-risk protocols and are not included in regular screening programs (A0007). It was estimated that, in the 50–74-year age group of nearly 152 million women and men living in EU member states, 72% (110 million) live in the 23 Member States that have adopted at least some policies for population-based CRC screening programs (A0023).

According to European Society for Medical Oncology (ESMO) guidelines, the treatment of early CRC evolves from local excision or simple polypectomy and segmentary/wide surgical resection in Stage 0 and I CRC to wide surgical resection and anastomosis in Stage III CRC. In Stage III CRC, surgical intervention is followed by adjuvant treatment based on oxaliplatin and 5-fluorouracil (5-FU). In high-risk patients, surgery should be accompanied by adjuvant therapy already for Stage II CRC. Treatment of metastatic (m)CRC does usually not include potentially curative resection, because most patients have metastatic disease that initially is not suitable for surgical intervention. However, patients in whom metastases are suitable for resection and those with initially unresectable disease in whom metastases can become suitable for resection after a major response has been achieved with combination chemotherapy should be selected for curative resection. In patients with clearly unresectable mCRC, first-line palliative chemotherapy alone or in combination with targeted agents comprises 5-FU or oral capecitabine. Bevacizumab or aflibercept in combination with chemotherapy should be considered in patients with mCRC (A0025).

Methods

A systematic literature search was performed in Medline, Cochrane Library and EMBASE in August 2018. The search strategy was checked by co-authors and dedicated reviewers. One primary study [3] with an abstract publication from 2016 [4] was added in October 2018 when it had been published as a full-text article (being the only study on ColoAlert®). Clinical trial registries (ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform and the EU Clinical Trials Register) were assessed for registered ongoing clinical trials or observational studies; an initial search was completed by an update search in March 2019. In addition, a hand search (in reference lists of relevant studies) as well as an internet search were performed.

Manufacturers identified during the scoping phase of the project at the time of the literature search were contacted by the EUnetHTA Joint Action 3 Work Package 4 (WP4) project manager (Ludwig Boltzmann Institute for Health Technology Assessment). Only one of the two manufacturers identified gave a (positive) reply. The completed short version of the submission file was received in due time and several device-specific questions and issues [as well as queries regarding the (manufacturer-sponsored) study on ColoAlert®] that were not clear enough or missing in the first submission were clarified further via correspondence with the manufacturer.

Abstracts were screened by two of the authors independently from each other based on population–intervention–comparison–outcomes (PICO) criteria for inclusion and exclusion. All abstracts deemed relevant were ordered as full publications and selected based on the same criteria by the same two authors independently from each other, with cases of dissent being discussed between the authors. For the selection of primary studies in the effectiveness (EFF) and safety (SAF) domains, language was restricted to English or German. All relevant systematic reviews and meta-analyses were checked for additional primary studies not identified by the systematic search. In addition, all abstracts were screened for literature that might be relevant for the other domains 'Health problem and current use of the technology' (CUR) and 'Description and technical characteristics of technology' (TEC). Data extraction of the identified test accuracy studies was performed by one reviewer and checked by another. Risk of bias was assessed using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2 [5]), carried out by two authors independently of each other. Discrepancies were resolved by consensus. The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Patients were involved during the scoping phase either via telephone or face to face, using a standardized open questionnaire. Patients were identified by personal communication and via a physician's office and had to fulfill the criteria of a typical CRC screening population that has experience with DNA stool testing, occult blood testing (gFOBT or FIT) or colonoscopy. All patients signed a conflict of interest form. They did not receive any remuneration for the interview. Information from patient involvement was used (or planned to be used if available) as additional information for: (1) assessing the relevance of ethical and social aspects; and (2) answering research questions related to patient aspects (mainly assessment elements D0011-13, D0030 and D0017).

An evidence-based decision-analytic Markov state-transition cohort model of CRC was developed following a colorectal adenoma-carcinoma sequence with a lifelong time horizon to assess benefits [life years gained (LYG), reduction in CRC-related deaths and reduction of CRC incidence], harms and/or burden [complications arising from colonoscopy (physical harm), positive test results as psychological harm, false positive test results and number of colonoscopies as patient burden] and benefit–harm tradeoffs of five screening strategies: (1) 'no screening'; (2) FIT (age, 50–74 years; screening interval, biennial); (3) stool DNA-based screening with Cologuard® (age, 50–74 years; screening interval, 3 years); (4) stool DNA-based screening with ColoAlert® (age, 50–74 years; screening interval, 3 years); and (5) colonoscopy (age, 50–74 years; screening interval, 10 years).

Results

Available evidence

Three test accuracy studies that investigated Cologuard® (two studies [2,6]) and ColoAlert® (one study [3]) were identified for the EFF and SAF domains. Additionally, five patient surveys [7-11] were identified that were used to complement the results from the five patient interviews that were done for this assessment. To assess the middle and long-term benefits as well as unintended harms of stool DNA as a CRC screening test, benefit–harm modeling was applied. The aim of this decision-analytic modeling was to systematically evaluate the long-term effectiveness, risks and/or harms, and burden of CRC screening strategies with stool DNA testing, FIT and colonoscopy compared with no screening for women and men aged 50–75 years of average risk for CRC. Natural-history parameters of disease progression were based on Austrian epidemiological data, and Austrian mortality rates were applied.

Clinical effectiveness

The Cologuard® DNA stool test was compared with two FITs [OC FIT-CHEK® (Polymedco) [2] and FOB Gold® (Sentinel Diagnostics) with adjusted cut-off 17 µg hemoglobin/g faces [6]]. The combined DNA stool assay [ColoAlert® combined with a gFOBT and a hDNA quantification test (threshold 15 ng/µL)] was compared with a single gFOBT (ColoScreen-ES®, Helena Biosciences), a single tumor Pyruvate Kinase Isoenzyme Type M2 (M2-PK) test (ScheBo Biotech AG) and a combined gFOBT/M2-PK assay [3].

Cologuard® showed a sensitivity of 92.3% for the detection of CRC (compared with 73.8% and 96.7% for OC FIT-CHEK and FOB Gold, respectively) and a sensitivity of 46.4% for the detection of CRC or advanced adenoma (compared with 27.7% and 51.1% for OC FIT-CHEK and FOB Gold, respectively). These results came at a specificity of 84.4% for the detection of CRC (compared with 93.4% and 83.0% for OC FIT-CHEK and FOB Gold, respectively) and a specificity of 86.6% for the detection of CRC or advanced adenoma (compared with 94.9% and 86.5% for OC FIT-CHEK and FOB Gold, respectively). The test failure rate was higher for Cologuard® (6.25%) than for FIT (0.31%) (D1001).

ColoAlert® showed a sensitivity of 84.6% for the detection of CRC (compared with 68.0% and 82.9% for gFOBT and M2-PK, respectively) and a sensitivity of 35.5% for the detection of CRC or (all) adenoma (compared with 22.3% and 54.7% for gFOBT and M2-PK, respectively). These results came at a specificity of 87.0% for the detection of CRC (compared with 95.5% and 58.7.0% for gFOBT and M2-PK, respectively) and a specificity of 88.4% for the detection of CRC or advanced adenoma (compared with 95.8% and 60.1% for gFOBT and M2-PK, respectively). The combined test failure rate of (all) stool tests in this study was higher (17.74%) than that of the FIT test, as found in the Cologuard® study (0.31%) (D1001).

No primary studies were identified regarding the expected effect of DNA stool tests on CRC or overall mortality. Modeling yielded the following results regarding mortality outcomes: compared with ‘no screening’, a cohort of 1000 50-year-old individuals screened from age 50 to 74 is expected to experience 394 LYG with 10-yearly colonoscopy (COL), 385 LYG with 3-yearly Cologuard® (Cologuard), 365 LYG with biennial FIT (FIT) and 358 LYG with 3-yearly ColoAlert® (ColoAlert). These and the following results represent long-term results of screening strategies including index testing, further diagnostics and surveillance, and (as base case) assuming 100% adherence rates for all strategies. COL, compared with ‘No Screening’, yielded 31 averted CRC-related deaths per 1000 screened individuals, and Cologuard, FIT and ColoAlert 30, 28 and 27 averted CRC-related deaths, respectively (D0001).

No primary studies were found on how DNA stool tests modify the magnitude and frequency of morbidity. The comparative effectiveness of modeling the five CRC screening strategies yielded the following results regarding morbidity outcomes: COL, Cologuard, FIT and ColoAlert averted 62, 52, 45 and 44 CRC cases, respectively per 1000 screened individuals (D0032).

Safety

None of the primary studies reported adverse events, no primary studies reported (or were found on) user-dependent harms of DNA stool tests, and no studies were found that directly investigated the consequences of false positive or false negative test results from the viewpoint of patient safety. Results regarding short- and long-term patient safety for different screening pathways can be drawn from the benefit–harm modeling. Comparative unintended physical and potential psychological harms had been measured by the number of positive (and false positive) test results as well as by the burden of colonoscopies for individuals undergoing screening and follow-up procedures. For all strategies, the additional complications resulting from colonoscopy leading to hospitalization were low compared with ‘no screening’. A cohort of 1000 50-year-old individuals, screened from age 50 to 74, is expected to experience an additional 679 positive tests with COL compared with ‘no screening’. Compared with COL, FIT leads to a similar number of additional positive tests (n=675) compared with ‘no screening’, whereas ColoAlert leads to 824 and Cologuard to over 1000 additional positive test results (n=1003). The expected additional total number of colonoscopies compared with to ‘no screening’, including index testing, further diagnostics and surveillance, are 2777 with COL, 1292 with Cologuard, 904 with FIT and 1053 with ColoAlert (C0007 and C0008).

Benefit–harm analysis

The benefit–harm analysis represents the tradeoffs between benefits and harms and/or burden for the individual undergoing screening, expressed as incremental harm–benefit ratios. On average in the population, moving from 'no screening' to biennial FIT had an expected incremental burden of two additional colonoscopies per LYG. Moving from FIT to Cologuard had an incremental burden of 19 additional colonoscopies per LYG. Moving from Cologuard to COL had an incremental burden of 167 additional colonoscopies per LYG. ColoAlert was dominated by biennial FIT; that is, it provides less health benefit (life years; LY) at higher harm and/or burden (number of colonoscopies). To avoid one CRC-related death with 3-yearly Cologuard compared with biennial FIT screening, there is an expected incremental burden of additional 208 colonoscopies. To avoid one CRC-related death with 10-yearly COL compared with 3-yearly Cologuard, there is an expected incremental burden of an additional 1235 colonoscopies. Considering the tradeoff between the potential psychological harm of positive test results versus the benefit of CRC death averted, all stool tests were dominated.

Organisational aspects

Regarding the (physical) point of care, access to many stool tests is not necessarily restricted to visiting a doctor, because most stool tests can also be ordered via the Internet or bought from a pharmacy. However, Cologuard® is available by prescription only [12,13].

The stool tests are administered by the user at home and specimens (mostly) have to be sent to a laboratory for analysis. Laboratories have to be specialized for the required analysis. Currently, two laboratories (in Germany) are qualified for analyzing ColoAlert® (Cologuard® is not currently available on the European market) [1]. Colonoscopy is restricted to visiting a specialized center, hospital or similar institution (G0001).

An increased usage of DNA stool testing will result in a higher demand for laboratories that have the relevant knowledge and experience. Moreover, the (diagnostic and surveillance) colonoscopy rate might change. As can be seen from the benefit–harm modeling, a screening strategy incorporating a 3-yearly stool DNA test overall leads to a higher expected number of colonoscopies per screenee (for the remaining life time) than a screening strategy incorporating biennial FIT (D0023).

Upcoming evidence

Six ongoing observational studies were identified, four on Cologuard® (ClinicalTrials.gov) and two on assays described as 'Stool multi-target DNA and microRNA-135b (combined)' and 'DNA methylation biomarkers' (Chinese Clinical Trial Registry). The latter two entries were unclear as to the estimated completion date. The four studies on Cologuard® report completion dates between March 2019 and May 2023. Three of them are focusing on an average-risk population, one being a subpopulation study of one of the other two. The fourth is being done in average-risk subjects 45–49 years of age. All four compare to colonoscopy as the reference standard and none include additional screening comparators. Included endpoints in the biggest of the Cologuard®-studies, with >2000 participants, involve test accuracy (also for repeat tests), CRC incidence, adherence and/or compliance issues, and test failure rate; another study includes test accuracy for advanced adenomas, compliance and feasibility and one study focusses on confirming the test specificity in 45–49-year-olds.

Reimbursement

Stool DNA testing currently is not reimbursed in European countries.

Table 0.1. Summary of findings table of the test accuracy of stool DNA testing (Cologuard®) versus FIT

Test result	Number of results per 1000 persons tested				Number of participants (studies)	Certainty of Evidence (GRADE)
	Stool DNA testing	FIT	Stool DNA testing	FIT		
Prevalence (CRC) 0.65% [2]			Prevalence (CRC) 0.86% [6]			
TP (patients with CRC)	6	5–6	8	6–8	95 (2)	⊕⊕⊕◯ MODERATE*
FN (patients incorrectly classified as not having CRC)	1	1–2	1	1–3		
TN (patients without CRC)	839	824–*928*	837	823–926	13,388 (2)	⊕⊕⊕⊕ HIGH
FP (patients incorrectly classified as having CRC)	155	66–170	154	65–168		
Prevalence (CRC + APL) 8.23% [2]			Prevalence (CRC + APL) 11.13% [6]			
TP (patients with CRC or APL)	38	23–42	52	31– 57	1211 (2)	⊕⊕⊕◯ MODERATE*
FN (patients incorrectly classified as not having CRC or APL)	44	40– 59	59	54– 80		
TN (patients without CRC or APL)	795	794– 871	770	769– 843	12,272 (2)	⊕⊕⊕⊕ HIGH
FP (patients incorrectly classified as having CRC or APL)	123	47– 124	119	46– 120		

CRC: sensitivity stool DNA testing, 0.92; specificity stool DNA testing, 0.84; range of sensitivities FIT, 0.74–0.97; range of specificities FIT, 0.93–0.83.

CRC or APL: sensitivity stool DNA testing, 0.46; specificity stool DNA testing, 0.87;, range of sensitivities FIT, 0.28–0.51; range of specificities FIT, 0.95–0.86.

*Moderate because of serious inconsistency in FIT results.

Abbreviations: APL=advanced precancerous lesions; CRC=colorectal cancer; FIT=Fecal immunochemical test; FN=false negative; FP=false positive; TN=true negative; TP=true positive.

Sources: Imperiale *et al.* [2], Brenner *et al.* [6].

Table 0.2: Summary of findings table of the test accuracy of stool DNA testing (ColoAlert®) versus gFOBT, M2-PK or gFOBT + M2-PK

Test result	Number of results per 1000 persons tested								Number of participants (studies)	Certainty of Evidence (GRADE)
	Stool DNA testing	gFOBT	M2-PK	gFOBT + M2-PK	Stool DNA testing	gFOBT	M2-PK	gFOBT + M2-PK		
	Prevalence (CRC) 0.65% [2]				Prevalence (CRC) 0.86% [6]					
TP (patients with CRC)	5 (5–6)	4 (3–5)	5 (4–6)	6 (5–6)	7 (6–8)	6 (5–7)	7 (6–8)	8 (7–8)	52 (1)	⊕◯◯◯ VERY LOW**
FN (patients incorrectly classified as not having CRC)	2 (1–2)	3 (2–4)	2 (1–3)	1 (1–2)	2 (1–3)	3 (2–4)	2 (1–3)	1 (1–2)		
TN (patients without CRC)	864 (831–893)	949 (926–966)	583 (535–630)	589 (543–634)	863 (829–891)	947 (924–964)	582 (534–629)	588 (542–633)	469 (1)	⊕⊕◯◯ LOW***
FP (patients incorrectly classified as having CRC)	130 (101–163)	45 (28–68)	411 (364–459)	405 (360–451)	128 (100–162)	44 (27–67)	409 (362–457)	403 (358–449)		
	Prevalence (CRC + adenoma*) 37.19% [2]				Prevalence (CRC + adenoma*) 10.78% [6]					
TP (patients with CRC or adenoma*)	132 (106–159)	83 (61–108)	203 (173–233)	207 (179–234)	38 (31–46)	24 (18–31)	59 (50–67)	60 (52–68)	186 (1)	⊕◯◯◯ VERY LOW**
FN (patients incorrectly classified as not having CRC or adenoma*)	240 (213–266)	289 (264–311)	169 (139–199)	165 (138–193)	70 (62–77)	84 (77–90)	49 (41–58)	48 (40–56)		
TN (patients without CRC or adenoma*)	555 (530–575)	602 (585–614)	377 (342–411)	377 (342–410)	789 (753–817)	855 (831–872)	536 (485–584)	535 (486–583)	335 (1)	⊕⊕◯◯ LOW***

Test result	Number of results per 1000 persons tested								Number of participants (studies)	Certainty of Evidence (GRADE)
	Stool DNA testing	gFOBT	M2-PK	gFOBT + M2-PK	Stool DNA testing	gFOBT	M2-PK	gFOBT + M2-PK		
FP (patients incorrectly classified as having CRC or adenoma*)	73 (53–98)	26 (14–43)	251 (217–286)	251 (218–286)	103 (75–139)	37 (20–61)	356 (308–407)	357 (309–406)		

CRC: sensitivity stool DNA testing, 0.85 (95% CI, 0.72–0.93); specificity stool DNA testing, 0.87 (95% CI, 0.84–0.90); sensitivity gFOBT, 0.68 (95% CI, 0.53–0.81); specificity gFOBT, 0.95 (95% CI, 0.93–0.97); sensitivity M2-PK, 0.83 (95% CI, 0.68–0.93); specificity M2-PK, 0.59 (95% CI, 0.54–0.63); sensitivity gFOBT+ M2-PK, 0.90 (95% CI, 0.79–0.97); specificity gFOBT+ M2-PK, 0.59 (95% CI, 0.55–0.64).

CRC or (advanced or nonadvanced) adenoma: sensitivity stool DNA testing, 0.35 (95% CI, 0.29–0.43); specificity stool DNA testing, 0.88 (95% CI, 0.84–0.92); sensitivity gFOBT, 0.22 (95% CI, 0.17–0.29); specificity gFOBT, 0.96 (95% CI, 0.93–0.98); sensitivity M2-PK, 0.55 (95% CI, 0.47–0.63); specificity M2-PK, 0.60 (95% CI, 0.54–0.66); sensitivity gFOBT+ M2-PK, 0.56 (95% CI, 0.48–0.63); specificity gFOBT+ M2-PK, 0.60 (95% CI, 0.55–0.65).

*Includes advanced and nonadvanced adenoma; **very low because of serious risk of bias and serious concerns about indirectness and about imprecision; ***low because of serious risk of bias and serious concerns about indirectness.

Abbreviations: CRC=colorectal cancer, gFOBT=Guaiac (based) fecal occult blood test, FN=false negative, FP=false positive, TN=true negative, TP=true positive.

Source: Dollinger *et al.* [3].

Discussion

The two CE-marked DNA stool tests represent products in a series of research developments that consistently try to find new and improved markers and analytical algorithms for the detection of CRC and precancerous lesions by the way of a non-invasive screening test. ColoAlert® is the most recent product, being authorized in 2016 and is of specific interest in the context of this assessment because it is the only DNA stool test currently sold on the European market. No European screening programs currently include DNA stool testing [14] and neither is it reimbursed. Most screening programs in Europe include colonoscopy, FIT and/or gFOBT, starting between the age of 50 and 60 up until the age of 70 to 75.

Given disease progression and prognosis, the main target for triage screening tests such as stool tests is to yield a positive test result in patients with advanced adenomas or CRC. It can be discussed whether the tests also should, preferably, yield a positive result (and, thus, reference to colonoscopy) in cases of nonadvanced adenomas. Therefore, the test accuracy of CRC screening tests (against the reference standard) cannot be reduced to one value for sensitivity and one value for specificity; neither is there clear guidance about which value is the 'right' one and at which of the many possible cut-offs screenees should be confronted with a positive test result and referred to colonoscopy. The importance of reliably ruling out CRC is without discussion, the same applies to advanced adenomas, because they can be removed by polypectomy, which should lead to shorter surveillance intervals thereafter. It applies to a lesser extent to nonadvanced adenomas. However, differentiation between these two groups of adenoma could not be made (directly) for the results of ColoAlert®, because advanced and nonadvanced adenomas were not reported separately in the study. In addition, the tradeoff between sensitivity and specificity is related to whether patients with nonadvanced adenomas should be seen immediately (and the adenoma possibly removed) under colonoscopy or should 'wait for later detection'. Lastly, test failure rates are a relevant issue for judging test accuracy. Stool tests might not be submitted by the screenee or might be unevaluable or unusable. It can be argued that, in the real world, a second specimen can or would be collected, although this is of course associated with increased time effort and potential costs.

Quality of the evidence for test accuracy results is mixed. The ColoAlert®-study was deemed to have a high risk of bias. Moreover, the currently available product differs in several components from the product that was evaluated in this study.

Given that both of the stool DNA tests have only been on the market for a few years, studies on their long-term effects on mortality and morbidity were not to be expected. In addition, no major adverse events or direct user-dependent harms were to be expected. By contrast, the consequences of false positive and false negative test results are of concern. Undetected (especially advanced) adenomas might progress further and false positive results lead to 'unnecessary' colonoscopies. In addition, all positive results lead to immediate worry and all tests, namely colonoscopies, imply some kind of immediate burden to the screenee. A specific strength of the decision-analytic modeling done for this assessment was that benefits, harms and burden over a lifelong time horizon were evaluated based on the natural history of the disease, including surveillance, capturing stage shifts and incorporating survival probabilities. In the benefit–harm analysis, tradeoffs between LYGs and CRC deaths averted on the benefit side, and the number of positive tests as well as the number of colonoscopies on the harm/burden side of the screening strategies were investigated.

Limitations

The incorporation of patient views into the assessment was limited by the difficulty of finding patients with stool DNA test experience. Results of patient surveys in the literature not only were heterogeneous and outside a European context, but mostly also referred to a precursor test of Cologuard®. Another limitation with regard to test accuracy results was the small number of available studies for the CE-marked products.

As with all model-based analyses, there are several limitations regarding the modeling: First, mortality information and epidemiological calibration target values for the distribution of cancer stages were based on the Austrian population. Second, perfect adherence to screening was assumed in the base-case analysis, including follow-up and surveillance tests to show the maximum achievable benefit for each strategy from the screenee/patient perspective. Therefore, benefits, harms and burden resulting from the screening strategies in the base-case analysis are overestimated and represent upper limits. The impact of adherence rates was tested in sensitivity analyses with varying adherence rates. Third, it was assumed that the test accuracies of consecutive annual fecal blood tests are independent conditional on disease because of limited evidence. The sensitivity of colonoscopy was assumed to be independent of previous tests. Fourth, some model input data were reported in a format in the literature that had to be transformed to be applied in the model. Fifth, reported sensitivities of FITs vary considerably depending on FIT brand and applied thresholds. For consistency reasons, sensitivity and specificity of the FIT were based on a recent clinical trial on 9989 patients reporting test results of FIT and Cologuard® using for both tests OC FIT-CHEK®. Sixth, an average number of lesions was used to model expected number of lesions, the onset of adenomas was age dependent, but the progression of adenomas was not age specific.

Conclusion

Stool DNA testing with Cologuard® showed higher sensitivity for the detection of CRC and advanced adenoma than FIT, but lower specificity. However, the results depended to a degree on the exact type of FIT used. The test failure rate was higher for Cologuard® than for FIT. Stool DNA testing with ColoAlert® (although referring to a former version of the product) had higher sensitivity for the detection of CRC and adenoma compared with gFOBT, but lower specificity. Sensitivity was comparable to M2-PK, whereas specificity was higher. The combined test failure rate of all three stool tests in this study was higher than that of FIT (as seen in the Cologuard® study [2]). There was no direct evidence of the test accuracy for only advanced adenoma and no information on the exact proportion of test failures in the DNA assay alone compared with the other stool tests. Overall, the certainty of evidence is moderate to high for Cologuard® results (two studies, both referring to the same Cologuard® study population) and low to very low for ColoAlert® results (one study).

Decision-analytic modeling enabled the assessment of comparative long-term screenee-/patient-relevant benefits, harms and burden and the benefit–harm balance of stool DNA testing, FIT and colonoscopy in a screening program. Based on this decision analysis, 10-yearly colonoscopy is the most effective strategy, but also leads to the greatest burden for the screenee because of colonoscopies. Three-yearly ColoAlert was dominated in the benefit–harm analysis. The choice between 10-yearly COL, 3-yearly Cologuard and biannual FIT depends on how much additional burden resulting from colonoscopies one is willing to accept to gain one additional LY or to avert one additional CRC death. Results were sensitive to screening adherence rates.

Stool DNA testing showed a promising benefit–harm balance when different screening strategies were compared, but is only currently relevant to Cologuard®. By contrast, ColoAlert® is the only stool DNA test currently sold in Europe and is available at a lower cost than Cologuard®. In addition, a high degree of uncertainty surrounds the evidence on ColoAlert®. A cross-sectional screening study including the current product version and FIT as well as gFOBT as comparators could shed light on these issues. In terms of the comparator tests, especially FIT, it would be desirable to carefully select one, or even more than one, different brand(s) as comparators and provide some rationale for those choices.

With regard to screening strategies, future research is recommended to assess further strategies including the effect of different screening intervals and (individualized) combinations of strategies and the impact of different thresholds for FIT. In addition, in country-specific cost-effectiveness and

budget-impact analyses, economic outcomes should be considered to support decision making by healthcare payers.

1 SCOPE

Table 1.1. Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project scope
Population	**Screening population:** asymptomatic, predominantly healthy persons aged 45 years or older, who do not belong to a high-risk group for the development of CRC. According to European (p. 285 ff.) and German Guidelines (p. 45 ff.), high-risk groups for the development of CRC include: people with a family history of CRC (one first-degree relative under 60 years of age or two first-degree relatives aged 60 years or more), people who are (proven or potential) carriers for hereditary CRC (e.g. Lynch syndrome, familial adenomatous polyposis or hereditary nonpolyposis CRC), people found to have five colorectal adenomas, and patients with inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis). **Screening for CRC and precancerous lesions** According to International Classification of Disease (ICD)-10 (WHO, Version 2016): C18: Malignant neoplasm of colon D01: Carcinoma *in situ* of other and unspecified digestive organs D01.0: Colon D01.2: Rectum D12: Benign neoplasm of colon and rectum D12.0: Caecum D12.2: Ascending colon D12.3: Transverse colon, including hepatic and splenic flexures D12.4: Descending colon D12.5: Sigmoid colon D12.6: Colon, unspecified; including adenomatosis of colon, large intestine not otherwise specified, polyposis (hereditary) of colon K63.5: Polyp of colon, including serrated polyps (sessile serrated adenoma and traditional serrated adenoma); excluding adenomatous polyp of colon (D12.6) and polyposis of colon (D12.6, see above) **Rationale:** Screening for CRC is recommended for asymptomatic persons aged: • 50–74 years by European Guidelines [15] • 50 or older by the German S3-Leitlinie [16] • 45–85 (maximum range, given as 'qualified recommendations') by the American Cancer Society Guideline for CRC Screening [17]
Intervention	Stool tests for the detection of altered DNA from cancerous and precancerous lesions of the colonic mucosa (also in addition to occult blood testing). The following tests were identified (both of which use a combination of DNA analysis and FIT for occult blood testing): • ColoAlert® (PharmGenomics) is a technology that supplements the established occult blood test (FIT) through stool samples for CRC with the analysis of tumor DNA. With the help of ColoAlert®, hDNA is extracted and analyzed for *KRAS* and *BRAF* mutations to detect tumor tissues, CRC and early lesions. • The Cologuard® DNA test (Exact Sciences) includes quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3*

Description	Project scope
	methylation, and *ACTB*, plus a hemoglobin immunoassay. Given that the hemoglobin immunoassay is essentially a FIT test, Cologuard® is a combination of gene mutation, methylation and occult blood tests. The multitarget stool DNA test provides various detecting technologies to detect CRC and early colorectal lesions.
Comparison	• Colonoscopy (which also is the reference standard for test accuracy studies) • (Flexible) Sigmoidoscopy • gFOBT • FIT • M2-PK test • *SEPTIN9* test • CT colonography **Rationale:** European Guidelines [15] as well as German S3-Leitlinie [16] recommend colonoscopy, flexible sigmoidoscopy, FIT and gFOBT as tests for CRC screening. European Guidelines and German S3-Leitlinie mention, but do not (explicitly) recommend, CT colonography, stool DNA tests, capsule endoscopy, and M2 pyruvate kinase stool test (M2-PK) as tests for CRC screening. In addition, *SEPTIN9* test is CE marked and available in (at least one) EU member state(s).
Outcomes	**Effectiveness** • sensitivity for CRC • sensitivity for precancerous lesions • specificity for CRC • specificity for precancerous lesions • positive predictive value • negative predictive value • CRC incidence • CRC mortality • overall mortality • number needed to screen (NNS) to detect CRC • NNS to detect advanced adenoma **Safety** • false negative rate for CRC and/or precancerous lesions • false positive rate for CRC and/or precancerous lesions • psychological harms from false negative and false positive test results • number needed to harm (NNH) **Other outcomes** • test performance: test failure rate • test performance: uncertain results rate • health-related quality of life

Description	Project scope
	• handling problems carrying out the test and/or taking the specimen • patient adherence (patient preference) • cost of test (intervention) **Rationale:** the intervention assessed is DNA stool testing CRC screening (i.e. adenocarcinoma) and/or for (advanced and nonadvanced) precancerous lesions. Grading and/or classification of precancerous lesions according to, for example, European Guidelines (2010), or WHO (Classification of Tumours Pathology and Genetics of Tumours of the Digestive System, 2010, 4th edition), or WHO ICD-10 Version 2016.
Study design	EFF: diagnostic accuracy studies, randomized controlled trials, prospective controlled studies, systematic reviews, and meta-analyses SAF: randomized controlled trials, prospective studies with or without a control group, qualitative studies for the psychological harm outcome, systematic reviews, and meta-analyses Other outcomes: qualitative studies, such as patient surveys

Abbreviations: BRAF=B-Raf; CRC=colorectal cancer; CT=computed tomography; DNA=deoxyribonucleic acid; EFF= 'Clinical effectiveness' domain; FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test; ICD=International Classification of Diseases; *KRAS*=Kirsten Rat Sarcoma 2 Viral Oncogene Homolog; M2-PK=Pyruvate Kinase Isoenzyme Type M2; SAF='Safety' domain.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The tasks were assigned to the agencies as follows:

Austrian Public Health Institute (GOEG) (Author)

- overall responsibility for the production and quality of report;
- first author of TEC, EFF and SAF; check CUR.

National Institute of Public Health (NIJZ) and Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) (Co-Authors)

- support production of report and check all steps;
- first author of CUR; check TEC, EFF and SAF.

Private University of Health Sciences, Medical Informatics and Technology (UMIT) (Co-Authors)

- benefit–harm modeling for answering research questions (EFF and SAF) for which no primary evidence was available.

National Institute for Health and Care Excellence (NICE), National Agency for Regional Health Services (AGENAS), Social & Health Services and Labour Market (DEFACTUM), Basque Office for Health Technology Assessments (HTA) (Osteba) (Dedicated Reviewers)

- thorough check of draft project plan and first draft report, including studies and results.

Slovenian Ministry of Health Observer Slovenia (observer).

2.2 Source of assessment elements

The selection of assessment elements was based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 [18]. Additional elements were added, if applicable, from the HTA Core Model® Version 3.0 [19], Application for Screening Technologies.

2.3 Search

A systematic literature search was performed in Medline (23/8/2018), the Cochrane Library as well as EMBASE (both 27/8/2018) based on a search strategy including relevant medical subject heading (MeSH) terms (e.g. colorectal neoplasms, early detection of cancer) and keywords (e.g. stool DNA testing, ColoAlert). The search strategy was checked by co-authors and dedicated reviewers. No restrictions were made to the systematic search strategy with regard to language, study design or year. The search yielded 645 hits in Medline, 152 hits in the Cochrane Library and 96 hits in EMBASE. After deduplication, 736 hits remained. One primary study [3] with an abstract publication from 2016 [4] was added in October 2018 when it was published as a full-text article (being the only study on ColoAlert®).

The following clinical trial registries were assessed for registered ongoing clinical trials or observational studies: ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (WHO ICTRP); and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). An initial search was completed by an update search in March 2019, which revealed six ongoing studies (although the status of two of them was unclear).

Detailed tables on the search strategies can be found in Appendix 1.

In addition, a hand search (in reference lists of relevant studies) as well as an internet search (of the manufacturers' and other relevant websites, via search engines for specific information needed for TEC or CUR research questions) was performed. One additional study was retrieved for the EFF domain and 35 articles and information sources (reviews, guidelines, book chapters, etc.) were added for the CUR and TEC domains.

Manufacturers identified during the scoping phase of the project at the time of the search were contacted by the EUnetHTA Joint Action 3 WP4 project manager (Ludwig Boltzmann Institute for Health Technology Assessment). Only one of the two manufacturers identified gave a (positive) reply. The short version of the submission file was sent to this manufacturer (PharmGenomics) by the EUnetHTA JA3 WP4 project manager on 19th April 2018. The completed submission file was received in time and several device-specific questions and issues that were not clear enough or missing in the first submission were clarified further following correspondence with the manufacturer. This correspondence was also used for queries regarding the (manufacturer-sponsored) study on ColoAlert® published in October 2018. Information was also checked via an internet hand search. Information from the submission file mainly was used for the TEC domain.

2.4 Study selection

The 736 abstracts identified in the systematic literature search were selected as being 'relevant' or 'not relevant' (for the EFF and SAF domain) based on the criteria for inclusion and exclusion defined in Table 2.1 by two of the authors independently from each other. All abstracts deemed relevant (n=53; Figure 1) were ordered as full publications and selected based on the same criteria by the same two authors independently from each other. Cases of dissent (in both steps) were discussed between the authors. Inclusion and exclusion of full-text articles additionally were checked by co-authors. No restrictions were made in the systematic search strategy with regard to language. However, for the selection of primary studies in the EFF and SAF domains, language was restricted to English or German. All relevant systematic reviews and meta-analyses where checked for additional primary studies not identified by the systematic search.

All abstracts were additionally screened for literature that might be relevant for the background CUR and TEC domains as well as the preselected ORG research questions (not shown in Figure 1).

Table 2.1. Selection criteria

Criteria for inclusion of studies	
P	Screening population as defined in Table 1.1
I	Stool DNA test as defined in Table 1.1
C	Comparator as defined in Table 1.1
O1	EFF outcomes as defined in Table 1.1
O2	SAF outcomes as defined in Table 1.1
O3	Other outcomes as defined in Table 1.1
S1	EFF study designs as defined in Table 1.1
S2	SAF study designs as defined in Table 1.1
F	Full publication available
L	Language English or German

Criteria for inclusion of studies	
Criteria for exclusion of studies	
D	Duplicates*

*Duplicates might remain after automatic deduplication that have to be identified manually.

Abbreviations: DNA=deoxyribonucleic acid; EFF='Clinical effectiveness' domain; SAF='Safety' domain.

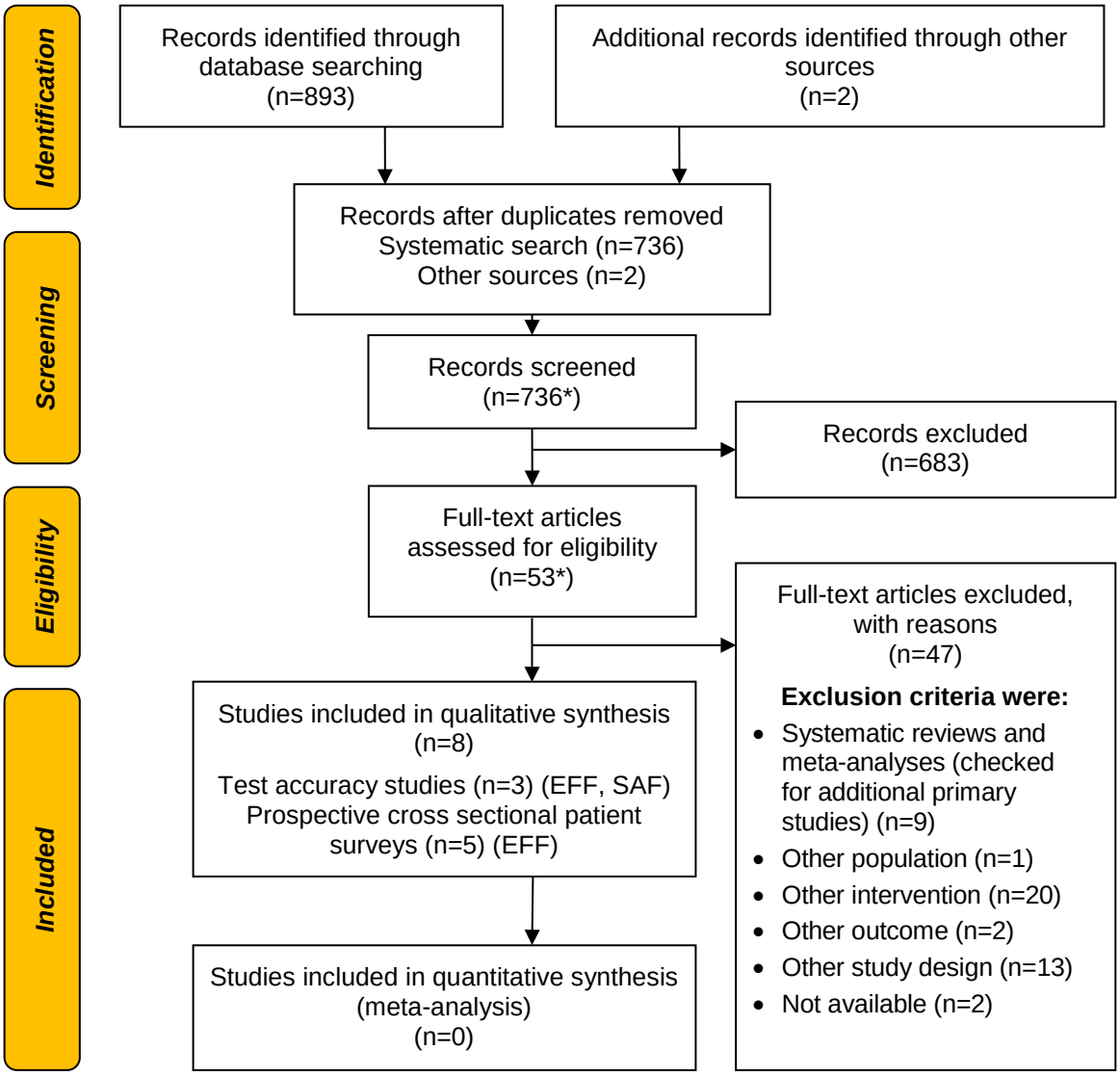


Figure 1. Flow chart of study selection process

* Excluding studies added through other sources.

2.5 Data extraction and analyses

The following characteristics and results (if available) of the identified test accuracy studies were extracted in evidence tables by one reviewer and checked by another:

- Study characteristics (study objective, country/ies of recruitment, setting, data collection period, study design, sponsoring, conflict of interest);

- Participant/patient characteristics [number of patients enrolled (age, gender), number of evaluable patients, number of test failures, patient eligibility criteria, characteristics of evaluable and nonevaluable group];
- Intervention and comparator characteristics [diagnostic test (index test) and cut-off, comparator test(s) and cut off, reference standard and type of quality assurance];
- Outcomes (results regarding the predefined outcomes, see section 1).

Detailed data extraction tables are reported in Appendix 1. Queries to the study sponsor were made for missing data in one of the test accuracy studies; details of which can be found in Appendix 4.

Given the limited number of studies and the heterogeneity, especially regarding the population and reported test accuracy outcomes, no further quantitative synthesis (meta-analysis) was done.

2.6 Quality rating

Test accuracy studies were assessed using QUADAS-2 [5], which comprises four key domains: patient selection, index test(s), reference standard and 'flow and timing' [i.e. flow of patients through the study and timing of the index test(s) and reference standard]. Each domain is assessed with regard to risk of bias and applicability concerns (except 'flow and timing', for which only risk of bias is assessed). The QUADAS-2 assessment was carried out by two authors independently of each other. Discrepancies were resolved by consensus.

The quality of the body of evidence was assessed using GRADE.

2.7 Patient involvement

Patients were involved during the scoping phase either via telephone or face to face, using a standardized open questionnaire (see also Appendix 4). This was deemed to be the most suitable way of involvement with regard to the number and location of patients. Patients were identified by personal communication and via a physician's office (general practitioner). They had to fulfill the criteria of a typical CRC screening population (asymptomatic persons aged according to national screening recommendations) who have experience with DNA stool testing, occult blood testing (gFOBT or FIT) or colonoscopy. All patients signed a conflict of interest form. They did not receive any remuneration for the interview. Information from patient involvement was used (or planned to be used if available) as additional information for: (1) assessing the relevance of ethical and social aspects; and (2) answering research questions related to patient aspects (mainly assessment elements D0011-13, D0030 and D0017).

2.8 Description of the evidence used

Three test accuracy studies were identified for the EFF and SAF domains. Additionally, five patient surveys were identified that were used to complement the results from the five patient interviews that were done for this assessment (see Section 2.7).

In the absence of trial-based data on middle- and long-term benefits as well as unintended harms of stool DNA as a CRC screening test, benefit-harm modeling was applied to simulate these longer-term outcomes. Evidence-based decision-analytic modeling studies are applied to evaluate a range of tests and technologies to detect adenomas and CRC in a screening setting [20-24]. Modeling studies allow for the evaluation of screening strategies before they are implemented. Key aspects, including screening intervals, starting age, or follow-up, can be assessed within one model synthesizing information on the natural history of the disease from different sources, including cancer registries, test characteristics from clinical trials or effectiveness of treatment options [25] The aim of the decision-analytic modeling in this assessment was to systematically evaluate the long-term effectiveness, risks and/or harms, and burden of CRC screening strategies with stool DNA testing, FIT and colonoscopy compared with no screening for average-risk women and men aged 50–75 years. Natural-history parameters for the progression of the disease were based on Austrian epidemiological data determined by Statistics Austria and model calibration. Austrian mortality rates were applied for: (i) age-specific mortality from other causes; and (ii) CRC-specific mortality rates.

For the TEC domain, the manufacturer submission file [1] was the main source of information regarding ColoAlert®, accompanied by (narrative) reviews and information from relevant websites. For the CUR domain, several guidelines, reviews and articles were used. In addition, a survey among EUnetHTA partners was done regarding the state of CRC screening and reimbursement in their countries. To answer the questions in the ORG domain, results from the other domains as well as from an internet search were used, accompanied by information from the manufacturer submission file.

In Table 2.2–Table 2.4, the primary evidence used for the EFF and SAF domain is described in more detail. Details for the methods of the benefit–harm modeling can be found in Section 2.9.

Table 2.2. Main characteristics of test accuracy studies included for EFF and SAF

Author, year	Study type	No. of patients fully evaluated (No. of patients enrolled)	Intervention(s)	Main endpoints
Imperiale *et al.*, 2014	Prospective screening cross-sectional study	9989 (12,776)	• Screening colonoscopy • Multitarget stool DNA test (Cologuard®, includes molecular assays for mutations in *BMP3*, *NDRG4*, *KRAS*, β-actin, and a FIT for human hemoglobin) • FIT (OC FIT-CHEK®, Polymedco)	Test accuracy data (sensitivity and specificity) for stool DNA test and FIT regarding CRC, (advanced and nonadvanced) precancerous lesions, non-neoplastic findings, and negative findings in screening colonoscopy
Brenner *et al.*, 2017	Prospective screening cohort study	3494 (4203)	• Screening colonoscopy • FIT (FOB Gold®; Sentinel Diagnostics)	Diagnostic performance of FIT regarding CRC, (advanced and nonadvanced) precancerous lesions, and negative findings in screening colonoscopy. Indirect comparison to reported performance of stool DNA test (Imperiale *et al.* 2014)
Dollinger *et al.*, 2018	Preclinical case cohort study	521 (734)	• Colonoscopy (screening of elective, e.g. in context of planned polypectomy) • Combined DNA stool assay (ColoAlert®, includes molecular assays for mutations in *KRAS* and *BRAF*, quantification of hDNA, and a gFOBT) • gFOBT (ColoScreen-ES®, Helena Biosciences) • M2-PK assay (ScheBo Biotech AG)	Test accuracy data for DNA stool assay, gFOBT and M2-PK assay regarding CRC, adenoma, hyperplastic polyps and negative findings in colonoscopy

Abbreviations: CRC=Colorectal cancer; FIT=fecal immunochemical test; gFOBT=guaiac fecal occult blood testing; hDNA, human deoxyribose nucleic acid; USA=United States of America.

Sources: Imperiale *et al.* 2014 [2], Brenner *et al.* 2017 [6] and Dollinger *et al.* 2018 [3].

Table 2.3. Patient surveys

Author, year	Title	Country	Design, year(s) of study recruitment	Tests	Number of responders (response rate)	Characteristics of respondents
Schroy *et al.*, 2005	Patient perceptions of stool-based DNA testing for colorectal cancer screening	USA	Prospective cross-sectional survey alongside a multicenter trial, August 2001–March 2003	PreGen-Plus® gFOBT, colonoscopy	4042 (84%)	Asymptomatic, mostly average-risk subjects after undergoing stool tests and colonoscopy Age: >50 years 57.2% female 89.3% white, 10.7% nonwhite
Berger *et al.*, 2006	Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests	USA	Prospective cross-sectional survey, provided with every collection kit distributed, August 2003–July 2004	PreGen-Plus®	1211 (18%)	Patients undergoing stool-based DNA testing* Age: 92% ≥50 years, Gender not reported Race not reported
Schroy *et al.*, 2007	Patient preferences for colorectal cancer screening: how does stool DNA testing fare?	USA	Prospective cross-sectional survey, September 2002–August 2003	PreGen-Plus® FOBT, colonoscopy	263 (100%**)	Asymptomatic, average-risk individuals with no previous CRC screening, except FOBT (48.7%) Age: 50–75 years 62.4% female 57.8% white, 35% black, 7.3% other
Calderwood *et al.*, 2011	Patient and provider preferences for colorectal cancer screening: how does CT colonography compare to other modalities?	USA	Prospective cross-sectional survey, October 2008–February 2010	PreGen-Plus® gFOBT, CT colonoscopy, colonoscopy	100	Asymptomatic patients with no previous endoscopic or radiological CRC screening Age: 50–75 years 37% female 19% white, 73% black, 8% other

Author, year	Title	Country	Design, year(s) of study recruitment	Tests	Number of responders (response rate)	Characteristics of respondents
Abola *et al.*, 2015	Stool DNA-based versus colonoscopy-based colorectal cancer screening: patient perceptions and preferences	USA	Prospective cross-sectional survey, year of study recruitment not reported	Cologuard®, FIT, colonoscopy	423	Patients referred for a screening colonoscopy Age: ≥30 and ≤80 years 63.6% female 67.1% Caucasian, 30.0% African-American, 2.8% other Previous screening experience not explicitly reported

*Survey provided with every distributed kit; **Not clear.

Abbreviations: FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test; USA=United States of America.

Sources: Schroy *et al.* [11], Berger *et al.* [9], Schroy *et al.* [8], Calderwood *et al.* [10], Abola *et al.* [7].

Table 2.4. Patient interviews done within the assessment

Number	Age	Gender	Screening-experience
1	65	Female	Colonoscopy, FIT
2	56	Male	Colonoscopy, gFOBT, FIT, stool DNA test
3	57	Female	FIT
4	60	Male	gFOBT, colonoscopy
5	57	Female	gFOBT, colonoscopy

Abbreviations: FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test.

2.9 Methods of the benefit–harm modeling

An evidence-based decision-analytic Markov state-transition cohort model [25-27]_ENREF_6 of CRC was developed to inform the EUnetHTA assessment on long-term comparative effectiveness, risks and/or burden and harms of CRC screening strategies and the related tradeoffs. The design of the model followed international guidelines and recommendations for decision-analytic modeling, such as the guidelines of the Joint Task Force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) [26-29], international key principles for HTA [30], reporting guidelines (CHEERS) [31] and the EUnetHTA Guideline for Health Economic Evaluations [32]._ENREF_10 External clinical experts provided clinical guidance.

Model description

In the decision-analytic model (Figure 2), a hypothetical healthy cohort of individuals with average CRC risk was followed. The natural history, that is, the description of health states without screening, assumed the occurrence and growth of adenomas, progression to advanced adenomas and progression to cancer. Advanced adenomas were defined as 'adenoma with villous histology or high-grade dysplasia or ≥10 mm in size' [33]. Preclinical (i.e. undiagnosed) cancers can progress from Stage I to Stage IV based on the Union for International Cancer Control (UICC) classification. Any cancer can be diagnosed by symptoms at any stage. In the model, individuals with adenomas were considered to have an average number of lesions. Gender and anatomical location of the adenoma and age-specific progression of adenomas were not explicitly modeled. Given that regression of adenoma is rare with limited evidence from literature [34], adenomas did not regress in the model.

Individuals found to have cancer in a specific stage remained in the 'health state' determined after the cancer diagnosis for their remaining lifetime. Cancer state-specific survival rates determined CRC death, and all-cause mortality was modeled according to Austrian life tables (see Appendix 4, Benefit–Harm Modeling).

Evaluated screening strategies that include surveillance can alter the risk of cancer progression and survival probability because of the removal of adenomas before they become malignant or because of early detection (with potential removal) of cancer. Incidental detection of asymptomatic disease was not considered in the model. Therefore, adenomas can only be detected by screening.

The analysis considers major adverse effects from colonoscopy (confirmatory or screening) leading to hospitalization or death. Given that symptomatic patients receive confirmatory colonoscopy, they also face the risk of adverse events. For confirmatory colonoscopies in symptomatic patients, false negative results were assumed to be negligible for our evaluation.

A state-transition cohort (Markov) decision-analytic model was chosen because the course of disease of CRC follows several well-defined histological and clinical states, repeated screening events are required and time-to-event is important (e.g. disease progression). A cohort analysis was chosen because the number of health states is manageable [26,27].

The CRC model was programmed and validated using the decision-analytic software package TreeAge Pro 2017 [TreeAge Software Inc., Williamstown, MA, United States of America (USA)].

Screening population and strategies

The implemented screening strategies include surveillance and are based on the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis [35], recommendations of the European Society of Gastrointestinal Endoscopy (ESGE) [33], the Austrian guidelines [36] and expert advice.

Five screening strategies are considered: (1) no screening; (2) FIT (age, 50–74 years; screening interval, biennial); (3) stool DNA testing using Cologuard® (Cologuard) (age, 50–74 years; screening interval, 3 years); (4) stool DNA testing using ColoAlert® (ColoAlert) (age, 50–74 years; screening interval, 3 years); and (5) colonoscopy (COL) (age, 50–74 years; screening interval, 10 years).

After a positive stool test in screening strategies 2–4 (FIT, Cologuard, and ColoAlert), individuals undergo diagnostic colonoscopy. Colonoscopy (either diagnostic or screening colonoscopy) can detect: (1) CRC; (2) one or more advanced adenomas; (3) nonadvanced adenomas; or (4) findings are negative. Patients with detected CRC do not enter the regular screening program again. Individuals with identified advanced adenomas continue screening after removal by polypectomy and start 3-yearly surveillance with colonoscopy. If an advanced adenoma (again) is found in the surveillance colonoscopy (and removed by polypectomy), patients continue with the 3-yearly surveillance. If only nonadvanced or no adenomas are found in the surveillance colonoscopy, individuals enter a 5-yearly surveillance. Five-yearly surveillance is continued as long as no advanced adenomas are detected. A detection of advanced adenomas again leads to the shorter 3-yearly surveillance. Individuals with detected nonadvanced adenomas continue with colonoscopy every 10 years after removal of the adenoma by polypectomy. Surveillance examinations are considered in all strategies until the age of 74.

In the No Screening strategy, CRC can be detected only by symptoms. Adenomas cannot be detected. There are no incidental findings or opportunistic screening tests considered in this strategy. No Screening serves as a comparator to show the full potential impact of other screening strategies.

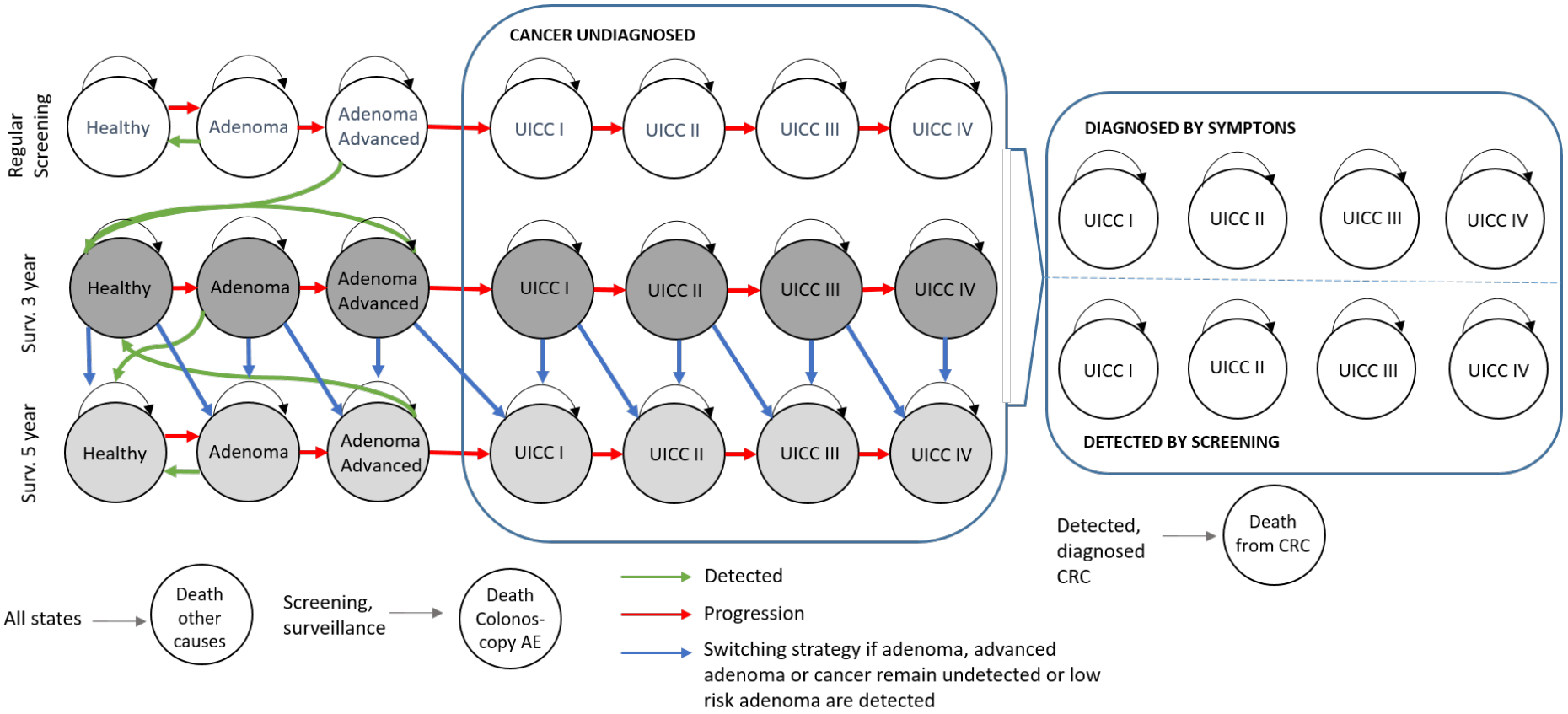


Figure 2. Colorectal cancer state-transition cohort model for screening evaluation

Abbreviations: AE=adverse effects; CRC = colorectal cancer; regular=regular screening; surv. 3 year=3-yearly surveillance; surv. 5 year=5-yearly surveillance; UICC=Union for International Cancer Control classification.

All individuals start in the healthy state with regular screening. Health states are represented by bubbles and annual transitions between health states are represented by arrows. Individuals can develop adenomas. These adenomas (nonadvanced and advanced) can be detected by screening, be removed and individuals move back to the healthy state. If nonadvanced adenomas are detected in the regular screening (i.e. according to the screening strategy), individuals will continue with screening using colonoscopy independent from the originally evaluated screening test. The detection and removal of advanced adenomas leads to 3-yearly surveillance starting in the healthy state. After detecting nonadvanced or no adenoma in the 3-yearly surveillance screening, individuals continue in the 5-yearly-surveillance program. Undetected adenomas can progress to advanced adenomas and cancer. Any cancer can be diagnosed at any stage by symptoms or screening. Individuals with diagnosed or detected CRC might die as a result of CRC. Individuals in any health state might die from other causes according to the age- and sex-specific mortality in Austria.

Model parameters

Natural-history parameters for the progression of the disease were based on Austrian epidemiological data determined by Statistics Austria [37] and model calibration. Further information is reported in the Appendix (see Appendix 4, Benefit–Harm Modeling).

Austrian mortality rates were applied for: (1) age-specific mortality from other causes; and (2) CRC-specific mortality rates. Age-specific mortality from other causes ('background' mortality) was derived from life tables for the year 2016 from Statistics Austria [38]. Mortality rates for age groups over 100 years were extrapolated applying an exponential distribution. CRC-specific mortality (post diagnosis) was derived from Statistics Austria (2010–2014), extrapolated and adjusted for screening and symptom detection [37] applying published hazard ratios between these two modes of detection for different cancer stages [39] (see Appendix 4, Benefit–Harm Modeling).

Information on screening test accuracy parameter values was based on the published evidence (see Appendix 4, Benefit–Harm Modeling, for details as well as the results of test accuracy in section 5.2). For Cologuard®, sensitivity and specificity were extracted from a study in which the test included a FIT (OC FIT-CHEK®) [2,40]. The sensitivity and specificity of FIT was obtained from the same study applying OC FIT-CHEK® [2] For ColoAlert®, sensitivity and specificity were extracted from a study in which the test included a gFOBT (ColoScreen-ES®) and a threshold of 15 ng/µL for hDNA was applied [41]. The sensitivity of nonadvanced and advanced adenomas was recalculated from the sensitivity for all adenomas (of 16.4% and assuming the distribution of nonadvanced and advanced adenomas seen in the Cologuard®-study [2]; 79% and 21%, respectively).

The sensitivity of colonoscopy for CRC (94.7%) was obtained from a meta-analysis including trials where CT colonoscopy was compared with optical colonoscopy (49 studies; 11,151 patients) [42]. The specificity of colonoscopy for adenomas and for CRC was assumed to be 100% according to the National Cancer Institute, Cancer Intervention and Surveillance Modeling Network [43] and further sources [44].

In the case of confirmatory colonoscopy, it was assumed that test accuracy after a positive stool test result was independent of this result.

Model analyses and outcomes

At the age of 20 years, individuals can start developing one or more adenomas according to their age-specific risk. The risk is low at age 20 and rises more quickly around the age of 50. The screening strategies were evaluated starting at the age of 50, in line with current screening guidelines (see 'Screening population and strategies' above). The Markov model had a cycle length of 1 year, simulating individuals until death. Half-cycle correction was used at the start and termination of the model. In the base-case analysis, perfect adherence to screening strategies including follow-up and surveillance tests was assumed to provide a strict comparison of the intended strategies without dilution by nonadherence. The impact of acceptance of, and adherence to, different screening strategies was assessed in the sensitivity analyses.

Analyses

The model was used to perform three sets of analyses including all screening strategies: (1) comparative effectiveness analysis describing the comparisons of patient-relevant benefits only; (2) comparative harm and burden analysis describing the comparisons of patient-relevant harms and burdens only; and (3) benefit–harm analysis focusing on the tradeoffs between the benefits of the different screening strategies on the one hand and the respective harm or burden on the other hand. It is the benefit–harm analysis that supports decision-making under uncertainty incorporating screenee-/patient-relevant tradeoffs between the different screening options [25]. For each of the three sets of analyses, screenee-/patient-relevant outcomes were defined a priori by the clinical expert team to be reported (see next section).

Outcomes

Benefits of the compared screening strategies were measured by screenee-/patient-relevant outcomes related to mortality (remaining LY gained, CRC-related deaths averted, and CRC cases averted).

Screenee-/Patient-relevant harms and burden were measured by:

- outcomes related to physical harm (complications resulting from colonoscopy leading to hospital admissions);
- outcomes resulting in potential psychological harm (positive or false positive results);
- overall number of colonoscopies, which in itself can be seen as a burden to screenees/patients.

Positive results included the initial screening test (stool tests or colonoscopy) or surveillance tests and did not include follow-up colonoscopy after positive stool tests.

For the comparative effectiveness of all five CRC screening strategies, additional benefits in comparison to 'no screening' of a cohort of 1000 individuals were calculated (i.e. remaining LYG, CRC-related deaths averted, and CRC cases averted). Similarly, additional burden and harms (see above) were calculated compared with 'no screening', also considering a cohort of 1000 individuals.

The benefit–harm analysis represents the tradeoffs between benefits and harms for the individual undergoing screening. The results of the benefit–harm analysis were expressed as incremental harm–benefit ratios (IHBR). To include the different dimensions (outcomes) of benefits, harms and burden relevant to the screenee/patient in the assessment, four IHBR were considered. The first IHBR was expressed as additional physical burden for the screenee/patient because of additional colonoscopies divided by LYG. Thus, this IHBR expresses the additional (incremental) burden of undergone colonoscopies that one has to take to gain one additional (incremental) LY when using one strategy compared with another. Similarly, the second IHBR contrasted the physical burden of colonoscopies against the benefit of reduced CRC-related mortality. Thus, additional colonoscopies were divided by the number of averted CRC-related deaths, yielding the number of additional colonoscopies per one CRC-related death averted. For the third and the fourth IHBRs, additional positive test results were divided by LYG and CRC-deaths averted, respectively.

Strategies were considered dominated if they provided less health benefit at higher harm and/or burden compared with any other strategy. Therefore, dominated strategies should not be considered by decision makers, they were eliminated from the pool of 'optimal choices', and no IHBR and no stepwise increments were calculated because there was no tradeoff to assess. Furthermore, extended dominance was applied to eliminate strategies for which burden, harm and benefits were dominated by a combination of two other alternatives.

Discounting was not applied because only screenee-/patient-relevant tradeoffs were considered.

Sensitivity analysis

Analyses were conducted in one-way deterministic sensitivity analyses on crucial input parameters and assumptions regarding test accuracy and adherence rates (for detailed explanations, see Section 7).

The decision-analytic model and the results were validated internally and externally according to ISPOR-SMDM Good Modelling Practice recommendations [45,46] for: (1) face validity; (2) internal validity, including, for example, debugging, consistency and plausibility checks; and (3) external validity for cumulative cancer mortality at age 75 from Statistics Austria [37] and data from the literature (see Appendix 4, Benefit–Harm Modeling).

2.10 Deviations from project plan

The systematic literature search only revealed (cross-sectional) test accuracy studies. For assessing middle and long-term benefits and unintended harms (taking into account also uncertainty), it was decided to apply a benefit–harm modeling. This had been foreseen in the project plan only as a potential option to be decided during the assessment phase.

Following a comment from dedicated reviewers, qualitative studies (e.g. patient surveys) were added as study design for 'other outcomes' in the Scope (PICO). These were included during study selection but had not been explicitly mentioned previously in the Scope.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is the test and the comparator(s)? What are the relevant features?
A0020	For which indications has the test received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the test in relation to the comparator(s)?
B0003	What is the phase of development and implementation of the test (and, if applicable, comparator tests)?
B0004	Who administers the test and the comparator(s) and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the test (and, if applicable, comparator tests)?
B0009	What equipment and supplies are needed to use the test (and, if applicable, comparator tests)?
B0018	Are reference values or cut-off points clearly established for the test?
B0012	What kind of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology?

3.2 Results

Features of the technology and comparators

[B0001] What is the test and the comparator(s)? What are the relevant features?

The stool DNA test for the early detection of CRC is a non-invasive technology that supplements established stool tests (e.g. FIT or gFOBT) for CRC detection with the stool-based analysis of tumor DNA.

Product overview

There are many types of test used to diagnose CRC. Colonoscopy visualizes the entire bowel with a complete evaluation of the gastrointestinal tract and is considered to be the gold standard with a complete diagnostic assessment. On the downside, it is an invasive procedure, as is flexible sigmoidoscopy. There are also several non-invasive technologies on the market that are used for early detection of CRC and can be used within a screening strategy. Further information on the different methods used for screening as well as diagnosis of CRC can be found in A0024 of the CUR domain. Table 3.1 provides an overview of the relevant features of the intervention and main comparators.

Table 3.1. Features of the intervention and comparators

Technology		Name of test	invasive (yes=✓, no=x)	main features
Endoscopic examinations	Colonoscopy	–	✓	Direct visual examination of entire colon and rectum with removal of polyps
	Flexible Sigmoidoscopy	–	✓	Visual examination of rectum and lower third of colon by insertion of a flexible tube into colon
Guaiac fecal occult blood test (gFOBT)		Miscellaneous	x	Detection of pseudoperoxidase activity of heme component of hemoglobin
Fecal immunochemical test (FIT)		Miscellaneous	x	Detection of presence of globin by immunochemical reactions
Stool DNA test + FIT		Cologuard® (Exact Sciences)	x	Detection of aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, *ACTB* (reference gene for hDNA quantity), FIT
		ColoAlert ® (PharmGenomics)	x	Mutant *KRAS*, mutant *BRAF*, quantification of hDNA, FIT
Methylated *SEPTIN9*		Epi proColon 2.0® (Epigenomics)	x	Detection of aberrantly methylated DNA of v2 region of *Septin9*
M2-PK		e.g. Schebo®	x	Detection of specific tumor enzyme M2-PK

Abbreviations: BMP3=bone morphogenetic protein 3; hDNA=human deoxyribonucleic acid; M2-PK=pyruvate kinase isoenzyme type M2; NDRG4=N-myc downstream regulated gene 4; KRAS=Kirsten rat sarcoma 2 viral oncogene homolog.
Source: Phalguni *et al.* [47].

Relevant features in detail: stool DNA tests and non-invasive comparators

Currently, there are two CE-marked stool DNA tests available in Europe, ColoAlert® (PharmGenomics) and Cologuard® (Exact Sciences). Only ColoAlert® is sold on the European market [1].

ColoAlert®

The technology combines a FIT-Test with a method to detect three molecular genetic markers: mutations in *KRAS* and *BRAF*, and quantification of hDNA. hDNA is extracted from the stool and analyzed for *KRAS* and *BRAF* mutations to detect tumor tissues, CRC and early lesions. Furthermore, a FIT test is performed, in which proteins are also extracted and tested for the presence of globin by immunochemical reactions.

The stool DNA test sample collection kit from ColoAlert® mainly comprises two CE-*in vitro* diagnostics (IVD)-certified components: (1) PSP® Spin Stool DNA Kit (by Stratec Molecular GmbH) for isolation of DNA from stool, including a DNA stabilization buffer; and (2) immunodiagnostic IDK Extract, which includes a hemoglobin stabilization buffer (Figure 3). Patients take two small samples out of one bowel movement and send them via the included shipping solution to PharmGenomic's lab in Mainz, Germany.

The complete product (patient kit) set, which as a whole also has a CE mark, further includes the following elements:

- Patient brochure (Figure 3);
- Packaging solution: used for sample shipment to the laboratory (Figure 3);
- Illustrated Instruction for Use (IFU);
- Order form;
- Paper stool collection aid;
- Zip pouch with absorption fleece.

Figure 3. The ColoAlert® kit

Source: Submission file by manufacturer [1].

Two product types of ColoAlert® are available from the manufacturer's online shop (https://coloalert.de/12-online-shop): 'ColoAlert Basic' with a price of €119.95 and 'ColoAlert Plus' (including, according to the manufacturer's website, determination of hemoglobin/haptoglobin complex) costing €169.95.

***Cologuard*®**

Cologuard® is available on the USA market and is approved by the US Food and Drug Administration (FDA). Furthermore, it is CE marked [48,49]. The test is reimbursed by Medicare. The patient stool samples are processed in laboratories to isolate the DNA for testing and for detection of fecal occult hemoglobin. Amplification and detection of methylated target DNA (*NDRG4* and *BMP3*), *KRAS* point mutations and *ACTB* is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology. Multiplexed QuARTS reactions are processed using a real-time cycler with each biomarker (*NDRG4*, *BMP3*, *KRAS* and *ACTB*) monitored separately through independent fluorescent detection channels [50].

Cologuard® currently is available at a cost of US$649 (www.cologuardtest.com/faq/cost), which converts to ~€580 (as of 6 May 2019, www.ecb.europa.eu/stats/policy_and_exchange_rates/euro_reference_exchange_rates/html/index.en.html).

The Cologuard®-patient kit comprises the following elements (Figure 4):

- an instruction booklet in English and Spanish;
- a sample collection container;
- a support bracket that rests on the toilet;
- a fecal hemoglobin sample tube;
- a bu ffer solu tion for DNA stabilization during sample transport;
- a prepaid return shipping label.

Figure 4. The Cologuard® kit

Source: Parks *et al.* 2018 [51].

gFOBT

The guaiac (based) fecal occult blood test or gFOBT is a screening method that has been used for ~40 years. Most chemical gFOBTs make use of guaiac gum, which is extracted from the hardwood tree *Guaiacum officinale*. 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 heme, a component of hemoglobin common to all species. The test is not specific for human blood and can generate false positive and false negative results because of peroxidase reactions (and their inhibitors) in food products, such as red meat. The low sensitivity of gFOBT means that two samples must be collected from each of three consecutive stools, giving six samples in total [52].

FIT

The immunochemical fecal occult blood test or FIT is a more recent test method that involves the immunological analysis of fecal samples for occult blood (also called iFOBT). These tests are specific for human blood. Analysis of quantitative FIT testing can be automated, thus increasing quality control and reducing cost. However, there is microflora 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 [52].

Methylated SEPTIN9

SEPTIN-9 is a protein that in humans is encoded by *SEPTIN9*, which has been shown to be methylated in CRC tissue compared with normal colonic mucosa. Methylated *SEPTIN9* tests, such as the Epi proColon 2.0 CE by Epigenomics, detect methylated *SEPTIN9* from blood-derived DNA. The test has been available since 2009 but is not yet reimbursed [53].

M2-PK

M2-PK is a synonym for the dimeric form of the pyruvate kinase isoenzyme type M2 (PKM2), a key enzyme within tumor metabolism. In CRC, tumor M2-PK is also excreted in the intestinal lumen

and, therefore, is detectable in the stool, which enables the utilization of a stool test such as the Schebo® M2-PK™ Stool test [54].

[A0020] For which indications has the test received marketing authorisation or CE marking?

According to the manufacturer, ColoAlert® is solely to be used for screening as well as prevention purposes in public health. ColoAlert® should not be used by patients with known irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) disorders [1]. Cologuard® has a CE mark as a non-invasive DNA CRC screening test [48].

[B0002] What is the claimed benefit of the test in relation to the comparator(s)?

Although colonoscopy is seen as the 'gold standard' in CRC screening, there is a need for non-invasive screening alternatives because colonoscopy participation rates often are not seen as sufficient. Generally, the expected benefit of DNA stool testing is having a non-invasive screening test that is superior to gFOBT and FIT in terms of test accuracy and comparable in terms of patient compliance, thus enabling it to replace gFOBT and FIT in the screening pathway.

[B0003] What is the phase of development and implementation of the test (and, if applicable, comparator tests)?

The stool DNA test technology is authorized for use in all countries that accept CE-IVD certifications, meaning all current 28 EU member countries [1]. There are several FIT and gFOBT technologies that are CE marked on the market. Currently, stool DNA tests are not part of screening strategies in Europe (see also Section A0021). Cologuard® in the USA is used within a screening program for CRC reimbursed by Medicare.

[B0004] Who administers the test and the comparator(s) and in what context and level of care are they provided?

As a screening measure for a nonrisk population, ColoAlert® is part of the screening process. A positive test result leads to an affirmative colonoscopy, which, in case of the presence of CRC, regularly leads to an immediate polypectomy if possible. The stool DNA test is usually administered by the patient/screenee and can be done at home. The same applies to Cologuard®, FIT and gFOBT. However, Cologuard® is only available by prescription through a healthcare provider [12,13], whereas ColoAlert® does not require a prescription.

[B0008] What kind of special premises are needed to use the test (and, if applicable, comparator tests)?

Strictly speaking, the ColoAlert® and Cologuard® systems do not require any bystander or healthcare provider interaction. For collecting a stool sample, access to a toilet is necessary and, therefore, the characteristics of the toilet (washout WC pan versus washdown WC pan) are of relevance. To compensate for washdown WC pans, both tests enclose a stool sample collector.

[B0009] What equipment and supplies are needed to use the test (and, if applicable, comparator tests)?

For the evaluation of ColoAlert® and Cologuard®, the samples have to be sent to a laboratory for analysis. Cologuard ® requires packaging of a complete stool sample, whereas ColoAlert® only requires two sample tubes to be shipped. The ColoAlert® lab technology, according to the manufacturer, is only suitable for lab personnel with an appropriate academic and/or technical degree and at least 3 years of experience with polymerase chain reaction who have attended and successfully completed PharmGenomics onsite training. In terms of the lab system, 8 m² of lab space is needed. A separate room for the DNA extraction process is further recommended. For the use of the technology, thermocycler capillaries pipettes, tips and laboratory gloves are required [1]. For Cologuard®, no detailed information regarding laboratory requirements is available.

[B0018] Are reference values or cut-off points clearly established for the test?

For Cologuard®, quantitative measurements of each marker (aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, *ACTB* and FIT) were incorporated into a validated, pre-specified logistic-regression algorithm, with a value of 183 or more indicating a positive multitarget stool DNA test result [2].

ColoAlert® comprises four markers (*KRAS* and *BRAF* mutations, quantification of hDNA and FIT). FIT is interpreted according to the manufacturer's specifications. For hDNA quantification, the positive test result cut-off concentration, as currently recommended by the manufacturer (written information from December 2018), is >1 ng of hDNA per µL of total DNA extracted. The combined DNA stool assay is considered to be positive if at least one of the four markers is positive and considered to be negative if none of the four testing systems is positive.

[B0012] What kind of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology?

For the evaluation of ColoAlert®, a qualified laboratory with trained personnel is required for quality assurance. For this reason, the ColoAlert® test is currently being evaluated (only) in two laboratories in Germany to maintain a high level of standards. Information regarding the requirements for Cologuard® evaluation is not available.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is colorectal cancer (CRC)?
A0003	What are the risk factors for CRC?
A0004	What is the natural course of CRC?
A0005	What are the symptoms and burden of CRC for the patient?
A0006	What are the consequences of CRC for the society?
A0024	How is CRC currently diagnosed according to published guidelines and in practice?
A0025	How is CRC currently managed according to published guidelines and in practice?
A0007	What is the target population for the test?
A0021	What is the reimbursement status of the test?
A0023	How many people belong to the target population?
A0011	How much are currently available tests utilized?
D1003	What is the reference standard and how likely is it to classify CRC correctly?

4.2 Results

Overview of the disease or health condition

[A0002] What is colorectal cancer (CRC)?

CRC is a multistage process by which healthy colonic epithelium slowly develops into polyps or adenomas and progresses over time into carcinomas [55,56]. It is the second most commonly diagnosed cancer in females and the third in males worldwide [57]. CRC is also a leading cause of cancer-related deaths in Europe. It is particularly suited to population screening because of a long premalignant phase and high population prevalence of premalignant lesions [58].

CRC arises in pre-existing benign polyps following genetic transformations in normal colonocytes. With time, further accumulation of genetic abnormalities (gene mutations, gene amplifications, etc.) and epigenetic alterations (aberrant DNA methylation, chromatin modifications, etc.) results in some polyps enlarging, eventually becoming severely dysplastic and later transforming into invasive malignancy. This highlights the significance of the removal of colorectal polyps during colonoscopy, which is considered to be a first-line tool in effectively reducing CRC mortality as well as in screening CRC in asymptomatic populations [59-61].

Colon cancers are classified as well differentiated, moderately well differentiated, or poorly differentiated on the degree of preservation of normal glandular architecture and cytologic features. Poor differentiation is a histological marker of further underlying genetic mutations, but the mutations associated with poor differentiation are currently unknown. Approximately 20% of CRCs are poorly differentiated with poor prognosis, whereas ~15% of CRCs are classified as mucinous or colloid because of the prominent intracellular accumulation of mucin. These cancers are very aggressive [62].

Approximately 65% of CRCs are distal to the splenic flexure and potentially detectable by sigmoidoscopy. By contrast, ~35% of CRCs are proximal to the sigmoid and not detectable by flexible sigmoidoscopy. CRC can occur in a pedunculated polyp, sessile polyp, mass or stricture. Small polyps rarely contain cancer given that only ~1% of diminutive polyps contain cancer. Cancer in a sessile polyp can metastasize faster than cancer in a pedunculated polyp because of the closer proximity of lymphatic drainage [62].

Carcinoma *in situ*, or high-grade dysplasia, is histologically cancer but is pathologically confined to the mucosa without penetration of the muscularis mucosa. Invasive CRC is commonly staged from A through D according to the Dukes classification, with stage A penetrating beyond the colonic muscularis mucosa into the submucosa. Stage B1 extends beyond the submucosa into the muscularis propria; stage B2 extends through the muscularis propria into the serosa. Stage C has regional lymph node metastases, and stage D has distant metastases. CRC was also recently staged according to the tumor–node–metastases (TNM) classification by mural depth of the primary tumor (T), by the presence of local lymph node metastases (N), and by the presence of distant metastases (M). This classification is particularly helpful in endosonographic staging of CRC. In the TNM classification, invasive CRC is classified from Stage I to IV. Stage I in the TNM classification corresponds to Dukes A or B1 lesions, Stage II corresponds to a Dukes B2 lesion, Stage III corresponds to a Dukes C lesion, and Stage IV corresponds to a Dukes D lesion. Pathological stage, as classified by either scheme, is correlated with cancer prognosis. Diagnostic delays result in a more advanced pathological stage at diagnosis [62].

In the USA, ~20–25% of patients initially present with Dukes D colon cancer with identifiable metastases. Another 30% of patients have no detectable metastases preoperatively or intraoperatively, but eventually succumb to CRC after surgery. The most common sites of gross metastases are the regional lymph nodes and liver. The lungs, peritoneum, pelvis and adrenals are less-common sites. These sites typically become involved only after hepatic or lymphatic metastases occur [62].

Late in CRC, when the prognosis is poor, symptoms are common and prominent, but are less common and less obvious early in disease. Common symptoms include abdominal pain, rectal bleeding, altered bowel habits and involuntary weight loss. They depend on cancer location and size and the presence of metastases. Left colonic cancers are more likely to cause partial or complete intestinal obstruction than are right colon cancers because the left colonic lumen is narrower and the stool in the left colon tends to be better formed because of reabsorption of water in the proximal colon. Large exophytic cancers are also more likely to obstruct the colonic lumen. Partial obstruction results in constipation, nausea, abdominal distention and abdominal pain. Partial obstruction sometimes paradoxically produces intermittent diarrhea as stool moves beyond the obstruction. Advanced cancer, particularly with metastasis, can cause cancer cachexia, characterized by a symptomatic tetrad of involuntary weight loss, anorexia, muscle weakness and a feeling of poor health [62].

According to the ICD-11 (2018 version) CRC is classified as:

- 2B90.0Y: other specified malignant neoplasm of ascending colon or right flexure of colon;
- 2B90.0Z: malignant neoplasm of ascending colon or right flexure of colon, unspecified;
- 2B90.1Y: other specified malignant neoplasm of descending colon or splenic flexure of colon;
- 2B90.1Z: malignant neoplasm of descending colon or splenic flexure of colon, unspecified;
- 2B90.2Y: other specified malignant neoplasm of transverse colon;
- 2B90.2Z: malignant neoplasm of transverse colon, unspecified;
- 2B90.3Y: other specified malignant neoplasm of sigmoid colon;
- 2B90.3Z: malignant neoplasm of sigmoid colon, unspecified;
- 2B90.Z: malignant neoplasms of colon, unspecified;
- 2B91.Z: malignant neoplasms of rectosigmoid junction, unspecified;
- 2D85: malignant neoplasm metastasis in large intestine.

The above codes were adopted from https://icd.who.int/ct11_2018/icd11_mms/en/release#/ on 7 December, 2018.

[A0003] What are the known risk factors for CRC?

There are numerous factors that are thought to influence risk for CRC. Non-modifiable risk factors include: older age, certain demographic subgroups, environmental factor (prevalence is increased in developed countries and urban areas), male gender, a personal or family history of CRC or adenomatous polyps, and a personal history of chronic inflammatory bowel disease. Modifiable risk factors that have been associated with an increased risk of CRC in epidemiological studies include physical inactivity, obesity, diabetes, high consumption of red or processed meats, smoking, vitamin D deficiency and moderate-to-heavy alcohol consumption [63-72].

The most important risk factor for CRC is older age. Most cases of CRC occur among adults older than 50 years, and the median age at diagnosis is 68 years. The age at which screening and surveillance can be stopped remains controversial. The risk of CRC increases with age, but so does the risk of complications through colonoscopy. Overall, the life expectancy benefits of CRC prevention diminish in older patients. A recent cost-effectiveness analysis suggested that screening with colonoscopy was indicated up to an age of 83 years, sigmoidoscopy was indicated up to 84, and FIT up to 85 and 86 years. In unscreened persons with moderate comorbid conditions, screening was cost-effective up to an age of 83 years (80 for colonoscopy, 81 for sigmoidoscopy, and 82–83 for FIT). By contrast, in unscreened persons with severe comorbid conditions, screening was cost-effective up to age 80 years (colonoscopy indicated up to age 77 years, sigmoidoscopy at age 78 years, and FIT at 79–80 years) [73].

The risk for CRC is also influenced by numerous behavior-related factors, including consumption of processed meats, consumption of alcoholic beverages, tobacco smoking and excess body fat. By contrast, consumption of dietary fiber and dairy products and increased levels of physical activity decrease the risk. In addition, certain subgroups of the population are at increased risk owing to genetic predisposition (e.g., Lynch syndrome), a family or personal history of colorectal neoplasia or certain medical conditions (e.g. inflammatory bowel disease) that have been associated with CRC [71].

CRC incidence and mortality rates are highest in African-American men and women; incidence rates are 20% higher and mortality rates are ~45% higher than those in Caucasians. High rates also have been reported for some American Indian groups and Alaska Natives. African-American adults have the highest incidence and mortality rates compared with other racial/ethnic subgroups. The reasons for these disparities are not clear. Studies have documented inequalities in screening, diagnostic follow-up and treatment; they also suggest that equal treatment generally appears to result in equal outcomes. Accordingly, this recommendation applies to all racial and/or ethnic groups, with the clear acknowledgment that efforts are needed to ensure that at-risk populations receive recommended screening, follow-up and treatment [65,74].

Incidence and mortality rates of CRC are ~35–40% higher in men than in women. The reasons for this are not completely understood but likely reflect complex interactions between gender-related differences in exposure to hormones and risk factors [65].

A positive family history (excluding known inherited familial syndromes) is thought to be linked to ~20% of cases of CRC. Approximately 3–10% of the population has a first-degree relative with CRC. People with a first-degree relative (parent, sibling or offspring) who has had CRC have two to three times the risk of developing the disease compared with individuals with no family history; if the relative was diagnosed at a young age or if there is more than one affected relative, risk increases to three to six times that of the general population. Moreover, ~5% of patients with CRC have a well-defined genetic syndrome that causes the disease. The most common of these is Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC), which accounts for 2–4% of all CRC cases. Although individuals with Lynch syndrome are predisposed to numerous types of cancer, risk of CRC is the highest [65,74,75].

A relationship between hyperplastic polyps and CRC is controversial. Hyperplastic polyps might slightly increase the risk of CRC, but the effect is small. Risk factors for malignancy in hyperplastic polyps include large polyp size (≥1 cm diameter); location in the right colon; a focus of adenoma within the polyp (mixed hyperplastic adenomatous polyp); occurrence of >20 hyperplastic polyps in the colon; a family history of hyperplastic polyposis; and a family history of CRC [62].

Serrated polyps, sometimes previously classified as a type of hyperplastic polyp, might, similar to adenomas, be a significant risk factor for CRC. Serrated polyps, unlike ordinary hyperplastic polyps, tend to be large and to occur in the right colon. The colonocytes in these polyps frequently have *BRAF* mutations and DNA methylation [62].

Although a few CRCs are known to be caused by mutations in high-penetrance cancer genes, such as those associated with familial adenomatous polyposis or Lynch syndrome (see earlier), most cases of CRC appear to be sporadic, and probably arise from risks associated with both low penetrance genes and environmental risks, such as dietary or toxin exposures.

People who have inflammatory bowel disease of the colon (both ulcerative colitis and Crohn's disease) have an increased risk of developing CRC that correlates with the extent and duration of the inflammation. It is estimated that 18% of patients with a 30-year history of ulcerative colitis will develop CRC [65,76]. Being overweight or obese is also associated with a higher risk of CRC, with stronger associations more consistently observed in men than in women. Obesity increases the risk of CRC independent of physical activity. Abdominal obesity (measured by waist circumference) might be a more important risk factor for CRC than over-all obesity in both men and women [65].

Several studies have found an association between diabetes and increased risk of CRC. Although adult-onset type 2 diabetes mellitus (the most common form of diabetes) and CRC share similar risk factors, including physical inactivity and obesity, a positive association between diabetes and CRC has been found even after accounting for physical activity, body mass index and waist circumference [65].

Diet and lifestyle strongly influence CRC risk; however, evidence for the role of specific dietary elements in CRC risk is still accumulating. Some countries in Eastern Europe and Asia have demonstrated increasing incidence rates (Slovakia, Czech Republic, Singapore and Japan), which have been attributed to behavioral risk factors related to westernization of diet and lifestyle. Several studies, including one by the American Cancer Society, found that high consumption of red and/or processed meat increases the risk of both colon and rectal cancer, and that people with very low fruit and vegetable intake are at above-average risk for CRC [77-80].

There is now sufficient evidence to conclude that tobacco smoking causes CRC. CRC has also been linked to excessive alcohol use. Individuals who have a lifetime average of two–four alcoholic drinks per day have a 23% higher risk of CRC than those who consume less than one drink per day [65].

CRC is, among other neoplasia, most frequently associated with vitamin D deficiency in epidemiological and observational studies in terms of incidence and mortality. Many mechanistic studies show that the active vitamin D metabolite (1α,25-dihydroxyvitamin D3 or calcitriol) inhibits proliferation and promotes epithelial differentiation of human colon carcinoma cell lines that express the vitamin D receptor via the regulation of a high number of genes [81,82].

One of the most consistently reported relationships between CRC risk and behavior is the protective effect of physical activity. Based on these findings, as well as the numerous other health benefits of regular physical activity, the American Cancer Society recommends engaging in at least moderate activity for 30 min or more for 5 or more days per week [65].

Certain characteristics infer a greater risk of progression. Factors, including severe dysplasia, a villous histological type, large size (≥1 cm), and the patient's age, are risk indicators of potential malignant transformation. Identification of these features in an adenomatous polyp and its subsequent removal can reduce the incidence of CRC and mortality in high-risk groups [83-85].

[A0004] What is the natural course of CRC?

Pathohistologically, CRC most commonly manifests as adenocarcinoma (98% of cases). The natural history of CRC is to develop from a benign adenoma. The estimated time interval for development from normal mucosa to adenoma to invasive adenocarcinoma is 5–10 years, whereas shorter intervals occur in patients with Lynch syndrome. Therefore, detecting the disease early is key to reducing mortality. Most patients with CRC are asymptomatic or have nonspecific symptoms in the early stages [47,64,86].

Polyps are either tubular adenomas or serrated polyps, which typically evolve into CRC over many years. The polyp to CRC sequence is heterogeneous and involves multiple different molecular pathways [87]. The heterogeneity of colon polyps and CRC can be appreciated on the basis of global DNA abnormalities (e.g. microsatellite instability), epigenetic alterations [e.g. CpG island methylator phenotype (CIMP)] and specific gene mutations. Normal epithelium transforms into invasive adenocarcinoma through the random accumulation of acquired genetic and epigenetic changes. Given the marked variation in the pattern and extent of these acquired molecular changes, no single, universal genetic marker of cancer or precancerous lesions has been detected. However, aberrant DNA methylation is a molecular alteration that occurs with most cancers and precancerous lesions during the early stages of tumorigenesis with greater frequency and predictability than gene mutations. Therefore, aberrantly methylated genes are particularly informative molecular markers for colorectal neoplasia [87,88].

Adenomas, also known as 'conventional adenomas', are precursors of perhaps 70% of all CRCs, but the process is slow, localized and asymptomatic, which is the primary factor contributing to late diagnosis. An estimated one-third to a half of all individuals will eventually develop one or more adenomas [63,65,89].

Adenomas can be distributed throughout the colon, although those with a flat or depressed morphology are distributed more in the proximal colon and pedunculated lesions more in the distal colon. Adenomas are by definition dysplastic. They can also be characterized by tubular versus villous histology, with most being tubular. Lesions with >25% villous elements are termed 'tubulovillous' and those with >75% villous elements 'villous'. Villous elements and invasive cancer are associated with increasing size of adenomas. Invasive cancer in adenomas ≤5 mm in size is rare, and the prevalence remains <1% in adenomas 6–9 mm in size [63]. An important clinical concept is that of 'advanced' adenoma, defined as a lesion ≥1 cm in size or having high-grade dysplasia or villous elements. Given that nonadvanced adenomas have a low prevalence of cancer and a long adenoma–cancer sequence, screening tests can remain useful if they target cancer and advanced adenomas and not small adenomas [63]. Serrated colorectal lesions represent an emerging area in the field of precancerous colorectal lesions. The serrated class of precursor lesions accounts for up to 30% of CRCs. Hyperplastic polyps are usually small lesions and are distributed toward the distal colon.

Survival largely depends on tumor stage at time of diagnosis, reaching a 5-year survival of up to 90% for localized disease, but only 10% for CRC with distant metastases. CRC does not often cause symptoms before it has reached an advanced stage. Therefore, only a few patients are found to have CRC while the tumor is still localized [90].

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of CRC for the patient?

Symptoms of adenomatous polyps

Adenomatous polyps are most commonly asymptomatic, but the occurrence of the symptoms depends on the size of the polyps. Polyps <0.5 cm rarely produce symptoms, but larger polyps (≥1 cm in diameter) are more likely to produce symptoms. The most common symptoms attributable to polyps are rectal bleeding, abdominal pain and a change in bowel habits. However, a large polyp rarely forms the leading edge of a colonic intussusception. Large villous adenomas can present with profuse diarrhea with mucus and hypocalcemia, but can rarely cause profuse watery diarrhea, especially in the distal colon. A rectal polyp can rarely cause rectal prolapse.

Approximately half of adenomas cause fecal occult bleeding. Large adenomas are more likely to cause occult bleeding, whereas small adenomas rarely cause occult bleeding. A benign colonic polyp rarely causes iron deficiency anemia; in malignant polyps, iron deficiency anemia is more common because of quantitatively greater chronic blood loss [62].

Symptoms and signs of CRC

Symptoms of CRC are less common and less obvious during the early stages of the disease, but are more common and prominent during late stages of CRC. Common symptoms include abdominal or back pain, rectal bleeding with hematochezia, iron deficiency anemia, and/or melena, altered bowel habits and shape, and involuntary body mass loss as well as diarrhea or constipation, nausea and vomiting, malaise, anorexia, and abdominal distention. Symptoms depend on cancer location and size, and presence of metastases. Left colonic cancers are more likely than right colonic cancers to cause partial or complete intestinal obstruction. In addition, large exophytic cancers are also more likely to obstruct the colonic lumen. Partial obstruction produces constipation, nausea, abdominal distention and abdominal pain as well as paradoxically intermittent diarrhea. Distal cancers sometimes cause extensive rectal bleeding, whereas proximal cancers rarely do so, primarily because the blood becomes mixed with stool and chemically degraded during colonic transit. Bleeding from proximal cancers tends to be occult and the patient might present with iron deficiency anemia without extensive rectal bleeding. The anemia can result in weakness, fatigue, dyspnea or palpitations. Possible complications include perforation, fistula, volvulus and inguinal hernia. Advanced cancer, particularly with metastasis, can cause cachexia with involuntary weight loss, anorexia, muscle weakness and a feeling of poor health [63,91,92].

Signs of CRC include pallor resulting from anemia from gastrointestinal bleeding. Iron deficiency anemia can cause koilonychia manifested by brittle, longitudinally furrowed, and spooned nails, glossitis manifested by lingual erythema and papillae loss, and cheilitis manifested by scaling or fissuring of the lips. Hypoalbuminemia can clinically manifest as peripheral edema, ascites or anasarca. Hypoactive or high-pitched bowel sounds suggest gastrointestinal obstruction. A palpable abdominal mass is a rare finding that suggests advanced disease [62].

Burden of the disease for patients

In several studies, CRC survivors in the first 5 years after diagnosis had lower quality of life (QoL) determinants because of additionally present comorbidities and are more likely to report lower QoL scores because of urinary leakage, difficulty controlling their bowels and stoma [93,94]. Additionally, female CRC survivors were mostly dissatisfied with their physical performance, intellectual function, financial situation and sexual function. CRC had the greatest negative impact within the first 3 years after diagnosis [95].

By contrast, long-term (≥5 years after diagnosis) CRC survivors reported a QoL that was comparable with the general population, with the exception of potentially slightly lower physical QoL. Depression and anxiety were more prevalent in patients with CRC than in the general population. Many were afraid of a recurrence, further spread of cancer or a second cancer, and consequentially showed distress regarding future diagnostic tests [96,97]. Female long-term survivors of CRC reported comparable health-related QoL to the general population of the same age. In the long-term, factors such as aging, body mass and chronic medical conditions dominate the CRC-related factors in determining physical and mental health. Only female CRC survivors with ostomies or with the recurrence of the disease might report decreased physical QoL [95].

The main determinants of QoL affected by CRC are:

- sociodemographic factors, such as gender (sexual problems in males and females, physical problems and pain in women), age (although controversial, because lower QoL with increasing age was only reported in some studies), income (low income correlates with worse physical, social and emotional condition) and width of social network (positively related to QoL) [95-97];

- health-related factors, such as comorbidities (heart disease, anxiety and/or depression, and urinary disorder have negative effects on overall, physical and psychological QoL) and body mass index (better physical QoL in healthy-weight and overweight versus obese cancer survivors) [95-97];

- cancer-related and surgical procedure-related factors, such as stage and site of CRC at diagnosis (Stage I patients experiencing positive trend in QoL and Stage IV patients a negative one, although some studies reported no association between tumor stage and QoL), surgical

procedures with rapid decline of QoL after surgery and gradual restoration approximately 3 months after (short-term differences in QoL between laparoscopic and open surgery; negative influence of stoma on QoL with fatigue, dyspnea, loss of appetite and changing of body image perception, feeling of stigma, decreased sexual activity, bowel dysfunction, fear of odor and leakage, and limited social life as well as low income and problems in paying for stoma supplies; worse psychological and physical QoL scores described in women and reduced mental health and sexual functioning in men), CRC bowel symptoms such as diarrhea, fecal control, constipation, fatigue and loss of appetite were reported to reduce QoL and urinary disfunction because of pelvic irradiation [95-97];

- other factors, such as physical activity (increase in physical QoL because of lower level of fatigue and distress), quality of diet (a diet rich in fruit and vegetables and low in fat as well as the administration of probiotics improves bowel dysfunction and QoL score) and smoking (lower QoL) [95-97].

[A0006] What are the consequences of CRC for the society?

CRC ranks third among the most commonly diagnosed cancers worldwide, affecting ~1.23 million patients each year, causing ~600,000 deaths annually. In developed countries, it is the second cause of cancer-related death in men and the third cause in women. The high incidence and associated mortality, and the natural history of CRC with slow progression from a premalignant polyp to cancer, makes CRC suitable for population screening [89,98-101].

The incidence of CRC exhibits a striking geographical variation: the age-adjusted incidence varies by up to 15-fold among different countries. Industrialized nations, except Japan, have the highest incidence, whereas South American countries and China have a relatively low incidence. The wide variation in incidence is largely attributed to national differences in diet and other environmental factors. In contrast to native Japanese, descendants of Japanese immigrants in America have, similar to other Americans, a high incidence of CRC attributed to dietary and other environmental adaptations. Indeed, the incidence of CRC has recently increased in native Japanese, attributed to their adopting a westernized diet and other environmental changes associated with industrialization [102]. Despite incidence rates showing a strong positive gradient with increasing level of economic development, the net 5-year rate of survival decreases with lower levels of income, with rates reaching 60% in high-income countries but falling to 30% or less in low-income countries [71].

In the USA, CRC is the second leading cause of cancer death, with an estimated incidence of 134,490 new cases and 49,190 deaths in 2016. Table 4.1 shows estimated numbers for incidence and mortality for the year of 2018 in Europe. The highest incidence was seen in Germany, with 58,047 new cases. In Austria, incidence amounted to 4421 and mortality to 2276, whereas, in Slovenia the related numbers were 1987 (incidence) and 740 (mortality).

Table 4.1. Estimated numbers of new cases of CRC and CRC-related deaths in 2018 for both sexes and all ages in European countries

Country	**Population** [1 January 2018 (Eurostat)]	**Incidence**	**Mortality**
Austria	8,822,267	4421	2276
Belgium	11,398,589	9346	3224
Bulgaria	7,050,034	4604	2714
Croatia	4,105,493	3387	2187
Cyprus	864,236	511	242
Czech Republic	10,610,055	7838	3421
Denmark	5,781,190	5585	1934
Estonia	1,319,133	942	482
Finland	5,513,130	3440	1393
France	66,926,166	47,025	19,962
Germany	82,792,351	58,047	27,334
Greece	10,741,165	7319	3430
Hungary	9,778,371	10,809	5076
Ireland	4,830,392	2968	82
Italy	60,483,973	49,327	21,172
Latvia	1,934,379	1550	706
Lithuania	2,808,901	1831	996
Luxembourg	602,005	323	134
Malta	475,701	302	121
Netherlands	17,181,084	14,921	6442
Poland	37,976,687	24,507	14,362
Portugal	10,291,027	10,270	4261
Romania	19,530,631	11,076	6319
Slovak Republic	5,443,120	4624	2396
Slovenia	2,066,880	1987	740
Spain	46,658,447	37,172	16,683
Sweden	101,20,242	6421	3062
UK	66,273,576	47,892	20,957

Source: International Association of Cancer Registries (IACR) www.iacr.com.fr/index.php?option=com_content&view=article&id=101&Itemid=578; Eurostat https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data/database

CRC survival rates vary based on the disease stage at the time of diagnosis. The 5-year survival rate is ~90% for localized disease (cancer has not spread beyond the bowel wall), 68% for regional disease (i.e. disease with lymph node involvement), and 5–10% for patients with distant metastasis. The overall 5-year relative survival rate for patients with colon cancer in Norway was 58.2% for women and 56.7% for men (1997–2001) and for patients with rectal cancer was 61.5% for women and 58.7% for men (1997–2001) [69].

In 2010, the national cost of cancer care in the USA was estimated to be US$124,57 billion, with CRC accounting for US$14,14 billion. If current trends continue, the cost of CRC care could increase to US$17.7 billion by 2020 [103].

In the EU, the estimated cancer incidence in 2012 was 2.6 million cases (1.2 million women and 1.4 million men). The estimated cancer mortality was 1.3 million deaths (0.6 million women and 0.7

million men), accounting for 26% of all deaths. The direct health cost of cancer in the whole EU increased from €79 billion to €86 billion during 2005–2014 (2014 prices). The cost of cancer drugs as a share of direct health costs increased from 12% to 22% during the same period. The direct health costs per capita varied with a factor of 5–6 within the EU during 2005–2014 [104].

Table 4.2. Direct health cost of cancer in each country in Euro (€) per capita adjusted for purchasing power parity (PPP) in 2014

<€100/capita	€100–200/capita	>€200/capita
Czech Republic/91	Ireland/164	Luxembourg/323
Croatia/81	Denmark/163	Austria/266
Poland/81	Italy/161	Germany/265
Portugal/81	Slovenia/139	Netherlands/264
Lithuania/79	UK/136	Belgium/227
Estonia/69	Malta/134	Sweden/223
Bulgaria/66	Spain/129	France/212
Latvia/62	Greece/127	
Romania/55	Finland/125	
	Slovak Republic/107	
	Hungary/105	
	Cyprus/105	

Source: Wilking *et al.* [104].

CRC treatment costs have increased dramatically over the past few years. From the early 1990s to 2003, treatment costs per person increased by up to 200%, depending on the stage of disease at diagnosis, whereas unit screening costs did not. With the US FDA approval of oxaliplatin in 2003 and the monoclonal antibodies bevacizumab and cetuximab for mCRC in 2004, treatment costs have increased even higher. Further developments in chemotherapy for CRC are to be expected, because, for example, the second-line treatment of bevacizumab for recurrent disease is being investigated as first-line treatment for Stage IV disease and as adjuvant therapy for Stage III and advanced Stage II disease [72].

Current clinical management of the disease or health condition

[A0024] How is CRC currently diagnosed according to published guidelines and in practice?

Screening for CRC

CRC screening is the process of detecting early-stage CRCs and precancerous lesions in asymptomatic people with no previous history of cancer or precancerous lesions and with no familial history of CRC. Screening aims to reduce the risk of death from CRC through early detection and the rate of complications associated with detection of cancer at a later stage. CRC can be classified on the basis of the location within the large bowel, histologic characteristics and molecular features. Advanced adenomas, in particular those measuring >10 mm in diameter, are the most well-known precursor lesions of CRC. Such screening also aims to reduce the incidence and mortality of CRC through the detection and removal of precancerous lesions.

There are several methods available for CRC screening:

- Stool-based tests to detect blood include the gFOBT and the more sensitive FIT;
- Endoscopic methods, which use optical approaches to directly examine the rectum and colon, include sigmoidoscopy and colonoscopy.

Colonoscopy is used both as a primary screening tool and as follow-up for individuals who have tested positive with other screening methods [71]. However, it has disadvantages as a screening test because it is resource intensive, invasive and entails a small, but significant, risk of serious complications. It also requires a team including a technician, nurse and highly trained colonoscopist [62].

In addition, CT colonography, an imaging method based on scanning technology, has been developed as a less invasive visualization technique for CRC screening [71].

Newer techniques that have recently emerged but have not all been widely tested are based on visual inspection (e.g. video capsule endoscopy) or the analysis of biomarkers in stool (e.g. multi-target-stool DNA, such as Cologuard® and ColoAlert®), in blood (e.g. methylated *SEPTIN9* DNA), or in breath (e.g. volatile organic compounds and various markers of protein, RNA and DNA) [71].

Diagnosis of CRC

Various technologies are available for the diagnosis of adenomas and CRC. Colonoscopy is widely accepted as the gold standard. It visually inspects the interior walls of the entire rectum and colon. Performance characteristics (such as sensitivity and specificity) of new tests are commonly evaluated compared with colonoscopy. By contrast, flexible sigmoidoscopy involves a more limited visual inspection of the distal colon and rectum. CT colonography and double-contrast barium enema are additional tests in diagnosis, offering enhanced X-ray images of the interior rectum and colon to aid the detection of abnormalities [105].

Colon cancers are rarely missed at colonoscopy because they tend to be larger than adenomatous polyps. During colonoscopy, polyps can be removed and masses biopsied for a pathological diagnosis. Endoanal ultrasound and pelvic magnetic resonance imaging (MRI) are used for staging rectal cancer. Chest, abdominal and pelvic MRI scanning are utilized to evaluate tumor size, local spread, and liver and lung metastases. Positron emission tomography (PET) scanning is performed for detecting occult metastases and for the evaluation of suspicious lesions found on CT or MRI. MRI can be used for evaluating suspicious lesions found on CT or ultrasound, especially in the liver. Carcinoembryonic antigen (CEA) can be used for follow-up, with increased levels suggesting recurrence [106].

Current situation regarding CRC screening guidelines across the world

Over the past 10 years, many CRC screening guidelines for average-risk adults have been published worldwide:

- Seven guidelines were published in North America [American College of Gastroenterology, ACG Guidelines 2009; American College of Physicians, ACP guidelines 2015; US Preventive Services Task Force, (USPSTF) Guidelines 2016; Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines 2016; National Comprehensive Cancer Network (NCCN) Guidelines 2017; United States Multi-Society Task Force of CRC Guidelines 2017; and American Cancer Society Updated Guidelines 2018] [17,107];
- The most important guidelines in Europe include: European CRC Screening Working Group Guidelines 2010; German Guideline Program in Oncology 2014; Spanish Society of Medical Oncology, SEOM Guidelines 2014; and Scottish Intercollegiate Guidelines Network, Healthcare Improvement Scotland 2016;
- Several guidelines were published in Asia, for example: Korean Guidelines for CRC Screening and Polyp Detection Guidelines 2012; Chinese Society of Gastroenterology Guidelines 2014; The Updated Asia-Pacific Consensus Recommendations on CRC Screening 2015; and National Guidelines for CRC Screening in Saudi Arabia 2015;
- Guidelines were also prepared by World Gastroenterology Organization (WGO, 2007).

Most guidelines recommend screening for average-risk individuals between the ages of 50 and 75.

Preferred screening methods include:

- colonoscopy (every 10 years);
- flexible sigmoidoscopy (every 5 years);
- gFOBT or FIT, both repeated annually or biennially.

FIT is often recommended over gFOBT, and combining flexible sigmoidoscopy with a stool-based test is an option that should be considered according to guidelines. The role of colonoscopy varies from one guideline to another, because some identify it as the screening gold standard, whereas others highlight the lack of high-quality evidence supporting its use. However, these are also areas of uncertainty [107].

EU guidelines and North American guidelines

EU guidelines

Multidisciplinary, evidence-based guidelines for quality assurance in CRC screening and diagnosis have been developed by experts in a project cofinanced by the EU. The 450-page guidelines were published in book format by the European Commission in 2010. They include ten chapters and over 250 recommendations, individually graded according to the strength of the recommendation and the supporting evidence. Adoption of the recommendations should improve and maintain the quality and effectiveness of the entire screening process, including the identification and invitation of the target population, diagnosis and management of the disease, and appropriate surveillance in patients with detected lesions [17].

The Council of EU Recommendation recommends the target average-risk population aged 50–74 years for CRC screening, where biennial performance of fecal occult blood test with FIT is considered as the current test of choice. Individuals identified with a family history of CRC, but not presenting with a hereditary syndrome should also be included in the average-risk screening [17].

By definition, average-risk persons are those in whom age is the only risk factor for CRC; high-risk individuals include those with history of adenomatous polyps, a personal history of CRC, a family history of CRC or adenomatous polyps diagnosed in a relative before age 60 years, a personal history of inflammatory bowel disease, a confirmed or suspected hereditary CRC syndrome, or a history of abdominal or pelvic radiation for a previous cancer [17].

North American guidelines

The USA has no national program for CRC screening, although several large healthcare plans offer programmatic screening, typically with a FIT [63].

According to the American Cancer Society 2018 Colorectal Cancer Screening Guideline Update for Average-Risk Adults, CRC screening is recommended for average-risk individuals of both genders aged 50–75 (strong recommendation), including populations that have CRC disproportionally, such as African-Americans, Alaska Natives and American Indians [17].

Given a marked increase in CRC incidence among younger individuals, the age interval 45–75 is considered a qualified recommendation because the benefit–burden balance is improved by lowering the age at initiation of CRC screening to 45 years. In the age interval 76–85 years, clinicians should individualize CRC screening based on patient preferences, life expectancy, health status and prior screening history. In individuals older than 85 years, CRC screening is discouraged. The recommended options for CRC screening are: FIT test annually; high-sensitivity, gFOBT annually; multitarget stool DNA test every 3 years; colonoscopy every 10 years; CT colonography every 5 years; and flexible sigmoidoscopy every 5 years [17].

Similarly, USPSTF recommends CRC screening for average-risk individuals in the age interval 50–75 years (Grade A recommendation), whereas in the age interval 76–85, the decision on CRC screening should be individualized (Grade C recommendation) [74].

A detailed overview of guidelines is provided in Table A7.

Situation in European Member States in practice

On-going, piloted and planned CRC screening programs in EU Member States in 2016 are presented in Table 4.4 (Section A0011).

[A0025] How is CRC currently managed according to published guidelines and in practice?

ESMO published several guidelines regarding the location and stage of the disease: *Early Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up* [108], *Metastatic Colorectal Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up* [109] and *Rectal Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up* [110].

Treatment

Treatment of CRC should be undertaken by multidisciplinary teams working in special units. Long-term survival rates relate to the stage of the primary tumor and the presence of metastatic disease. Long-term survival is only likely when the cancer is completely removed by surgery with adequate clearance margins and regional lymph node clearance [76].

Treatment of early colon cancer according to ESMO guidelines

Management of local and/or locoregional disease treatment of malignant polyps

Complete endoscopic polypectomy should be carried out whenever the morphological structure of the polyp permits. Making the decision to undergo surgical resection for a neoplastic polyp that contains invasive carcinoma involves the uncertainties of predicting and balancing adverse disease outcome against operative risk. When unfavorable histological features are present in a polyp from a patient with an average operative risk, resection is recommended. Standard surgical resection is recommended in patients with average operative risk [108].

Localized disease

The goal of surgery is wide resection of the involved segment of bowel together with the removal of its lymphatic drainage. The extent of the colonic resection is determined by the blood supply and distribution of regional lymph nodes. The resection should include a segment of colon of at least 5 cm on either side of the tumor, although wider margins are often included because of obligatory ligation of the arterial blood supply. Laparoscopic colectomy can be safely carried out for colon cancer, particularly for left-sided cancer [108].

Obstructive CRCs can be treated in one or two stages. Endoscopic stenting can be used to relieve obstruction from rectosigmoid cancer and allow subsequent one-step resection [108].

Treatment by stage

Treatment options by stage are [108]:

- Stage 0 (Tis N0 M0): (i) local excision or simple polypectomy; or (ii) segmentary en-bloc resection for larger lesions not amenable to local excision;
- Stage I [T1-2 N0 M0 (old staging: Dukes' A or modified Astler–Coller A and B1)]: wide surgical resection and anastomosis, no adjuvant chemotherapy;
- Stage II A,B,C (T3 N0 M0, T4 a-b N0 M0): (i) wide surgical resection and anastomosis; and (ii) following surgery, adjuvant therapy should not be routinely recommended for unselected patients;
- Stage III (any T, N1-N2, M0): (i) wide surgical resection and anastomosis; and (ii) following surgery, the standard treatment is a doublet schedule with oxaliplatin and a fluoropyrimidine.

Although all three combination regimens are superior to 5-FU/folinic acid (FA) alone, FA + fluorouracil + oxaliplatin (FOLFOX) or oxaliplatin + capecitabine (XELOX) should be preferred to 5-FU, leucovorin, and oxaliplatin (FLOX). When oxaliplatin is contraindicated, monotherapy with infusional or oral fluoropyrimidines should be preferred to bolus 5-FU/leucovorin (LV).

Treatment of metastatic colorectal cancer according to ESMO guidelines

Treatment of potentially resectable mCRC

Most patients have metastatic disease that initially is not suitable for potentially curative resection. However, it is important to select patients in whom the metastases are suitable for resection and those with initially unresectable disease in whom the metastases can become suitable for resection after a major response has been achieved with combination chemotherapy. Therefore, the aim of the treatment in the last group of patients might be to convert initially unresectable mCRC to resectable disease [109].

Unresectable mCRC

The optimal treatment strategy for patients with clearly unresectable mCRC is rapidly evolving. The treatment of patients should be seen as a continuum of care in which the determination of the goals of the treatment is important: prolongation of survival, cure, improving tumor-related symptoms, stopping tumor progression and/or maintaining QoL. Re-evaluation of patients during treatment by a multidisciplinary team, including interventional radiologists and radiation oncologists, is recommended. The outcome of patients with mCRC has improved during recent years, with median survival now reaching (nearly) 30 months in clinical trials [109].

Systemic treatment with cytotoxic agents

The backbone of first-line palliative chemotherapy alone, as well in combination with targeted agents, comprises a fluoropyrimidine (FP) [intravenous (i.v.) 5-FU or the oral FP capecitabine] in various combinations and schedules. Infused regimens of 5-FU/LV are less toxic than bolus regimens and should preferably be used. The oral FP capecitabine is an alternative to i.v. 5-FU/LV. Combination chemotherapy with FOLFOX or 5-FU/LV/irinotecan (FOLFIRI) provides higher response rates (RRs), longer progression-free survival (PFS) and better survival than 5-FU/LV alone. FOLFOX and FOLFIRI as chemotherapy alone have similar activity and are both partners for biologicals, but have a different toxicity profile: Nevertheless, combination chemotherapy remains the preferred option because it allows better tumor growth control plus the option of de-escalation to FP alone. The exposure to all three cytotoxics (FP, oxaliplatin and irinotecan) in various sequences can result in the longest survival, as a retrospective analysis indicates [109]. Second-line chemotherapy should be offered to patients with good performance status and adequate organ function [109].

Systemic treatment with biological targeted agents

Monoclonal antibodies (bevacizumab) or proteins (aflibercept) against vascular endothelial growth factor and epidermal growth factor receptor in combination with chemotherapy should be considered in patients with mCRC, because they improve the outcome of mCRC. Strategic scenarios in the continuum of care of mCRC are presented in Figure 5.

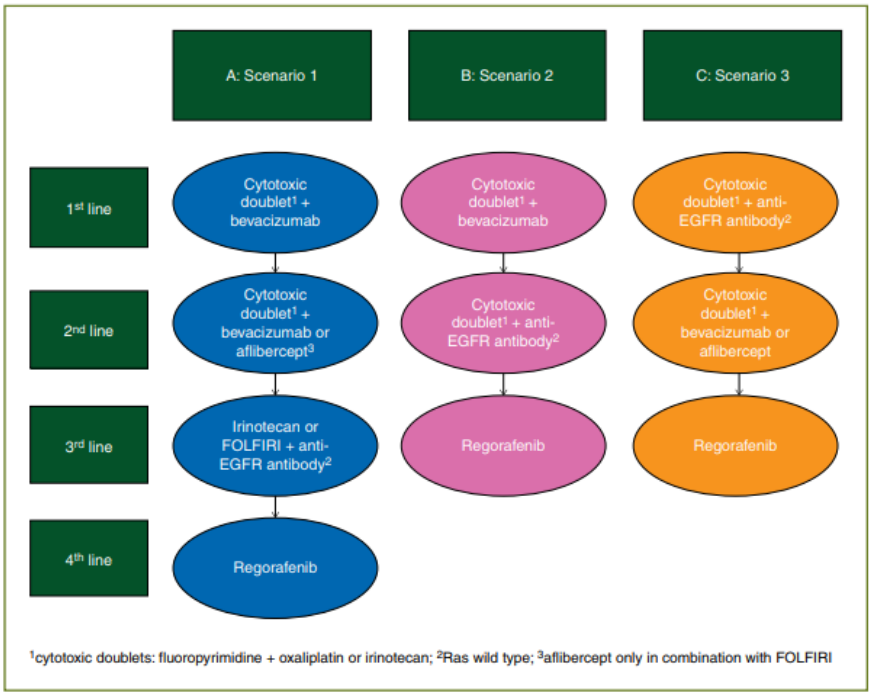


Figure 5. Strategic scenarios in the continuum of care for patients with metastatic colorectal cancer

Abbreviations: EGFR=epidermal growth factor receptor; FOLFIRI=folinic acid + 5-fluorouracil + irinotecan.

Resection of metastatic disease

Surgical resection of R0-resectable colorectal liver metastases is a potentially curative treatment, with reported 5-year survival rates of 20–45% [109]. The criteria for R0-resectability of liver metastases are not standardized and vary, depending on the experience of the multidisciplinary expert team. Resectability is not limited by number, size or bilobar involvement [109].

Treatment of rectal cancer according to ESMO guidelines

The following paragraphs provide a summary of recommendations for the treatment of rectal cancer [110].

Staging and risk assessment

- A history and physical examination including digital rectal examination (DRE), full blood count, liver and renal function tests, serum CEA, and CT scan of thorax and abdomen should be carried out to define functional status and presence of metastases.
- Rigid rectoscopy and preoperative colonoscopy to the cecal pole are required, or, in the case of obstruction, virtual colonoscopy to exclude synchronous colonic tumors. If no preoperative (virtual) colonoscopy was carried out, completion colonoscopy is recommended within 6 months of surgery.
- At least 12 regional lymph nodes should be examined. For mesorectal resections, histopathological examination should include a photographic record of the surgical specimen and assessment of tumor immune microenvironment (TME) quality, which is a strong quality-control measure.

Management of local and/or locoregional disease

- Local excisional procedures, such as transanal endoscopic microsurgery (TEM), are appropriate as a single modality for early cancers (cT1 N0 without adverse features, such as G3,

V1 or L1). Local radiotherapy can also be used as an alternative to local surgery, alone or combined with chemoradiotherapy (CRT);

- More advanced tumors up to and including cT2c/T3a/b should be treated by radical TME surgery because of higher risks of recurrence and the higher risk of mesorectal lymph node involvement;

- For patients with long-acting reversible contraceptives (LARC), treatment decisions regarding neoadjuvant therapy should be based on preoperative, MRI-predicted circumferential resection margin (CRM), extramural venous invasion (EMVI) and more advanced T3 substages;

- Postoperative CRT could be selectively used in patients with unexpected adverse histopathological features after primary surgery (e.g. positive CRM, perforation in the tumor area, incomplete mesorectal resection, extranodal deposits or nodal deposits with extracapsular spread close to the mesorectal fascia), or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given.

Follow-up, long-term implications and survivorship

- During follow-up, clinical examination, completion colonoscopy and pelvic imaging using MRI and/or CT and, for distant metastases, CT of the chest, abdomen and pelvis are recommended.

  A minimum provisional recommendation for average-risk patients is as follows:

See above Target population

[A0007] What is the target population for the test?

In general, the CRC screening target population includes asymptomatic people of either gender, who are at average risk and aged 50–74. Average-risk persons are those in whom age is the only risk factor for CRC [92]. Recommendations from the American Cancer Society have extended the age interval to 45–85 years (qualified recommendation), but strong recommendation for regular CRC screening is only given for adults aged 50 years or older [111].

The target population age 50–74 is recommended for CRC screening by the Council of EU Recommendation [15,112]. High-risk individuals should follow high-risk protocols, if available [112], and, therefore, are not included in regular screening programs. Given that the relative variation in the moderate risk of developing CRC in most individuals with a family history of CRC is less than the geographical variation in average risk between the EU Member States, the recommendations were not tailored to this subgroup. Therefore, individuals identified with a family history of CRC, but not presenting with a hereditary syndrome, should be included in the average-risk screening [15].

Similar recommendations were also set by *S3-Leitlinie Kolorektales Karzinom* (2017), where CRC screening is recommended for asymptomatic adults from 50 years of age, but the upper age limit is not determined. High-risk CRC adults include individuals with a family history of CRC (one first-degree relative under the age of 60 years or more, or two second-degree relatives aged 60 or more), individuals who are (proven or suspected) carriers of hereditary CRC (e.g. Lynch syndrome, hereditary CRC without polyposis, or familiar adenomatous polyposis) and patients with inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease) [113].

According to the *American Cancer Society 2018 Colorectal Cancer Screening Guideline Update* for *Average-Risk Adults*, the CRC screening is recommended for average-risk individuals of either genders aged 50 or more (strong recommendation), including high-risk CRC populations, such as African-Americans, Alaska Natives and American Indians. Additionally, qualified recommendation for regular CRC screening of individuals from the age of 45 up to the age of 75 or in certain circumstances up to 85 years was set because there is clear evidence of benefit, but less certainty either about the balance of benefits and harms or about patients' values and preferences. Over the past two decades, the CRC incidence have steadily declined in the population aged 50 years or older, but there has been a 51% increase in CRC among individuals younger than 50 years. However, current age-specific incidence rate among adults aged 45–49 years is still lower compared with

those in the 50–54 age group (31.4 versus 58.4 per 100,000). The Guideline is intended to be used in average-risk individuals with the exclusion of high-risk individuals (a history of adenomatous polyps, a personal history of CRC, a family history of CRC or adenomatous polyps diagnosed in a relative before age 60 years, a personal history of inflammatory bowel disease, a confirmed or suspected hereditary CRC syndrome, or a history of abdominal or pelvic radiation for a previous cancer), who should follow high-risk protocols [111].

[A0023] How many people belong to the target population?

The 2003 Council of the European Union recommendations indicated to offer screening with biennial fecal occult blood testing to all subjects aged 50–74 or, based on national prioritization for a narrower age band. Most programs start screening between age 50 and 60, with a 2-year interval, if the screening test is the gFOBT or FIT, or a 10-year interval or more if the screening test is flexible sigmoidoscopy or total colonoscopy, and to continue sending invitations to screen up to the age 70–75 years [14].

Following the 2003 Council of the European Union recommendations on the principles of best practice in the early detection of cancer, a first analysis of the state of implementation was performed in 2008. In 2017, the second report on the implementation of the Council recommendations on cancer screening was issued reviewing the state of play of screening of breast cancer, cervical cancer and CRC in 28 EU countries. The information reflected the screening program situation in 28 EU member states on 1 July 2015, with the addition of supplementary information at the end of July 2016. It was estimated that, in the age group of 50–74 years, nearly 152 million women and men live in the EU member states, of which 72% (110 million) live in those 23 Member States that have adopted at least some policies to implement, pilot or plan for population-based CRC screening programs [14].

Table 4.3 shows the data for all 28 EU member states on total population, estimated target population and projected population in the age group 50–74 for the years of 2030 and 2040 [14,114].

Table 4.3. Data on total population, estimated target population and estimated population in the age group 50–74 years in 2030 and 2040

	(x 1000)			
EU country	**Total population in 2016[1]**	**Estimated number of women and men, aged 50–74 in 2016[2]**	**Projected number of women and men, aged 50–74 in 2030[1]**	**Estimated number of women and men, aged 50–74 in 2040[1]**
Austria	8700	2625	3048	3115
Belgium	11,311	3329	3638	3646
Bulgaria	7153	2320	2232	2168
Croatia	4190	1336	1304	1247
Cyprus	848	233	266	314
Czech Republic	10,553	3248	3501	3628
Denmark	5707	1735	1833	1833
Estonia	1315	387	406	420
Finland	5487	1758	1672	1662
France	66,730	19,139	20,431	19,763
Germany	82,175	26,798	28,118	26,871
Greece	10,783	3215	3570	3330
Hungary	9830	3000	3188	3163
Ireland	4726	1142	1524	1658
Italy	60,665	18,090	21,923	20,663
Latvia	1968	603	593	564

	(x 1000)			
EU country	**Total population in 2016[1]**	**Estimated number of women and men, aged 50–74 in 2016[2]**	**Projected number of women and men, aged 50–74 in 2030[1]**	**Estimated number of women and men, aged 50–74 in 2040[1]**
Lithuania	2888	876	848	724
Luxembourg	576	153	221	259
Malta	450	136	142	152
Netherlands	16,979	5279	5563	5323
Poland	37,967	11,316	11,826	12,386
Portugal	10,341	3201	3565	3333
Romania	19,760	5.613	6142	6133
Slovak Republic	5426	1576	1778	1873
Slovenia	2064	651	708	693
Spain	46,440	13,387	16,949	16,064
Sweden	9851	2881	3075	3303
United Kingdom	65,382	18,450	20,264	20,889
Total	**510,265**	**152,477**	**168,328**	**165,177**

[1]Total population and projection of the number of individuals was made on the basis of Eurostat data.

[2]Estimated numbers from the *Cancer Screening in the European Union Report* on the implementation of the Council Recommendation on Cancer Screening 2017.

[A0011] How much are currently available tests utilized?

According to a 2017 report, population-based CRC screening programs (i.e. programs that individually identify people in the eligible target population and personally invite them to attend screening) had been implemented in 20 of the 28 EU Member States, three member states (Germany, Greece and Latvia) had only nonpopulation-based programs, and three member states (Estonia, Germany and Luxembourg) were planning to start a population-based program. No program had been initiated in Bulgaria, Romania and Slovak Republic. In two countries (Austria and Sweden) reporting population-based programs, the screening activity did not cover the entire country, but was limited to a single region. In Portugal, a population-based program was implemented only in two regions (Alentejo and Centro) [14].

The screening interval for gFOBT/FIT programs was 2 years in all the countries except Austria and Latvia, where screening is done yearly. Screening with colonoscopy was offered at 10-year intervals in Austria, Czech Republic and Germany and at 5-year intervals in Greece. Colonoscopy was offered for screening once in a lifetime in Poland, as was the case for sigmoidoscopy in Italy and England [14].

The participation rate is defined as the percentage of subjects screened in a particular year out of the total number of those who had received a personal invitation in that year. The average participation rates across the EU for FIT/gFOBT (defined as the number of invited and screened individuals out of personally invited individuals) are 44.4/22.7% in the age range 50–59 years, 53.0/41.5% in the age range 60–69 years, 33.0/40.7% in the age range 70–74 years, and 65.6/90.0% in the age range 75–79 years [14]. Huge differences exist between member states and even between regions within the same country. In some member states, this can be explained by an incomplete roll-out process.

Coverage by invitation is defined as the proportion of the subjects in the target age range who received a screening invitation within the scheduled interval in the index year, over the total number of eligible subjects; whereas coverage by examination is the proportion of subjects in the target age range who had a screening test within the scheduled interval over the total number of subjects in

the target population [14]. Given screening intervals of 2 or 3 years, the measurement on a single year might be inaccurate and reflected by some Member States exceeding 100% invitation coverage.

Table 4.4 provides the details of on-going, piloted or planed CRC screening programs for all 28 EU member states regarding their organization, screening test used, recommended age range as well as invitation/examination coverage in country-specific target populations within the screening age range where available [14].

Table 4.4. On-going, piloted or planned CRC screening programs in EU Member States in 2016

EU country	Screening test	Population-/Nonpopulation-based program[2]	Nationwide versus regional	Age range (years)	Women (in annual population)		Men (in annual population)	
					Invitation coverage (%)[4]	Examination coverage (%)	Invitation coverage (%)[4]	Examination coverage (%)
Austria – Burgenland	FIT	Population-based	Regional	40–80	No data provided		No data provided	
Austria – other regions	gFOBT	Nonpopulation-based	Regional		No data provided		No data provided	
Austria	TC	Nonpopulation-based	Nationwide		No data provided		No data provided	
Belgium – Flemish region	FIT	Population-based	Regional	56–74	98.3	48.7	100.5	47.1
Belgium – Wallonia-Brussels	FIT[1]	Population-based	Regional	50–74	96.5	6.7	101.6	6.4
Bulgaria	No program							
Croatia	gFOBT	Population-based	Nationwide	50–74	100.5[3]	15.3[3]	100.5[3]	15.3[3]
Cyprus	FIT	Population-based	Nationwide		No data provided		No data provided	
Czech Republic	FIT	Population-based	Nationwide	50+	No active invitation system	26.0	No active invitation system	21.2
	TC	Population-based	Nationwide	55+	No active invitation system	1.2	No active invitation system	1.6
Denmark	FIT	Population-based	Nationwide	50–74	No data provided		No data provided	

EU country	Screening test	Population-/Nonpopulation-based program[2]	Nationwide versus regional	Age range (years)	Women (in annual population)		Men (in annual population)	
					Invitation coverage (%)[4]	Examination coverage (%)	Invitation coverage (%)[4]	Examination coverage (%)
Estonia	FIT	Population-based (planned)	Nationwide	60–69	Program is in planning phase		Program is in planning phase	
Finland	gFOBT	Population-based	Nationwide	60–69	23.7	17.4	24.2	14.3
France – Calvados	FIT	Population-based	Regional	50–74	85.8	26.5	90.8	22.1
France – other regions	gFOBT	Population-based	Regional	50–74	95.4	27.7	103.5	25.2
Germany	FIT	Population-based (planned)	Nationwide	50–74	Program is in planning phase		Program is in planning phase	
	TC	Population-based/Nonpopulation-based	Nationwide	50–74	No data provided		No data provided	
	gFOBT	Nonpopulation-based	Nationwide	50–74	No data provided		No data provided	
Greece	gFOBT	Nonpopulation-based	Regional	50–70	No data provided		No data provided	
	TC	Nonpopulation-based	Regional		No data provided		No data provided	
Hungary	FIT	Population-based	Nationwide	50–70	1.7	0.7	1.8	0.6
Ireland	FIT	Population-based	Nationwide	60–69	28.6[3]	11.5[3]	28.6[3]	11.5[3]
Italy – Piedmont	FS + FIT	Population-based	Nationwide	58–60 (FS)	83.5	17.4	84.1	19.7
Italy north	FIT	Population-based	Regional	50–69	95.4	52.1	95.0	47.6
Italy – center					60.5	24.2	59.5	21.2
Italy – south					26.8	8.4	28.6	7.7

EU country	Screening test	Population-/Nonpopulation-based program[2]	Nationwide versus regional	Age range (years)	Women (in annual population)		Men (in annual population)	
					Invitation coverage (%)[4]	Examination coverage (%)	Invitation coverage (%)[4]	Examination coverage (%)
Latvia	gFOBT	Nonpopulation-based	Nationwide	50–74	No active invitation system	11.1[3]	No active invitation system	11.1[3]
Lithuania	FIT	Population-based	Nationwide	50–74	No active invitation system	57.7	No active invitation system	47.0
Luxembourg	FIT	Population-based (planned)	Nationwide	55–74	Program is in planning phase		Program is in planning phase	
	TC	Population-based (planned)	Nationwide	55–74	Program is in planning phase		Program is in planning phase	
Malta	FIT	Population-based	Nationwide	55–66	127.1[3]	45.4[3]	127.1[3]	45.4[3]
Netherlands	FIT	Population-based	Nationwide	55–75	38.3	27.7	38.0	26.7
Poland	TC	Population-based	Nationwide	55–64	10.4	1.6	9.8	1.8
Portugal – Alentejo, Central	gFOBT	Population-based	Regional	Central 50–70; Alentejo 50–74	1.8[3]	1.1[3]	1.8[3]	1.1[3]
Portugal – other regions	No program							
Romania	No program							
Slovak Republic	No program							
Slovenia	FIT	Population-based	Nationwide	50–74	93.8	51.7	93.0	42.5
Spain	FIT	Population-based	Nationwide	50–69	16.8	8.7	16.0	7.8

EU country	Screening test	Population-/Nonpopulation-based program[2]	Nationwide versus regional	Age range (years)	Women (in annual population)		Men (in annual population)	
					Invitation coverage (%)[4]	Examination coverage (%)	Invitation coverage (%)[4]	Examination coverage (%)
Sweden – Stockholm	gFOBT	Population-based	Regional	60–69	20.4	13.2	19.3	10.6
Sweden – other regions	No program							
UK – England	gFOBT	Population-based	Nationwide	60–74	104.2	60.1	94.8	50.1
	FS	Population-based	Nationwide	55–59	No data provided		No data provided	
UK – N. Ireland	gFOBT	Population-based	Nationwide	60–74	98.1[3]	53.6[3]	98.1[3]	53.6[3]
UK – Scotland	gFOBT	Population-based	Nationwide	50–74	108.6	64.6	112.1	60.9
UK – Wales	gFOBT	Population-based	Nationwide	60–74	88.3	56.4	89.3	52.1

[1]Wallonia-Brussels regions in Belgium replaced gFOBT with FIT in 2016. [2]In each round of screening, population-based programs individually identify people in the eligible target population in the area served by a program and personally invite them to attend screening. [3]The percentages were reported as overall percentages of invitation/examination coverage, the data were not provided separately for men and women. [4]Given screening intervals of 2 or 3 years, measurement on a single year might be inaccurate and is reflected by some Member States exceeding 100% invitation coverage.

Abbreviations: FIT=fecal immunochemical test; FS=flexible sigmoidoscopy; gFOBT=guaiac fecal occult blood test; TC=total colonoscopy; UK=United Kingdom.

Source: Ponti *et al.* [14].

In the USA, after the FDA approval of the Cologuard stool DNA test in August 2014, early data in June 2015 showed that ~36,000 patients had been screened with this stool DNA test since it became clinically available, 36% of whom were screened for the first time for CRC. There were nearly 80,000 orders placed by 13,800 physicians with a 73% test completion rate (April–June 2015) [100]. In the intend-to-screen population, the availability of multitarget stool DNA CRC screening led to high screening compliance (88%) and diagnostic colonoscopy compliance of multitarget stool DNA-positive cases (96%) in a cohort of previously noncompliant patients, aged 50–85 [115].

[A0021] What is the reimbursement status of the test?

According to *2017 Cancer Screening in the European Union Report* on the implementation of the Council Recommendation on cancer screening, CRC screening programs are mandated by a law or an official recommendation in all EU member states, except Bulgaria, Romania and the Slovak Republic. CRC screening, within an organized screening program or as opportunistic screening, is publicly funded in Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, Estonia, France, Germany, Hungary, Ireland, Italy, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovenia, Spain, Sweden and UK, and tests are provided free of charge in all except Croatia, where the costs are reimbursed through health insurance [14].

Nine EUnetHTA Partners provided data on CRC screening reimbursement status for the technologies used in their respective countries (England, Germany, Austria, Switzerland, Romania, Ireland, Spain, Italy Region Emilia-Romagna and Scotland). In all cases, regardless of the technology used (FIT, gFOBT or colonoscopy), the CRC screening program is fully reimbursed. A stool DNA test was not included in the national/regional screening program in any of these countries. Stool DNA testing (ColoAlert®) is only available in some countries on a private-payer basis (Germany, Austria, Norway and Turkey) [1].

In the USA, Cologuard® has been fully covered by Medicare and Medicaid since mid-2014 at a 3-year testing interval [116].

[D1003] What is the reference standard and how likely is it to classify the CRC correctly?

Colonoscopy is considered the reference standard for the detection of CRC. However, based on the studies comparing colonoscopy to CTC or CTC-enhanced colonoscopy, the sensitivity for detecting ≥6 mm adenomas was in the range of 75–93%, with a specificity of 94%, and for detecting ≥10 mm adenomas in the range of 89–95%, with a specificity of 89% [117]. In tandem colonoscopy studies, the missing rates were associated with the size of adenoma: a 2% miss rate was reported for adenomas ≥10 mm, a miss rate of 13% for adenomas 5–10 mm, and of 26% for adenomas 1–5 mm [118]. In another systematic review, the mean ± standard deviation sensitivity of colonoscopy for large polyps (≥10 mm) and cancer was 92.5 ± 6.2% and 94.7 ± 4.6%, respectively. The overall specificity of colonoscopy for detecting CRC was 99.8 ± 0.2%. Several comparators were used for the determination of sensitivity and specificity, such as cancer registry, CT colonography, colonoscopy, barium enema examination, pathological findings of the surgical specimen, or medical records [119].

Ideally, the reference standard would provide error-free detection of CRC, could be used to verify all screening test results and be performed within a short interval to avoid changes in target condition status. The imperfection of a reference standard translates into a misclassification of patients with regard to the target condition and, in principle, leads to biased estimates of the prevalence of the condition and accuracy of new diagnostic tests. Thus, although colonoscopy is currently the best-available method for CRC detection, it is not without error or uncertainty. A tumor might be missed by imaging because it is too small for the resolution of the technique applied [120,121].

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D1001	What is the accuracy of the test against reference standard?
D1005	What is the optimal threshold value in this context?
D1006	Does the test reliably rule in or rule out the target condition?
D0026	How does the test modify the effectiveness of subsequent interventions?
D0001	What is the expected beneficial effect of the test on mortality?
D0032	How does the test modify the magnitude and frequency of morbidity?
D0011	What is the effect of the test on patients' body functions?
D0012	What is the effect of the test on generic health-related quality of life?
D0013	What is the effect of the test on disease-specific quality of life?
D0030	Does the knowledge of the test result affect the patient's nonhealth-related quality of life?
D0017	Were patients satisfied with the test?

The order of the research questions in the table as well as in text further below has been arranged to ensure good readability of the results section and, therefore, does not follow the order of the element IDs.

5.2 Results

Included studies

Regarding the outcomes on test accuracy, two studies were identified that investigated Cologuard® (Imperiale *et al.* [2], Brenner *et al.* [6]) and one that investigated ColoAlert® (Dollinger *et al.* [3]). Detailed extraction tables for these studies can be found in Appendix 1. Regarding outcomes on mortality, morbidity, health-related and nonhealth-related QoL, no (primary) studies were identified. Five patient interviews were done for this assessment (see Section 2.7), which inform outcomes on patient satisfaction as well as some QoL aspects. For the outcomes on patient satisfaction, an additional five surveys were identified [7-11], but only one of which investigated one of the currently available tests [7] (Cologuard®). With regard to the comparators defined in PICO, none of the included studies investigated (flexible) sigmoidoscopy, *SEPTIN9* test or CTC compared with stool DNA testing.

Study characteristics

One of the test accuracy studies of the Cologuard® DNA stool test (Imperiale *et al.* [2]) was conducted as a cross-sectional screening study including persons at average risk for CRC, who were recruited in 90 sites (private-practices and academic settings) throughout the USA and Canada from June 2011 through November 2012. Blinded screening colonoscopy was used as the reference standard. Independently of colonoscopic findings, a multitarget stool DNA test (Cologuard®) and a commercially available FIT (OC FIT-CHEK®) were processed, whereby FIT served as the comparator test.

According to selection criteria, participants had to be asymptomatic persons, between 50 and 84 years of age, who were scheduled to undergo screening colonoscopy. However, enrolment was intentionally weighted toward persons 65 years of age or older to increase the prevalence of CRC within the study population. Exclusion criteria comprised patients with a personal history of CRC, digestive cancer or inflammatory bowel disease, as well as persons that had undergone previous colonoscopy, CTC or sigmoidoscopy. Persons with positive results on fecal blood testing within the previous 6 months, who had undergone colorectal resection for any reason other than sigmoid diverticula, had overt rectal bleeding within the previous 30 days, or had a family history of CRC were also excluded from study participation.

The overall dropout rate was 21.8% (n=2787). Reported reasons for dropout were (among others): withdrawn consent (n=464); 'did not undergo colonoscopy' (n=1168); 'did not submit stool sample' (n=128); insufficient stool sample (n=474); technical failure (e.g. owing to insufficient DNA or hemoglobin sample) (n=213); problems/issues with colonoscopy [n=304, e.g. incomplete colonoscopy, colonoscopy before stool sample or too late (>90 days after stool sample)]; or insufficient hemoglobin sample for FIT (n=43). Compared with the evaluable group, mean age was significantly higher in the dropout group (64.2 versus 65.4 years, no p-value reported), and distribution of race (Caucasian and African-American) also differed significantly, although the magnitude of these differences was small [evaluable group: Caucasian, n=8392 (80.0%); African-American, n=1068 (10.7%); Other, n=523 (5.2%). Dropout group: Caucasian, n=2080 (75.6%); African-American, n=480 (17.5%); Other, n=190 (6.9%)].

Table 5.1. Summary of study characteristics of included test accuracy studies

	Imperiale *et al.* 2014	**Dollinger *et al.* 2018**	**Brenner *et al.* 2017**
Study objective	Comparison of noninvasive, multitarget stool DNA test (Cologuard®) with FIT in persons at average risk for CRC	Investigate whether non-invasive stool assay can offer sufficient sensitivity and specificity to supplement colonoscopy-based screening	Assess diagnostic performance of FIT among participants of screening colonoscopy and to compare it with previously reported performance of Cologuard® (Imperiale *et al.* 2014)
Country/ies of recruitment	USA, Canada	Germany	Germany; recruitment for Cologuard® study (Imperiale *et al.* 2014) in USA and Canada
Setting	90 sites throughout USA and Canada, including private-practice and academic settings	16 different centers (no further details reported)	Gastroenterology practices
Study design	Preclinical case cohort study	Preclinical case cohort study	Prospective screening cohort study
Data collection period	June 2011 to November 2012	Not reported	November 2008 to September 2014
Diagnostic test (index test)	Multitarget stool DNA test (Cologuard®; Exact Sciences)	Combined DNA stool assay (ColoAlert®; PharmGenomics)	FIT (FOB Gold®; Sentinel Diagnostics)
Comparator test(s)	FIT (OC FIT-CHEK®, Polymedco)	▪ gFOBT (ColoScreen-ES®,) ▪ M2-PK assay (ScheBo Biotech AG) ▪ Combined gFOBT and M2-PK assay	Performance data of Cologuard®, as reported by Imperiale *et al.* 2014
Reference standard	Histologically confirmed screening colonoscopy	Histologically confirmed screening colonoscopy	Histologically confirmed screening colonoscopy
Participants (inclusion criteria)	Asymptomatic persons aged 50–84 at average risk for CRC scheduled for screening colonoscopy. Enrolment weighted toward persons ≥65 years of age to increase prevalence of CRC	Patients aged 38–85 before elective or screening colonoscopy or before surgery in case of recent diagnosis of CRC	Participants of screening colonoscopy, no previous diseases of colon
No. of patients enrolled	12,776	734	4203

	Imperiale *et al.* 2014	Dollinger *et al.* 2018	Brenner *et al.* 2017
No. of patients fully evaluated	9989	566 (521, when patients with IBS and IBD excluded)	3494

Abbreviations: CRC=colorectal cancer; FIT=fecal immunochemical test; gFOBT=Guaiac (based) fecal occult blood testing; IBD=inflammatory bowel disease; IBS=Irritable bowel syndrome.

Sources: Imperiale *et al.* [2], Brenner *et al.* [6], Dollinger *et al.* [3].

Based on the prospective screening cohort study by Brenner *et al.* [6], the diagnostic performance of a quantitative FIT (FOB Gold®) was assessed and compared with performance data of Cologuard®, as reported by Imperiale *et al.* [2]. The study group included asymptomatic participants of a screening colonoscopy, aged 50–84 years (true screening setting), which were consecutively recruited from 20 gastroenterology practices in Southern Germany and invited to collect stool samples for evaluation with FIT. Patients were informed about the study at a preparatory visit in the practice, typically about 1 week before colonoscopy. The following exclusion criteria were applied: history of CRC or inflammatory bowel disease (n=32); colonoscopy in the preceding 5 years (n=193); inadequate bowel preparation before colonoscopy (n=432); or incomplete colonoscopy (cecum not reached, n=52). Patient recruitment for this study took place from November 2008 to September 2014 and was conducted within the context of the German BLITZ study (Begleitende innovative Testverfahren zur Darmkrebsfrüherkrennung, German Clinical Trials Register ID: DRKS00008737). Laboratory staff for the analyses for the FIT was blinded to colonoscopy findings; in addition, colonoscopies were conducted blinded with respect to the results of FIT. To facilitate comparisons of diagnostic performance, sensitivities and specificities were calculated after adjustment of the FIT cutoff so that they yielded the same specificity (86.6%) as reported for Cologuard® by Imperiale *et al.*. This was achieved by lowering the cutoff from the value recommended by the manufacturer (i.e., from 17 µg hemoglobin/g feces to 8.4 µg hemoglobin/g feces).

The study by Dollinger *et al.* [3] was conducted as a preclinical multicentric case cohort study to evaluate test accuracy for a combined DNA stool assay (ColoAlert®), a gFOBT (ColoScreen-ES®), and a tumor M2-PK assay (ScheBo Biotech AG) to supplement colonoscopy-based CRC screening. Patients were recruited from 16 different sites in Germany from August 2005 to May 2007. Patients aged 38–85 years before screening or elective colonoscopy (e.g. in the context of planned polypectomy) or before surgery (in cases of a recent diagnosis of CRC) were included. Exclusion criteria were as follows: patients with known hereditary risk for developing CRC (familial adenomatous polyposis or hereditary nonpolyposis CRC); patients who had had a second tumor or malignant illness identified in the previous 5 years; and patients with impaired coagulation and/or those taking anticoagulant therapeutics. Other contraindications prohibiting colonoscopy or surgery were also considered. Six subgroups were defined a priori: control group (no chronic symptoms and no pathological findings from elective colonoscopy, n=252); patients with hyperplastic polyps (n=83); patients with adenomas (n=134); patients with IBS (n=26) or IBD (n=19), and patients with CRC (n=52). IBD and IBS patient groups were explicitly excluded from the calculations of all related statistics, because these patients clinically disqualify for such a screening test given that most commercially available CRC tests frequently deliver false positive results and using them for patients with IBD and/or IBS is not recommended.

Five prospective cross-sectional patient surveys [7-11] were identified that had been done among USA (asymptomatic) screening populations, some with and some without previous CRC screening experience. The oldest study, by Schroy *et al.* [11], used a (self-developed) 25-item questionnaire in persons undergoing DNA testing, gFOBT and colonoscopy as part of a large multicenter trial [122] for assessing and comparing perceptions of the tests and screening preferences. A similar study by the same first author published in 2007 [8] addressed patient preferences among persons without previous screening experience (except possibly FOBT). The authors of this study used an educational decision aid informing the pros and cons about the different screening tests, assessed patient preference regarding screening strategy, factors influencing their choices, as well as preferences on participating in the decision-making process. Both studies referred to a USA precursor test (PreGen-Plus®) of Cologuard®, which is no longer available [123]. In another study, Berger *et al.* [9] analyzed a ten-question patient survey that had been provided with every PreGen-Plus®-kit distributed. It included questions on the handling of the test and the likelihood of using the test again for future screening. The three studies [8,9,11] were either supported by Exact Sciences or had employees among the authoring team. In a study from 2011, Calderwood *et al.* [10] used a similar

instrument as used by Schroy *et al.*, including an educational component and questions on screening preferences and test features influencing choice. They included patients without previous endoscopic or radiological CRC screening who had an upcoming primary care appointment. Only one survey (Abola *et al.* [7]) referred to the currently available Cologuard®. They conducted a comparative study of colonoscopy versus DNA stool testing for CRC screening to assess potential differences in the perception of the DNA stool test between Caucasians and African-Americans. A 19-question survey was sent to patients after completing both tests.

Risk of bias and quality of evidence for test accuracy studies

Table 5.2 details the consensual results of the risk of bias assessment for the three included test accuracy studies using the QUADAS-2 tool. Risk assessment was conducted by two reviewers independently of each other.

As indicated in Table 5.2, the risk of bias regarding patient selection for the Cologuard® study (Imperiale *et al.* [2]) was rated as high, because patient enrolment was intentionally weighted toward persons 65 years of age or older to increase CRC prevalence within the study population. A consistent consecutive patient recruitment does not appear to be compatible with this procedure. In all other key domains of the QUADAS-2 tool, a low risk of bias was assessed for Imperiale *et al.*

Performance data of Cologuard® were taken from Imperiale *et al.* [2] in the screening study by Brenner *et al.* [6] for indirect comparison with a quantitative FIT. Accordingly, the risk of bias regarding patient selection was also rated as high for this study. In all other QUADAS-2 domains, a low risk of bias was assessed.

For the case cohort study by Dollinger *et al.* [3] (combined stool assay, ColoAlert®) considerable risk of bias as well as applicability concerns were noted by the reviewers: Regarding patient selection, it was not clear whether patient enrolment was consecutive and whether inappropriate exclusions were avoided in this study. The analyzed study population did (by design) not represent an average screening population, such as in terms of CRC and precancerous lesions prevalence, or regarding age (patients <40 years of age were included). Overall, concerns were high that the study population did not match well with the research question of this assessment. Regarding the applicability of the index test, concerns were noted because the combined stool assay evaluated in this study incorporates a gFOBT, whereas the CE-marked ColoAlert® stool DNA test includes a FIT. In terms of dropouts, the following reasons, and related numbers, were reported: 'no or incomplete colonoscopy' (n=32); 'could not be assigned to any group' (n=7); 'failed to submit a stool sample' (n=69); and 'delivered unusable stool samples due to not following the instructions for correct use' (n=60). Furthermore, 28 M2-PK tests could not be interpreted for technical issues. No more detailed information was reported regarding unusable DNA stool samples or problems with the M2-PK test.

Table 5.2. Risk of bias for test accuracy studies (QUADAS-2)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Imperiale *et al.* 2014 (Cologuard)	☹	☺	☺	☺	☺	☺	☺
Brenner *et al.* 2017 (Cologuard)	☹	☺	☺	☺	☺	☺	☺
Dollinger *et al.* 2018 (ColoAlert®)	☹	☺	☺	☹	☹	☹	☺

Legend: ☺ low risk; ☹ high risk.

Patient interviews

Five patients out of a typical CRC screening population were interviewed during the scoping phase, either via telephone or face to face, using a standardized open questionnaire (see Section 2.7). Table 5.3 summarizes main results.

Table 5.3. Patient interviews done within the assessment and main results

Age	Gender	Screening experience	Problems, barriers, harm and/or complications with test	Benefits	Conclusion regarding the screening experience
65	Female	Colonoscopy	Bowel preparation unpleasant, pain during procedure	Immediate result	Overall unpleasant, would recommend it only if necessary
		FIT	Collection of specimen was difficult; worry about possible positive test result	Non-invasive	Preferred screening instrument because of non-invasiveness
56	Male	Colonoscopy	Bowel preparation unpleasant; anaesthetic induction problematic	Immediate result and, therefore, good feeling without worrying about undetected lesions	Colonoscopy under light sedation, without (experienced) anesthetic induction problems, is a good solution
		gFOBT	Collection of specimen difficult because of characteristics of toilet (washdown WC pan)	Non-invasive	Would do it again
		FIT	Collection of specimen difficult because of characteristics of toilet (washdown WC pan)	Non-invasive	Would do it again
		Stool DNA test	No problems	Non invasive	Would do it again
57	Female	FIT	Irregular bowel movement and being away from home with no permanent access to toilet as well as forgetting test strips at home are identified barriers to handing in tests	Non-invasive	Would do it again, rather than colonoscopy
60	Male	gFOBT	Irregular bowel movement and missing washdown WC pan made it difficult	Non-invasive	Preferred screening instrument because of non-invasiveness
		Colonoscopy	Bowel preparation difficult; colonoscopy without sedation caused a lot of pain	Fast result	Would rather do gFOBT than colonoscopy
57	Female	gFOBT	No problems	Non-invasive	Would do it again
		Colonoscopy	Invasive	Fast result	Would rather do gFOBT than invasive colonoscopy

Abbreviations: DNA=deoxyribonucleic acid; FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test.

Source: Patient interviews.

Test accuracy

[D1001] What is the accuracy of the test against reference standard?

Table 5.4 provides the test accuracy data for the Cologuard® DNA stool test compared with two FITs (OC FIT-CHEK® and FOB Gold®, with adjusted cutoff 17 µg hemoglobin/g feces), as well as for a combined DNA stool assay [ColoAlert® combined with a gFOBT and a human DNA quantification test (threshold 15 ng/µL)] compared with a single gFOBT (ColoScreen-ES®), a single tumor M2-PK test (ScheBo Biotech AG), and a combined gFOBT/M2-PK assay.

Table 5.4. Test accuracy data – sensitivity and specificity

	CRC	APL	CRC or APL	CRC or adenoma	Non-APL	Non-neoplastic findings	No CRC or adenoma	No CRC or APL	No CRC	Negative (no findings)
Imperiale *et al.* 2014, DNA stool test (Cologuard®, Exact Sciences)										
Colonoscopy findings	65	757	822	3715	2893	1817	6274	9167	9924	4457
Positive (n)	60	321	381	879	498	278	733	1231	1552	455
Negative (n)	5	436	441	2836	2395	1539	5541	7936	8372	4002
% Test positive* (95% CI)	92.3 (83.0–97.5)	42.4 (38.9–46.0)	46.4***	23.7***	17.2 (15.9–18.6)					
% Test negative** (95% CI)					82.8***	84.7***	88.3***	86.6 (85.9–87.2)	84.4***	89.8 (88.9–90.7)
Imperiale *et al.* 2014, FIT (OC FIT-CHEK®, Polymedco)										
Positive	48	180	228	448	220	90	252	472	652	162
Negative	17	577	594	3267	2673	1727	6022	8695	9272	4295
% Test positive* (95% CI)	73.8 (61.5–84.0)	23.8 (20.8–27.0)	27.7***	12.1***	7.6 (6.7–8.6)					
% Test negative** (95% CI)					92.4***	95.0***	96.0***	94.9 (94.4–95.3)	93.4***	96.4 (95.8–96.9)
Brenner *et al.* 2017, FIT (FOB Gold®, Sentinel Diagnostics; adjusted cutoff 8.4 µg hemoglobin/g faces)										
Colonoscopy findings	30	359	389	1077	688	n.r.	2417	3105	3464	n.r.
Positive (n)	29	170	199	333	134		n.r.	419	589	
Negative (n)	1	189	190	744	554		n.r.	2686	2875	
% Test positive* (95% CI)	96.7 (82.8–99.9)	47.4 (42.1–52.7)	51.1 (46.1–56.2)	30.9**	19.5 (16.6–22.6)					
% Test negative** (95% CI)					80.5**			86.5 (85.3–87.7)	83.0***	
Dollinger *et al.* 2018, Combined DNA stool assay [ColoAlert®, PharmGenomics; gFOBT and DNA quantification test (threshold 15 ng/µL)]										
	CRC	**APL**	**CRC or APL**	**CRC or adenoma**	**Non-APL**	**Hyperplastic polyps**	**No CRC or adenoma**	**No CRC or APL**	**No CRC**	**Negative (no findings)**
Colonoscopy findings	52	n.r.	n.r.	186	n.r.	83	335	n.r.	469	252
Positive (n)	44			66		18	39		61	21
Negative (n)	8			120		65	296		408	231

% Test positive* (95% CI)	84.6 (71.9–93.1)			35.5 (28.6–42.8)						
% Test negative** (95% CI)						78.3***	88.4 (84.4–91.6)		87.0 (83.6–89.9)	91.7 (87.5–94.8)
Dollinger *et al.* 2018, gFOBT (ColoScreen-ES®, Helena Biosciences)										
Colonoscopy findings	50	n.r.	n.r.	184	n.r.	83	335	n.r.	469	252
Positive (n)	34			41		5	14		21	9
Negative (n)	16			143		78	321		448	243
% Test positive* (95% CI)	68.0 (53.3–80.5)			22.3 (16.5–29.0)						
% Test negative** (95% CI)						94.0***	95.8 (93.1–97.7)		95.5 (93.2–97.2)	96.4 (93.3–98.4)
Dollinger *et al.* 2018, M2-PK (ScheBo Biotech AG)										
Colonoscopy findings	41	n.r.	n.r.	159	n.r.	78	313	n.r.	431	235
Positive (n)	34			87		33	125		178	92
Negative (n)	7			72		45	188		253	143
% Test positive* (95% CI)	82.9 (67.9–92.8)			54.7 (46.6–62.6)						
% Test negative** (95% CI)						57.7***	60.1 (54.4–65.5)		58.7 (53.9–63.4)	60.9 (54.3–67.1)
Dollinger *et al.* 2018, gFOBT + M2-PK										
Colonoscopy findings	51	n.r.	n.r.	185	n.r.	83	335	n.r.	469	252
Positive (n)	46			103		38	134		191	96
Negative (n)	5			82		45	201		278	156
% Test positive* (95% CI)	90.2 (78.6–96.7)			55.7 (48.2–63.0)						
% Test negative** (95% CI)						54.2***	60.0 (54.5–65.3)		59.3 (54.7–63.8)	61.9 (55.6–67.9)

*Sensitivity; **specificity; ***calculated by the authors (not directly reported in the study).

Abbreviations: APL=advanced precancerous lesion(s); CI=confidence interval; CRC=colorectal carcinoma; FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test; n.r.=not reported.

Sources: Imperiale *et al.* [2], Brenner *et al.* [6], Dollinger *et al.* [3].

Table 5.5 provides the positive and negative predictive values (PPV and NPV) for CRC and advanced precancerous lesions (APL) as well as the NNS for the stool DNA tests and included comparators. The PPV is the proportion of patients with a positive test result who have the disease, and the NPV is the proportion of patients with a negative test result who are free of the disease [124]. The NNS is the number of persons who would need to be screened to identify one person with the disease. The prevalence data for CRC and APL shown in Table 5.5 are as reported by Imperiale *et al.* and Brenner *et al.*, respectively.

Table 5.5. Test accuracy data – positive and negative predictive values, and number needed to screen

CRC prevalence* (no. of CRC/n of subjects)	**PPV** for CRC** (95% CI)	**NPV** for CRC** (95% CI)	**APL prevalence*** (no. of APL/n of subjects)	**PPV** for APL** (95% CI)	**NPV** for APL** (95% CI)	**NNS to detect CRC** (95% CI)	**NNS to detect APL** (95% CI)
Imperiale *et al.* 2014, DNA stool test (Cologuard®, Exact Sciences)							
0.0065 (65/9989)	0.037 (0.029–0.048)	0.999 (0.998–1.00)	0.076 (757/9989)	0.206*** (n.r.)	0.948*** (n.r.)	166 (130–217)	13 (12–14)
Imperiale *et al.* 2014, FIT (OC FIT-CHEK®, Polymedco)							
0.0065 (65/9989)	0.068 (0.051–0.090)	0.998 (0.997–0.999)	0.076 (757/9989)	0.277*** (n.r.)	0.938*** (n.r.)	208 (156–286)	55 (48–65)
Brenner *et al.* 2017, FIT (FOB Gold®, Sentinel Diagnostics; adjusted cutoff 17 µg hemoglobin/g faces)							
0.0086 (30/3494)	0.047***	0.999***	0.103 (359/3494)	0.287*** (n.r.)	0.935*** (n.r.)	120*** (n.r.)	21*** (n.r.)
Dollinger *et al.* 2018, Combined DNA stool assay [ColoAlert®, PharmGenomics; gFOBT and DNA quantification test (threshold 15 ng/µL)]							
0.0086****	0.053*** (n.r.)	0.998*** (n.r.)	–	n.r.	n.r.	138*** (n.r.)	n.r.
Dollinger *et al.* 2018, gFOBT (ColoScreen-ES®, Helena Biosciences)							
0.0086****	0.116*** (n.r.)	0.997*** (n.r.)	–	n.r.	n.r.	171*** (n.r.)	n.r.
Dollinger *et al.* 2018, M2-PK (ScheBo Biotech AG)							
0.0086****	0.017*** (n.r.)	0.997*** (n.r.)	–	n.r.	n.r.	140*** (n.r.)	n.r.
Dollinger *et al.* 2018, gFOBT + M2-PK							
0.0086****	0.019*** (n.r.)	0.999*** (n.r.)	–	n.r.	n.r.	129*** (n.r.)	n.r.

*Colonoscopy findings in study population; **for calculation formula, see [124], page 15; ***calculated by the authors (not directly reported in the study); ****no prevalence data reported by Dollinger *et al.* 2018; data taken from Brenner *et al.* 2017.

Abbreviations: APL=advanced precancerous lesion(s); CI=Confidence interval; CRC=colorectal carcinoma; FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test; n.r.=not reported; NNS=number needed to screen; NPV=negative predictive value; PPV=positive predictive value.

Sources: Imperiale *et al.* [2], Brenner *et al.* [6], Dollinger *et al.* [3].

Table 5.6 provides details on the test performance (number of patients excluded because of test failure and reasons for test failure). No information was reported by the study authors regarding uncertain test results.

Table 5.6. Test performance – failure rates

No. of patients enrolled	No. of patients that could not be evaluated	No. of patients that could be evaluated	Test	No. excluded because of test failure (%)	Test failure details	No. of patients fully evaluated
Imperiale *et al.* 2014						
12,776	1760: 464 withdrew consent 1168 did not undergo colonoscopy 128 did not submit stool sample	11,016	Colonoscopy (reference standard)	304 (2.76%)	194 negative but incomplete examinations 94 not have insertion to cecum documented 79 poor bowel preparation 21 incomplete examination 71 underwent biopsy, but did not have pathology result owing to no tissue or loss of specimen 20 underwent colonoscopy before stool collection 19 underwent colonoscopy >90 days after enrollment	9989
			DNA stool test (Cologuard®)	689 (6.25%)	474 stool samples that could not be evaluated owing to leakage in shipping or repeat specimen not received before colonoscopy 213 technical failures owing to insufficient DNA (low β-actin), hemoglobin sample volume, stool supernatant for target capture, or material for repeat assay 2 missing samples	
			FIT (OC FIT-CHEK®)	34 (0.31%)	All excluded because of insufficient hemoglobin sample	
Brenner *et al.* 2017						
4203	225 32 with history of CRC or IBD	3978	Colonoscopy (reference standard)	484 (12.17%)	432 inadequate bowel preparation 52 incomplete colonoscopy	3494
			FIT (FOB Gold®)	Not reported		

	193 had colonoscopy in the preceding 5 years					
Dollinger *et al.* 2018						
734	7 could not be assigned to any group	727	Colonoscopy (reference standard)	32 (4.40%)	No or incomplete colonoscopy	566 (521, when IBS and IBD excluded)
			DNA stool assay (ColoAlert®)	For all stool tests together: 129 (17.74%*)	No failure details regarding single stool tests reported For all stool tests together: 69 failed to submit a stool sample 60 delivered unusable stool samples because of not following instructions for correct use	
			gFOBT (ColoScreen-ES®)			
			M2-PK (ScheBo®)			
			gFOBT+M2-PK			

*During the fact check process for this assessment, information was received from the manufacturer that, in 100 consecutive ColoAlert® samples that were sent to the laboratory during the first quarter of 2019, a test failure rate for ColoAlert® of ~8% was observed.

Abbreviations: CRC=colorectal carcinoma, FIT=fecal immunochemical test, gFOBT=guaiac (based) fecal occult blood test, value IBD=inflammatory bowel disease, IBS=irritable bowel syndrome.

Sources: Imperiale *et al.* [2], Brenner *et al.* [6], Dollinger *et al.* [3].

[D1005] What is the optimal threshold value in this context?

The multitarget stool DNA test (Cologuard®) as described by Imperiale *et al.* [2] comprises molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, and *ACTB* (reference gene for human DNA quantity), as well as an immunochemical assay for human hemoglobin (FIT). Quantitative measurements of each marker were incorporated into a validated, prespecified logistic-regression algorithm, with a value of 183 or more indicating that the multitarget stool DNA test result was positive. FIT (OC FIT-CHEK®) was performed according to the manufacturer's instructions (e.g. stool samples with >100 ng hemoglobin per milliliter of buffer were considered to be positive).

The manufacturer's recommended cutoff for the FIT (FOB Gold®) used in the study by Brenner *et al.* [6] was 17 µg hemoglobin/g feces for a positive test result. To facilitate comparisons of diagnostic performance of this FIT (FOB Gold®) with Cologuard®, Brenner *et al.* calculated sensitivities after adjustment of the FIT cutoff in such a way that it yielded the same specificity (86.6%) as reported for Cologuard® by Imperiale *et al.*. This specificity (86.6%) was achieved by lowering the cutoff for the FIT from the value recommended by the manufacturer (i.e. from 17 µg hemoglobin/g feces to 8.4 µg hemoglobin/g feces).

The combined DNA stool assay as conducted in the study by Dollinger *et al.* [3] comprised four markers: mutations in *KRAS*, mutations in *BRAF*, quantification of hDNA, and a commercially available gFOBT (ColoScreen ES®). gFOBT was interpreted according to the manufacturer's specifications (no cutoff value was reported). For hDNA quantification, Dollinger *et al.* reported two cutoff concentrations for a positive test result (≥5 ng/µL as well as ≥15 ng/µL of hDNA extracted). They did not explicitly recommend one cutoff over the other; however, the difference in resulting test accuracy using these two cutoffs was minimal. However, according to written information (December 2018) from the manufacturer of ColoAlert® (PharmGenomics), the threshold for hDNA is currently set at 1 ng/µL because of improvements regarding the stabilization and quality of extracted DNA. The combined DNA stool assay is considered to be positive if at least one of the four markers is positive and considered to be negative if none of the four testing systems are positive.

[D1006] Does the test reliably rule in or rule out the target condition?

The potential role of stool DNA tests in CRC screening depends on current screening strategies. They can either act as replacements for other common screening tests (e.g. gFOBT or FIT) or (could) serve as an additional triage test before a screening colonoscopy. Thus, the question relates to: (1) a comparison to other screening tests with regard to higher or lower sensitivity and specificity values; and (2) the sensitivity and specificity being in itself high enough for the specific screening situation. By contrast, the target condition has to be specified: with regard to disease prognosis, the main target conditions are CRC and advanced adenomas/APL (see also A0004 in Section 4.2).

Compared with a FIT test, Cologuard® reached higher sensitivities for CRC and APL and lower specificity for not having CRC or APL in one study [2], but another study showed that results might change with the use of other (better) FIT tests as comparators [6]. A higher sensitivity for CRC and lower specificity for not having any findings compared with gFOBT can be found for ColoAlert® [3], with no results on APL (and no direct comparison to FIT).

The reported DNA stool test sensitivities for CRC were high, with 85% (ColoAlert®) and 92% (Cologuard®); but not so high for APL, with 42% for Cologuard® and no reported value for ColoAlert®. The specificity for Cologuard® with 87% remains below 90% for not having CRC or APL and reaches 90% for not having any findings (i.e. also no nonadvanced adenomas and non-neoplastic findings). For ColoAlert®, the specificity for not having any findings reaches 92%; other data were not reported.

[D0026] How does the test modify the effectiveness of subsequent interventions?

One study by Johnson *et al.* [125] compared colonoscopy results in an unblinded and a blinded group with positive DNA test. This controlled cohort study was conducted from September 2014 to September 2015 with n=172 DNA-test (Cologuard®)-positive patients in the unblinded group (colonoscopy team had knowledge of the test result) and n=72 DNA test-positive patients in the blinded group. More total adenomatous/sessile serrated polyps (70% versus 53%, p=0.013) and advanced

neoplasms (28% versus 21%, p=0.27) were detected in the unblinded than in the blinded group. Among polyps detected, flat or slightly raised lesions in the right colon were proportionately more frequent with unblinded (40%) than with blinded examinations (9%; p=0.0017). Median withdrawal time was 19 min in the unblinded group compared with 13 min in the blinded group (p<0.001). The study authors concluded that knowledge of a positive DNA test result had a beneficial impact on the diagnostic yield and quality of subsequent colonoscopy.

Mortality

[D0001] What is the expected beneficial effect of the test on mortality?

No primary studies were identified regarding the expected effect of DNA stool tests on CRC or overall mortality.

Modeling the five CRC screening strategies yielded the following results regarding mortality outcomes (see also Table 7.1, for explanation of strategies see Section 2.9): compared with No Screening, a cohort of 1000 50-year-old individuals screened from age 50 to 74 is expected to experience 394 LYG with COL, 385 LYG with Cologuard, 365 LYG with FIT, and 358 LYG with ColoAlert. These and the following results represent long-term results of screening strategies including index testing, further diagnostics and surveillance, and (as base case) assuming 100% adherence rates for all strategies. COL, compared with No Screening, yielded 31 averted CRC-related deaths per 1000 screened individuals, and Cologuard, FIT and ColoAlert 30, 28 and 27 averted CRC-related deaths, respectively.

The benefits of the screening strategies can be transformed and interpreted on an individual level. That is, when compared to No Screening, one 50-year-old individual is expected to gain, on average, 144 life days with the COL strategy, 141 life days with Cologuard, 133 life days with FIT, and 131 life days with the ColoAlert strategy.

Morbidity

[D0032] How does the test modify the magnitude and frequency of morbidity?

No primary studies were found on how DNA stool tests modify the magnitude and frequency of morbidity.

The comparative effectiveness of modeling the five CRC screening strategies yielded the following results regarding morbidity outcomes (see Table 7.1): per 1000 screened individuals, COL, Cologuard, FIT and ColoAlert averted 62, 52, 45 and 44 CRC cases, respectively.

[D0011] What is the effect of the test on patients' body functions?

Included studies for this assessment as well as the five patient interviews done for this assessment did not provide results or information on the effect of DNA stool tests on patients' body functions. Given the non-invasive character of intervention, effects of DNA stool tests on patients' body functions are not expected.

Health-related quality of life

[D0012] What is the effect of the test on generic health-related quality of life?

No primary studies were found on how DNA stool test modifies the generic health-related QoL. In the five patient interviews done for this assessment, all interviewees mentioned the non-invasive nature of stool tests on the one hand and the advantage of having an immediate result with colonoscopy on the other hand as perceived benefits of the respective tests. One interviewee explicitly appreciated the 'good feeling without worrying about undetected lesions' with colonoscopy. No (other) QoL-specific effects of the stool DNA test were mentioned.

[D0013] What is the effect of the test on disease-specific quality of life?

No primary studies were found on how DNA stool tests modify the disease-specific health-related QoL.

Nonhealth-related quality of life

[D0030] Does the knowledge of the test result affect the patient's nonhealth-related quality of life?

No primary studies were found on how DNA stool tests modify the nonhealth-related QoL.

Satisfaction

[D0017] Were patients satisfied with the test?

Two outcomes were specified for this assessment dealing with patient satisfaction: handling problems carrying out the test and/or taking the specimen, and patient adherence (patient preferences).

Handling problems carrying out the test and/or taking the specimen

Of the five persons interviewed for this assessment, four said they had difficulties with sample collection for the stool tests (FIT and gFOBT), mainly because of the characteristics of the toilet (wash-down WC pan). One interviewee reported one-time difficulties with having a bowel movement.

According to Schroy *et al.* [11], the stool sample collection process (PreGen-Plus®) has in general not been perceived as difficult by patients, with a small but significant difference between DNA stool tests and gFOBT, in favor of the DNA test. Also in the study by Berger *et al.* [9], a majority of responding patients using a DNA stool test (PreGen-Plus®) found it 'very easy' or 'somewhat easy' to perform the sample collection (64% respectively 23%) and 3% found it to be (somewhat or very) difficult (10% 'neutral'). A higher percentage of participants found it very (83%) or somewhat (11%) easy to obtain collection materials versus 1% finding it somewhat difficult. Returning the specimen was 'very easy' for 74% and 'somewhat easy' for 17% versus 3% finding it (somewhat or very) difficult. Abola *et al.* [7], the only study that investigated the currently available Cologuard®, did not find significant differences between Caucasian and African-American patients' perceptions of the test. Instructions about the preparation and sample collection were easy to understand for >85% of participants in both groups. For 6% (Caucasian) and 10% (African-American), it was difficult to have a bowel movement, whereas 83% and 76%, respectively, found it easy. For 9% and 10%, respectively, the test was uncomfortable, whereas 76% and 77%, respectively, found it comfortable. Of the respondees, 2% and 10%, respectively, felt that taking the test was embarrassing, whereas, for 89% and 84%, respectively, it was not embarrassing. Preparation for the test and taking the test caused anxiety or nervousness in 4–9%, respectively, versus 79–85%, respectively, who did not feel anxious or nervous.

Patient adherence (patient preferences)

Of the five persons interviewed for this assessment, four said they would rather do the experienced stool test (FIT in two persons and gFOBT in the two other) than colonoscopy (only three of them had already undergone a colonoscopy). One patient, experienced in FIT, gFOBT, stool DNA test and colonoscopy, appeared to be indifferent.

When asked for the preferred strategies for routine CRC screening, 45% of patients in the study by Schroy *et al.* [11] preferred DNA testing, 32% gFOBT, and 15% colonoscopy, with 8% expressing no preference. In the survey of patients without CRC-screening experience (Schroy *et al.* [8]), 51% preferred colonoscopy as a screening option, versus 28% for DNA testing and 18% for gFOBT. Subjects who preferred colonoscopy rated accuracy as the most influential test feature. For those who preferred DNA, concerns about the amount of discomfort were rated highest and for those who preferred gFOBT, frequency of testing was rated highest. In the 2011 survey by Calderwood *et al.* [10] 59% of patients preferred colonoscopy as screening modality, 17% gFOBT, 14% DNA testing and 10% CT colonography. Subjects who preferred colonoscopy also rated accuracy as the most influential test feature, for patients preferring any of the stool tests it was discomfort, whereas for

patients preferring CT colonography it was accuracy (but with small subgroups). In the Caucasian subgroup in the study by Abola *et al.* [7] 43% preferred DNA testing as a screening option, 22% were unsure, 14% preferred FIT, 11% colonoscopy, and 10% had no preference. In the African-American subgroup, 32% preferred DNA testing, 30% were unsure, 17% preferred colonoscopy, 13% had no preference, and 8% preferred FIT.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is the test in relation to the comparator(s)?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the test?
C0006	What are the consequences of false positive, false negative and incidental findings generated by using the test from the viewpoint of patient safety?
C0007	Are the test and comparator(s) associated with user-dependent harms?

6.2 Results

Included studies

No additional studies were found with regard to this domain. Test accuracy studies included for the EFF domain were also included for the SAF domain as giving information on the number of false positive and false negative test results. Modeling five CRC screening strategies yielded further insights regarding screening related physical and potential psychological harms and burden for individuals undergoing screening and follow-up procedures.

Patient safety

[C0008] How safe is the test in relation to (the) comparator(s)?

[C0004] How does the frequency or severity of harms change over time or in different settings?

[C0005] What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

[C0006] What are the consequences of false positive, false negative and incidental findings generated by using the test from the viewpoint of patient safety?

[C0007] Are the technology and comparator(s) associated with user-dependent harms?

None of the primary studies reported adverse events of DNA or the other included stool tests. No studies were found that investigated (if and) how the frequency or severity of harms change over time or in different settings. None of the primary studies distinguished susceptible patient groups that are more likely to be harmed through the use of DNA stool tests. No primary studies reported (or have been found on) user-dependent harms of DNA stool tests. In addition, no studies were found that directly investigated consequences of false positive or false negative test results from the viewpoint of patient safety (e.g. delayed treatment or overtreatment). No study reported on incidental findings of DNA stool testing (because the test only gives either a ‘negative’ or a ‘positive’ finding). The numbers of false positive and false negative test results for each of the tests included within the test accuracy studies are detailed in Table 5.4

Results regarding short- and long-term patient safety for different screening pathways can be drawn from the benefit-harm modeling. Comparative unintended physical and potential psychological harms (measured by the number of positive and false positive test results) as well as burden of colonoscopies (for individuals undergoing screening and follow-up procedures) are shown in Table 7.1. For all strategies, the additional complications because of colonoscopy leading to hospitalization were low compared with No Screening (COL n=1.17, Cologuard n=0.54, FIT n=0.38, ColoAlert n=0.44 expected cases per 1000 screenees). A cohort of 1000 50-year-old individuals, screened from age 50 to 74, is expected to experience additional 679 positive tests with COL compared with No Screening. Compared with COL, FIT leads to a similar number of additional positive tests (n=675) compared with No Screening, whereas ColoAlert leads to 824 and Cologuard to over 1000 additional positive test results (n=1003). Among 1000 screened individuals, screening with stool tests leads to 389 false positive test results with Cologuard, 198 with FIT, and 317 with ColoAlert. The expected additional total number of colonoscopies compared with No Screening, including index testing, further diagnostics and surveillance, are 2777 with COL, 1292 with Cologuard, 904 with FIT, and 1053 with ColoAlert.

7 BENEFIT–HARM ANALYSIS

Base-case analysis

Table 7.1 summarizes the benefits, harms and burden of CRC screening strategies compared with No Screening. Details of the incremental benefit–harm analysis with the tradeoffs between the patient-relevant outcomes for all screening strategies are shown in Table 7.2 and Figure 67.1–7.4. Based on the base-case analysis with a screening adherence of 100% in all screening strategies and considering the total number of colonoscopies as a measure of burden for individuals on the one hand, LYG and CRC deaths averted as measures of benefits on the other hand, the 3-yearly ColoAlert strategy was dominated by biennial FIT (i.e. provided less health benefit at higher burden). To gain one additional LY with the 3-yearly Cologuard strategy compared with biennial FIT, there is an expected incremental burden of additional 19 colonoscopies. To gain one LY with 10-yearly colonoscopy compared with the Cologuard strategy, there is an expected incremental burden of additional 167 colonoscopies. To avoid one CRC-related death with 3-yearly Cologuard compared with biennial FIT, there is an expected incremental burden of additional 208 colonoscopies. To avoid one CRC-related death with 10-yearly colonoscopy compared with 3-yearly Cologuard, there is an expected incremental burden of additional 1235 colonoscopies.

Moving from No Screening to FIT would result in an average benefit of 133 additional life days for the screenee and an average burden of ~1 expected additional colonoscopies during their lifetime. Moving from FIT to Cologuard would result in an additional benefit of 8 life days and an additional average burden of ~0.4 colonoscopies. Finally, moving from Cologuard to COL would result in a further additional benefit of 3 life days and an additional average burden of ~1.5 colonoscopies.

Considering the tradeoff between the potential psychological harm of positive test results versus the benefit of CRC death averted, all stool tests were dominated.

Table 7.1. Benefits, harms and burden of colorectal cancer screening strategies compared with No Screening

Strategy	LYG	CRC-specific deaths averted	CRC cases averted	Complications	Positive test results	False positive test results	Colonoscopies
ColoAlert	358	27	44	0.44	824	317	1053
FIT	365	28	45	0.38	675	198	904
Cologuard	385	30	52	0.54	1003	389	1292
COL	394	31	62	1.17	679	0	2777

Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening. All screening strategies include index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); CRC=colorectal cancer; FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); LY=life years.

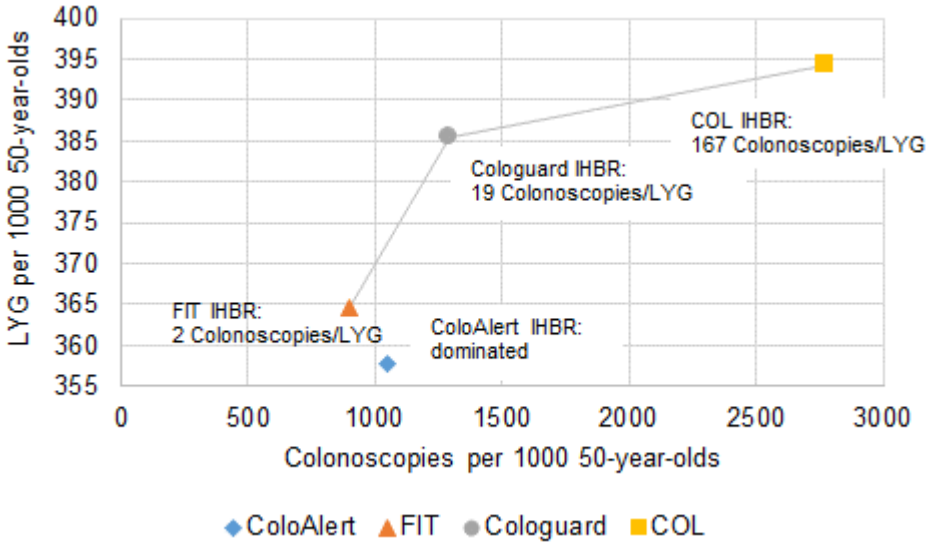
Table 7.2. Benefit–harm analysis results of colorectal cancer screening strategies with incremental comparisons (base-case analysis)

Screening strategy	LY	CRC deaths **	Positive test results**	Colonoscopies*, **	IHBR 1: Δ colonoscopies/Δ LY	IHBR 2: Δ colonoscopies/Δ CRC death	IHBR 3: Δ positive test results/Δ LY	IHBR 4: Δ positive test results/Δ CRC death
No Screening	32.040	0.037	0.00	0.08				
ColoAlert	32.398	0.010	0.82	1.13	D	D	D	D
FIT	32.405	0.010	0.68	0.98	2	33	D	D
Cologuard	32.426	0.008	1.00	1.37	19	208	D	D
COL	32.435	0.007	0.68	2.86	167	1235	2	22

All screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy). *Colonoscopies representing burden to the patient; **numbers per patient.

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); CRC=colorectal cancer; D=dominated; FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); IHBR=incremental harm–benefit ratio; LY=life years; Δ=difference.

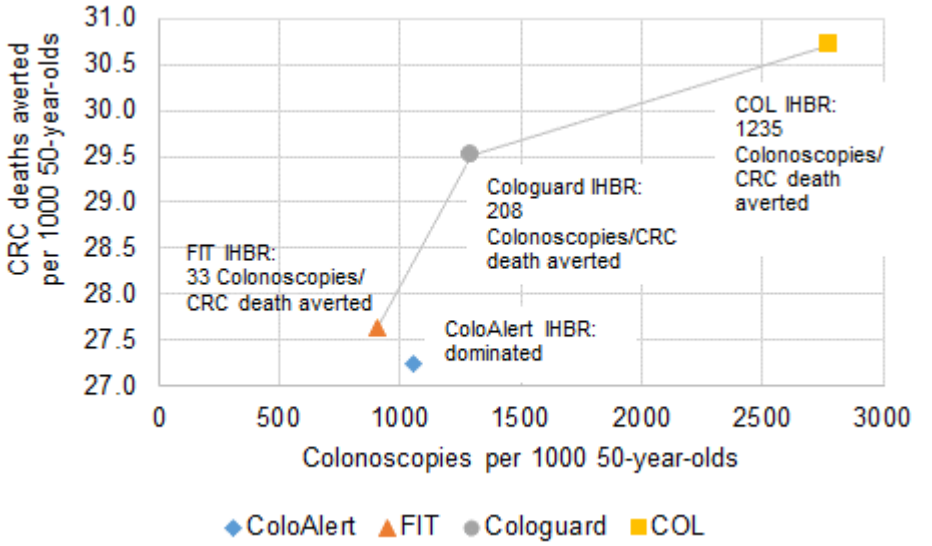
Figure 6. Benefit–harm plane of colorectal cancer screening strategies in terms of additional colonoscopies per additional life year gained (base-case analysis)



Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); IHBR=incremental harm–benefit ratio; LYG=life years gained.

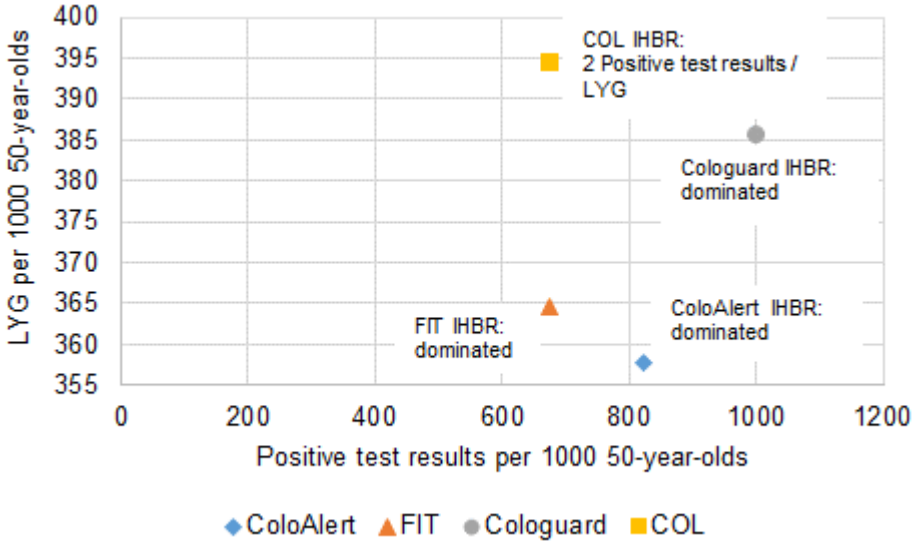
Figure 7. Benefit–harm plane of colorectal cancer screening strategies in terms of additional colonoscopies per additional colorectal cancer death averted (base-case analysis)



Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); CRC=colorectal cancer; FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); IHBR - incremental health-benefit ratio.

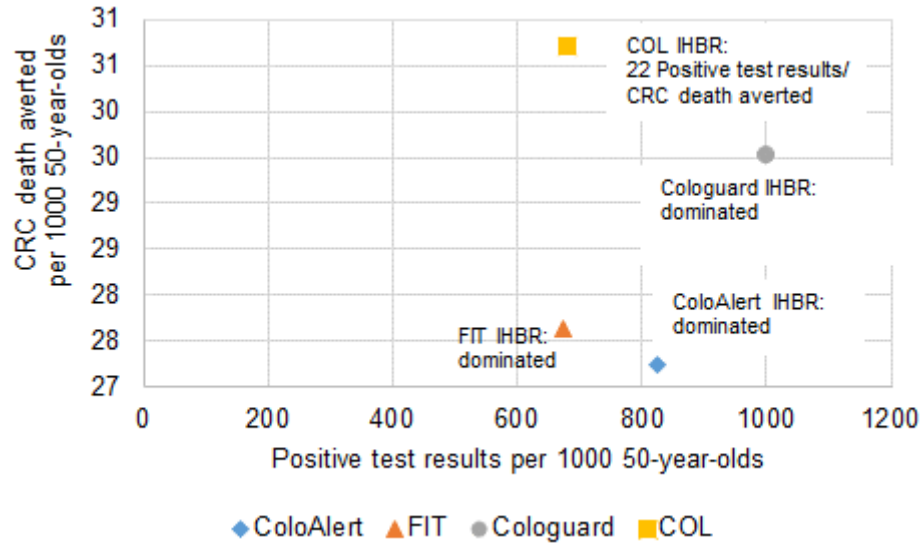
Figure 8. Benefit–harm plane of colorectal cancer screening strategies in terms of additional positive test results per additional life year gained (base-case analysis)



Numbers pertain to a cohort of 1,000 persons 50 years of age who were followed until death in comparison to No Screening, all screening strategies include index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy)

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); LYG=life years gained; IHBR - incremental health-benefit ratio.

Figure 9. Benefit–harm plane of colorectal cancer screening strategies in terms of additional positive test results per additional colorectal cancer death averted (base-case analysis)



Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); CRC=colorectal cancer; FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); IHBR - incremental health-benefit ratio.

Sensitivity analyses

The robustness of results was tested by varying parameters on test accuracy and assumptions on adherence rates:

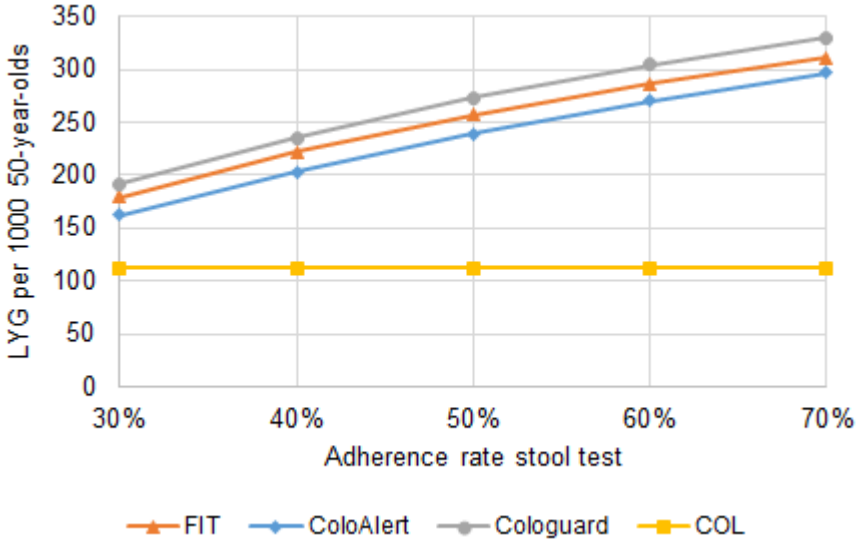
- To account for an improved overall sensitivity with unchanged specificity of ColoAlert® when FIT is administered instead of gFOBT, the sensitivity of ColoAlert® was increased by up to 8%. In the ColoAlert® study by Dollinger *et al.* [3], specificity of gFOBT in the no findings group was similar to the specificity of FIT in the study by Imperiale *et al.* [2]. Therefore, specificity for ColoAlert® was assumed to be constant for this sensitivity analysis;

- Adherence rates of screening colonoscopy range from 18% in Poland to 26% in the region of Vorarlberg in Austria. In organized screening programs with stool tests in England, Scotland and Italy, adherence varies between 48% and almost 58%. In France and Australia, adherence rates of organized stool-test screening between 33% and 36% are reported [126]. Therefore, the impact of screening participation and/or adherence rates was investigated assuming a reduced adherence rate for COL of 20% and varying the adherence rate of stool tests between 30% and 70% to reflect the variability within current screening programs within the EU [126].

The systematic sensitivity analyses showed that model-predicted benefit–harm results were particularly sensitive to screening participation and/or adherence rates. At a 20% adherence rate of 10-yearly colonoscopy and a 30% adherence rate of stool test screening, COL is dominated in the benefit–harm analysis considering the tradeoff between LYG and colonoscopies (

Figure 10 to Figure 12). Increasing the adherence rates of stool tests led to not only increasing LYG, but also increasing numbers of colonoscopies. Nevertheless, COL is dominated on the whole range of adherence rates.

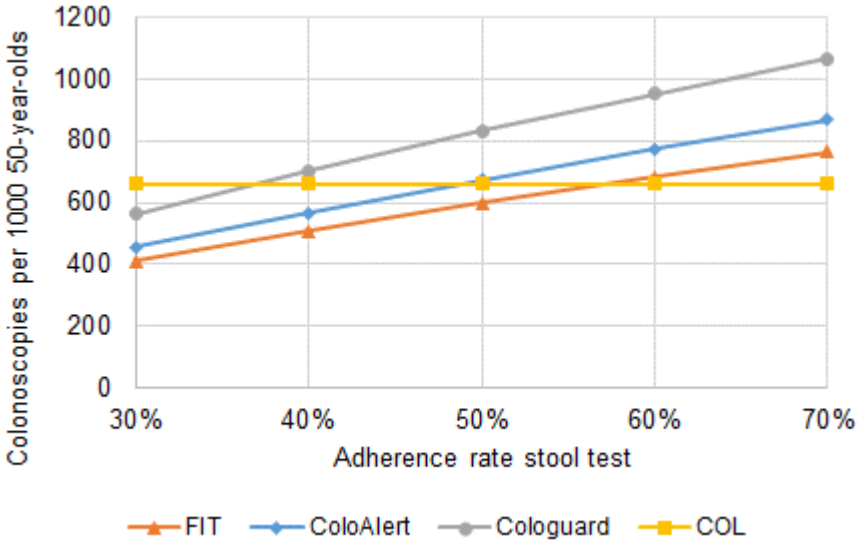
Figure 10. Sensitivity analysis of the impact of adherence rates in stool test-based screening strategies on life years gained at a (fixed) 20% adherence rate in COL



Adherence rate: COL 20%, Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); LYG=life years gained.

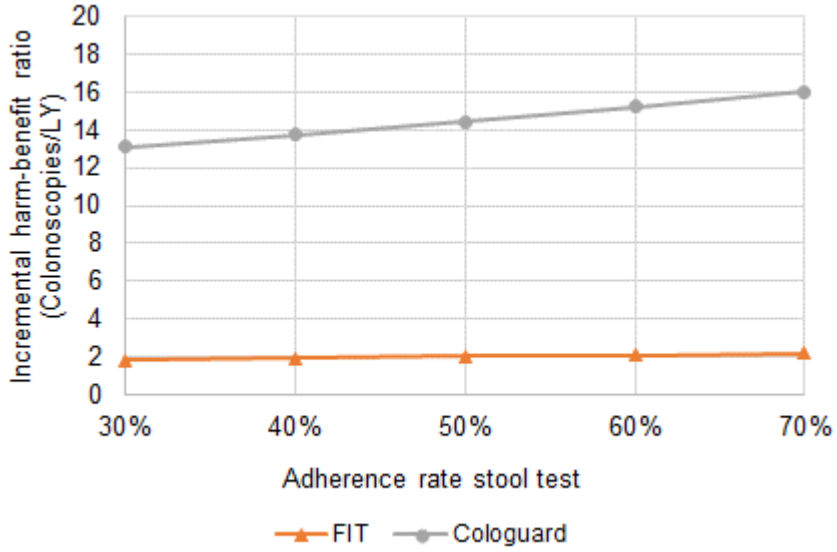
Figure 11. Sensitivity analysis of the impact of adherence rates in screening strategies based on stool tests on the number of colonoscopies at a 20% adherence rate in COL



Adherence rate COL 20%, Numbers pertain to a cohort of 1,000 persons 50 years of age who were followed until death in comparison to No Screening, all screening strategies include index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial).

Figure 12. Sensitivity analysis of the impact of adherence rates in screening strategies based on stool tests on the incremental benefit–harm ratio at a 20% adherence rate in COL

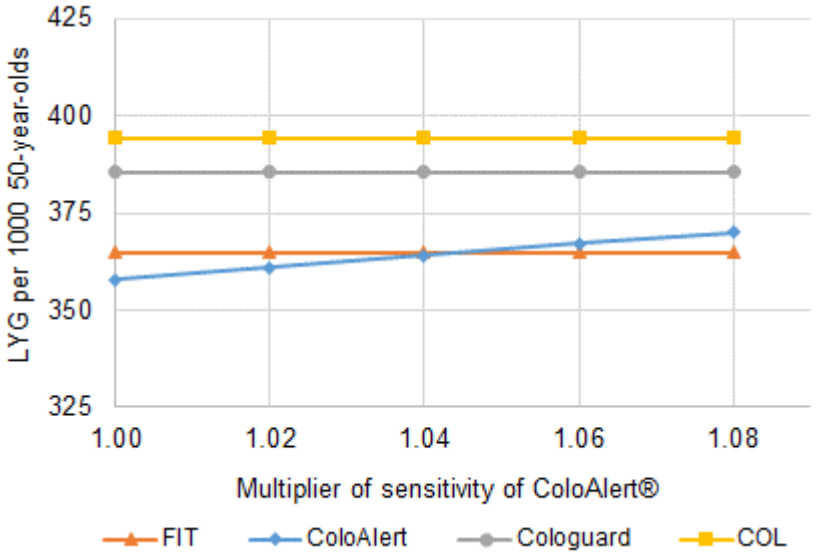


Adherence rate: COL 20%, ColoAlert and COL were dominated and, therefore, are not shown; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); LY=life year.

When the sensitivity of ColoAlert® increased (i.e., by applying a multiplier for sensitivity while keeping specificity on base-case value), 3-yearly ColoAlert remained dominated over the range of increased sensitivity (up to an 8% increase). The choice between the three remaining screening strategies depends on how much burden because of additional colonoscopies one is willing to accept to gain one additional LY. For this analysis, specificity of ColoAlert® was assumed to remain constant (Figure 13 to Figure 15).

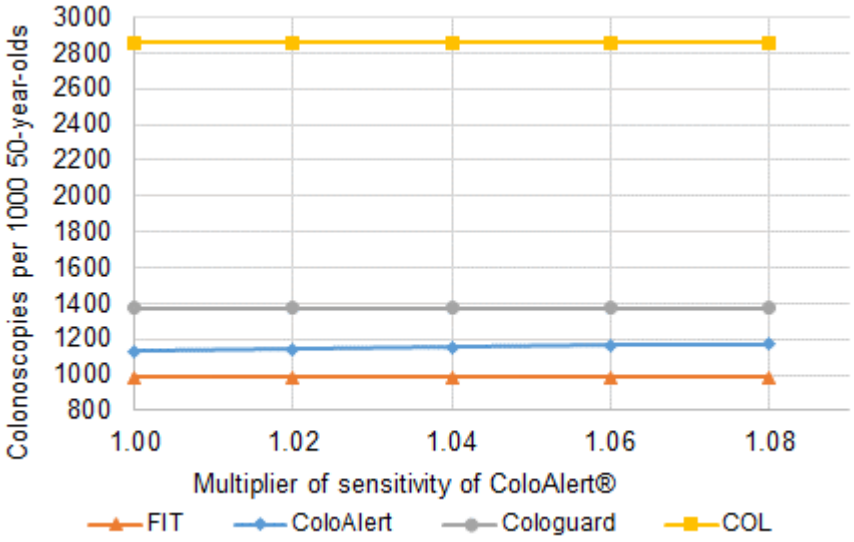
Figure 13. Sensitivity analysis of the impact of ColoAlert® sensitivity on life years gained



Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies include index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial); LYG=life years gained.

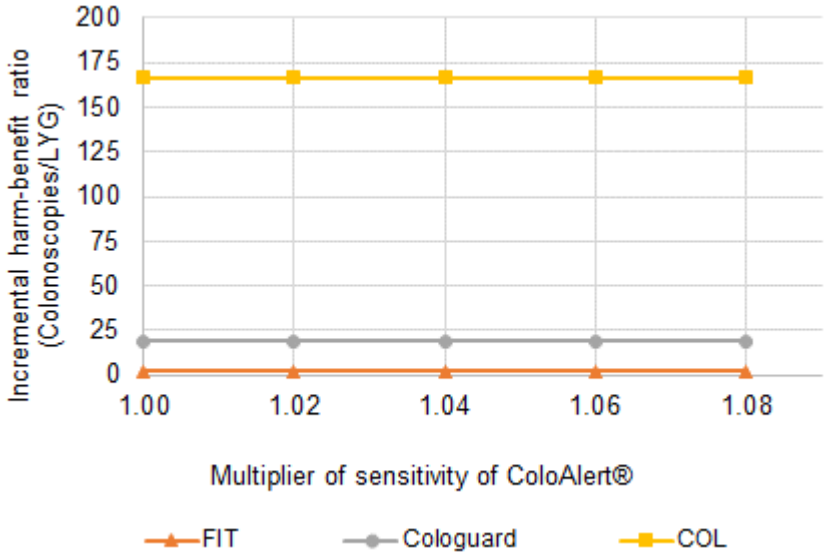
Figure 14. Sensitivity analysis of the impact of ColoAlert® sensitivity on the number of colonoscopies



Numbers pertain to a cohort of 1000 persons 50 years of age who were followed until death compared with No Screening; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial).

Figure 15. Sensitivity analysis of the impact of ColoAlert® sensitivity on the incremental harm–benefit ratio (colonoscopies/life years gained)



ColoAlert was dominated and, therefore, is not shown; all screening strategies included index testing, further diagnostics (including colonoscopy) and surveillance (colonoscopy).

Abbreviations: COL=colonoscopy-based strategy (age 50–74 years; every 10 years); ColoAlert=stool DNA-based strategy with ColoAlert® (age 50–74 years; every 3 years); Cologuard=stool DNA-based strategy with Cologuard® (age 50–74 years; every 3 years); FIT=immunochemical fecal occult blood stool test strategy (age 50–74 years; biennial).

8 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

8.1 Research questions

In the Project Plan, the questions 'Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organizational changes?' and 'Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organizationally relevant?' were identified as relevant.

The following assessment elements were identified accordingly:

Element ID	Research question
G0001	How does the test affect the current work processes?
D0023	How does the test modify the need of other technologies and use of resources?

8.2 Results

[G0001] How does the test affect the current work processes?

Within the screening pathway, stool DNA testing, depending on the chosen screening strategy, could act as: (1) a replacement for non-invasive screening tests such as gFOBT and FIT; or (2) a direct replacement of a screening colonoscopy.

Regarding the (physical) point of care, access to stool tests is not necessarily restricted to visiting a doctor: (versions of) most of the stool tests can also be ordered via the Internet or bought from a pharmacy. However, of the two stool DNA tests, Cologuard® is only available by prescription from a healthcare provider [12,13]. The stool tests are administered by the user screenee/patient at home and specimens (mostly) have to be sent to a laboratory for analysis. By contrast, colonoscopy is restricted to visiting a hospital, specialized center or similar institution. There are some differences regarding the administration and handling between the stool tests. Laboratories have to be specialized for the required kind of analysis. Currently, only two laboratories in Germany are qualified for analyzing ColoAlert® (Cologuard® is not currently available on the European market) [1].

[D0023] How does the test modify the need of other technologies and use of resources?

An increased usage of DNA stool testing will result in a higher demand for laboratories that have the relevant knowledge and experience. Moreover, the (diagnostic and surveillance) colonoscopy rate might change. As can be seen from the benefit–harm analysis (Section 7), a screening strategy incorporating a 3-yearly stool DNA test overall leads to a higher expected number of colonoscopies per screenee (for the remaining life time) than a screening strategy incorporating biennial FIT.

9 PATIENT INVOLVEMENT

Patients have been be involved during the scoping phase either via telephone or face to face, using a standardized open questionnaire (see also Appendix 4). This was deemed to be the most suitable way of involvement with regard to the number and location of patients. Patients were identified by personal communication and via a physician's office (general practitioner). They had to fulfill the criteria of a typical CRC screening population (asymptomatic persons aged according to national screening recommendations) that have experience with DNA stool testing, occult blood testing (gFOBT or FIT) or colonoscopy. All patients signed a conflict of interest form. They did not receive any remuneration for the interview. Information from patient involvement was used (or planned to be used if available) as additional information for: (1) assessing the relevance of ethical and social aspects; and (2) for answering research questions related to patient aspects (mainly assessment elements D0011-13, D0030 and D0017).

10 DISCUSSION

The two CE-marked DNA stool tests represent products in a series of research developments that consistently try to find new and better markers and analytical algorithms for the detection of CRC and precancerous lesions by the way of a non-invasive screening test. They are mainly designed for screening and prevention purpose. Similar to other stool tests, they are administered at home and the specimen is sent to (specialized) laboratories for analysis. ColoAlert® is the most recent product, being authorized in 2016. Thresholds and algorithms for the test being positive or negative had been set after the Phase II trial before market authorization, but have been further refined and the components (FIT instead of gFOBT) have been changed. ColoAlert® is of specific interest in the context of this assessment because it is the only DNA stool test currently sold on the European market (currently in Germany, Austria, Norway and Turkey).

There is a spectrum of CRC screening strategies in Europe, many being organized, some being opportunistic [14]. None of the screening programs currently include DNA stool testing; neither is it reimbursed in any European country. Most screening programs in Europe include colonoscopy, FIT and/or gFOBT, starting between the age of 50 and 60 up until the age of 70–75, thereby comprising a considerable proportion of the population.

In general, colonoscopy is accepted as the gold standard for detecting CRC and adenomas. However, detection rates, especially for adenomas, can vary among colonoscopists. Given disease progression and prognosis, the main target for triage screening tests such as stool tests is to yield a positive test result in persons with advanced adenomas or CRC. It can be discussed whether the tests also should, preferably, yield a positive result (and, thus, reference to colonoscopy) in cases of only nonadvanced adenomas.

For this reason, the test accuracy of CRC screening tests (against the reference standard) cannot be reduced to one value for sensitivity and one value for specificity; neither is there clear guidance regarding which value is the ‘right’ one, and at which of many possible cutoffs screenees, after a triage test, should be confronted with a positive test result and referred for colonoscopy. The importance of reliably ruling out CRC is without discussion and the same applies to advanced adenomas, given that they can be removed by polypectomy, preferably leading to shorter surveillance intervals thereafter. It applies to a lesser extent to nonadvanced adenomas. However, differentiation between these two groups of adenomas could not (directly) be made for the results of ColoAlert®, because advanced and nonadvanced adenomas were not reported separately in the study and were not available after request through the authors of this assessment.

In addition, the trade-off between sensitivity and specificity is related to whether nonadvanced adenomas should be seen immediately (and possibly removed) in colonoscopy or should ‘wait for later detection’. Depending on the approach taken, either the proportion of negative test results in all persons without CRC or adenoma, or the proportion of negative test results in all persons without CRC or advanced adenoma, is of interest with regard to specificity. Again, this differentiation cannot directly be made for ColoAlert®.

With regard to the reference standard, there might be an additional positive effect of a positive (DNA) stool test result, that of enhancing the awareness of the colonoscopist, thereby increasing the colonoscopy detection rate of adenomas.

Test failure rates are a relevant issue for judging test accuracy. Stool tests might not be submitted by the screenee or might not be evaluable or unusable for different reasons. It can be argued that, in the real world, a second specimen can or will be collected, although this would be associated with increased time effort and potential costs. Cologuard® had a higher failure rate than FIT; although numbers for ColoAlert® have been reported, they were only for all stool tests together. The exact failure rate for the ColoAlert® DNA assay was not reported[1].

[1] During the fact check process for this assessment, information was received from the manufacturer that, in 100 consecutive ColoAlert® samples that were sent to the laboratory during the first quarter of 2019, a test failure rate for ColoAlert® of ~8% was observed.

Given that both stool DNA tests have only been on the market for a few years, studies investigating the long-term effects of these tests on mortality and morbidity were not to be expected. In addition, no major adverse events or direct user-dependent harms were to be expected. By contrast, the (consequences of) false positive and false negative test results are of concern. Undetected (especially advanced) adenomas can progress further and false positive results lead to 'unnecessary' colonoscopies. Similarly, all positive results lead to immediate worry and all tests, namely colonoscopies, imply some kind of immediate burden to the screenee.

A specific strength of the decision-analytic modeling done for this assessment is that benefits, harms and burden over a lifelong time horizon were evaluated based on the natural history of the disease, including surveillance, capturing stage shift and incorporating survival probabilities. In the benefit–harm analysis, the tradeoffs between LYG/CRC deaths averted on the benefit side, and the number of positive tests as well as the number of colonoscopies on the harm/burden side of the screening strategies were investigated.

Findings of the decision-analytic modeling were consistent with the results of other published modeling studies, in terms of COL being the most effective strategy when benefit was expressed as LYG [21,127,128] and decreased CRC-specific mortality [21,23]. Applying the SimCRC model, Knudsen *et al.* [21] reported for 10-yearly colonoscopy (aged 50–75) expected 275 LYG and 24 averted CRC deaths per 1000 screenees. For biennial fecal immunochemical tests (aged 50–75), 234 LYG and 20 averted CRC cases were reported per 1000 screenees. For 3-yearly fecal immunochemical tests combined with a DNA stool test (aged 50–75), 250 LYG and 22 averted CRC deaths were reported per 1000 screenees [21]. In general, results differ across modeling studies because of key model assumptions, including age of initiation and termination of screening, screening intervals, surveillance, sensitivities of tests (depending on brand, cutoff values and source of information) evaluation period, and country-specific epidemiology, as well as healthcare and resource utilization structures. Most of the published studies presented cost-effectiveness but results on the screenee-/patient-relevant benefit–harm balance were limited, although this should be the first concern in such analyses. The USPSTF evaluated colonoscopy every 10 years and annual FIT as well as DNA stool test to provide comparable balance of benefits and screening burden [127]. The report found that 3-yearly fecal immunochemical tests with a DNA stool test (aged 50–75) were dominated [127].

Quality of the evidence for test accuracy results was mixed. The ColoAlert®-study was deemed to have a high risk of bias. Moreover, the currently available product differs in several components from the product that was evaluated in this study (with patient recruitment between 2005 and 2007). However, with replacement of gFOBT by FIT and further refinement of thresholds, it can be argued that test accuracy should have increased. However, there is no evidence from clinical trials currently available.

Commonly (besides colonoscopy) recommended and/or used screening tests such as FIT and gFOBT were included in the identified primary studies, as well as M2-PK-test. For other comparators defined within the scope of this assessment [(flexible) sigmoidoscopy, *SEPTIN9* test or CT colonography), no evidence was found that directly compared them with stool DNA testing.

Limitations

The incorporation of patient views into the assessment was limited by the difficulty of finding patients with stool DNA test experience. Results of patient surveys in the literature not only were heterogeneous and outside a European context, but also mostly referred to a precursor test of Cologuard®. Another limitation with regard to test accuracy results was the small number of available studies for the CE-marked products. Many studies have been done during the past decades on precursors of the tests or on different components of DNA testing, but it was decided not to include them within this assessment because of limited direct evidence regarding the actual products available.

As with all model-based analyses, there are several limitations regarding the modeling. First, mortality information and epidemiological calibration target values for the distribution of cancer stages were based on the Austrian population. Data and results might differ slightly in other European countries. Within the calibration, patients with reported unknown cancer stages in the registry were distributed among all cancer stages assuming random causes, and individuals with a death certificate only (i.e. patients for whom the death certificate provides the only notification to the registry) were assumed to be more severe and, therefore, distributed among UICC III and UICC IV stages.

Second, perfect adherence to screening was assumed in the base-case analysis, including follow-up and surveillance tests to show the maximum achievable benefit for each strategy from the screenee/patient perspective (if compliant). On a population level, implemented screening programs often do not achieve such benefits because of lower screening adherence, either because some individuals do not participate in a recommended screening strategy or do not fully adhere (during all intervals and follow-ups) to the respective screening strategy. Acceptance of a certain screening strategy and adherence to it might depend on several factors, such as the screening test itself with the related convenience, the preferences of individuals, comorbidities, or the response to respective mass campaigns [129-132]. Therefore, benefits, harms and burden resulting from the screening strategies in the base-case analysis might be overestimated. Therefore, the impact of adherence rates was tested in a systematic sensitivity analysis with varying adherence rates.

Third, it was assumed that the test accuracies of consecutive annual fecal blood tests were independent conditional on disease because of limited evidence. Therefore, our results might overestimate the effectiveness of fecal occult blood tests and DNA stool tests that include fecal occult blood tests. In practice, adenomas might be missed sequentially for systematic reasons despite 2-yearly or 3-yearly screening and could progress to cancer. In addition, the sensitivity of colonoscopy was assumed to be independent from previous tests. For a confirmatory colonoscopy, in practice, a physician examining a patient with a positive stool test might adapt clinical practice, spending more time and, therefore, increasing the chance of detecting lesions.

Fourth, some model input data were reported in a format in the literature that had to be transformed to be applied in our model. For example, test sensitivity data for ColoAlert were based on a clinical trial [3] that did not evaluate sensitivity for nonadvanced adenomas and advanced adenomas separately. Based on the total number of detected adenomas, sensitivity for nonadvanced adenomas and advanced adenomas needed to be recalculated. In addition, fecal occult blood testing was performed with ColoScreen-ES®. However, in recent applications, the DNA test is combined with a FIT. Therefore, the impact of improved sensitivity of ColoAlert® in a systematic sensitivity analysis was tested. Specificity of ColoAlert® was not assumed to increase further because the specificity of ColoScreen-ES® in the trial reported by Dollinger *et al.* [3] was similar to the specificity of OC FIT-CHEK® reported by Imperiale *et al.* [2].

Fifth, reported sensitivities of fecal immunochemical tests vary considerably depending on FIT brand and applied thresholds. Sensitivities of FIT for different brands for advanced adenomas were reported in a recent systematic review to range from 6% to 44% (median 28%) and for CRC from 25% to 100% (median 88%) [2]. A German study of nine quantitative fecal immunochemical tests reported sensitivities depending on various thresholds [41]. For consistency reasons, sensitivity and specificity of the FIT was based on a recent clinical trial of 9989 patients reporting test results of FIT and Cologuard® using for both tests OC FIT-CHEK® [2].

Sixth, an average number of lesions was used to model the expected number of lesions, the onset of adenomas was age dependent, but the progression of adenomas was not age specific. These simplifications are reasonable for our evaluation, but could be overcome by running a microsimulation.

Seventh, the number of evaluated screening strategies had to be restricted to a reasonable amount. The selection of strategies was based on guidelines and expert advice.

11 CONCLUSION

Stool DNA testing with Cologuard® had higher sensitivity for the detection of CRC and advanced adenoma compared with FIT, but lower specificity. However, these results depend to a degree on the exact type of FIT used. The test failure rate was higher for Cologuard® than for FIT. Given that FIT is not only a comparator, but also a component of Cologuard® itself, test failure rate (and costs, if the economic side is considered[2]) are important points of consideration.

Stool DNA testing with ColoAlert® (although referring to a former version of the product) had higher sensitivity for the detection of CRC and adenoma compared with gFOBT, but lower specificity. Sensitivity was comparable to M2-PK, whereas specificity, compared with M2-PK, was higher. The combined test failure rate of all three stool tests in this study was higher than of FIT (as seen in the study by Imperiale *et al.* [2]). There was no direct evidence available for the test accuracy for only advanced adenoma and no information on the exact proportion of test failures in the DNA assay alone compared to the other stool tests[3].

Overall certainty of evidence was moderate to high for Cologuard® results (two studies, both referring to the same Cologuard® study population) and low to very low for ColoAlert® results (one study).

Based on the decision-analytic modeling, CRC screening with a 10-yearly colonoscopy screening strategy was more effective than all other investigated screening strategies when considering long-term screenee-/patient-relevant outcomes, such as remaining life expectancy, CRC mortality and risk of developing CRC, and when assuming 100% adherence rates. The 3-yearly ColoAlert® screening strategy, the 3-yearly Cologuard® screening strategy and the biennial FIT screening were less effective than 10-yearly colonoscopy screening, but also led to less burden resulting from colonoscopies. The ColoAlert® strategy yielded fewer LYGs and caused more additional colonoscopies, compared with a 'no screening' strategy, than biennial FIT and, therefore, was dominated.

On average in the population, moving from 'no screening' to FIT caused an expected incremental burden of two additional colonoscopies per LYG; moving from FIT to Cologuard® strategy an incremental burden of 19 additional colonoscopies, and from a Cologuard® strategy to colonoscopy screening strategy an incremental burden of 167 additional colonoscopies per LYG. If harm of screening was measured in the psychological burden of positive test results instead of colonoscopies, colonoscopy screening strategy remained the only non-dominated strategy besides 'no screening' in the base-case analysis. However, the base-case result showed the maximum attainable effect with perfect adherence of patients to the screening schedule. By varying adherence rates to 20% for colonoscopy screening and 40% for the stool tests, both the colonoscopy screening strategy and the ColoAlert® strategy were dominated. Increasing the sensitivity of ColoAlert® by 8%, to take into account the replacement of gFOBT by FIT, led to ColoAlert® remaining dominated.

Stool DNA testing shows a promising benefit–harm balance when comparing different screening strategies, although this only currently refers to Cologuard®. By contrast, ColoAlert® is the only stool DNA test currently sold in Europe and, moreover, is available at a lower cost than Cologuard®. A high degree of uncertainty surrounds the evidence on ColoAlert®. A cross-sectional screening study including the current product version, and including FIT as well as gFOBT as comparators, could shed light on these questions. Regarding the comparator tests, especially FIT, it would be desirable to carefully select one, or even more than one, different brand(s) as comparator and provide some rationale for those choices. Among the six identified ongoing studies (Table A9), no study relates to ColoAlert®.

With regard to screening strategies, future research is recommended to assess further strategies, including the effect of different screening intervals (e.g. annual FIT screening or colonoscopy every 5 years) and combinations of, for example, stool tests and colonoscopy in one screening strategy.

[2] As foreseen in EUnetHTA Joint Assessments, no economic domain is included within this assessment.

[3] During the fact check process for this assessment, information was received from the manufacturer that, in 100 consecutive ColoAlert® samples that were sent to the laboratory during the first quarter of 2019, a test failure rate for ColoAlert® of ~8% was observed.

If data are available from primary studies, different thresholds for FIT and DNA-based tests could also be investigated in modeling studies.

In addition, in country-specific cost-effectiveness and budget-impact analyses of economic outcomes should be considered to support decision-making for healthcare payers.

12 REFERENCES

[1] PharmGenomics. Evidence submission templates to support production of core HTA information and rapid assessments: Medical devices evidence submission template short version. ColoAlert – Next Generation Colorectal Cancer Screening PharmGenomics GmbH, Mainz/Germany. 2018.
[2] Imperiale TR, DF.; Itzkowitz, SH., Levin, TR; Lavin, P; Lidgard, GP; Ahlquist, DA; Berger, BM. Multitarget stool DNA testing for colorectal-cancer screening. The New England Journal Of Medicine. 2014;370(14): 1287-97.
[3] Dollinger MM BS, Fleig WE. Early Detection of Colorectal Cancer: a Multi-Center Pre-Clinical Case Cohort Study for Validation of a Combined DNA Stool Test Clin Lab. 2018;64 (10): 1719-30. Epub 2018/10/20.
[4] Dollinger M, Hiemer S, Behl S, T. S, Fleig W. Frühdetektion kolorektaler Karzinome: Multizentrische Phase II-Studie zur Validierung eines neuen DNA-basierten Stuhltest. Der Internist. 2016: S53-S53.
[5] Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. American College of Physicians. 2011;155(8): 529-536.
[6] Brenner H, Chen H. Fecal occult blood versus DNA testing: Indirect comparison in a colorectal cancer screening population. Clinical Epidemiology. 2017;9: 377-84.
[7] Matthew V. Abola TFF, Marcia M. Chen, Zhengyi Chen, Ashutosh K. Sheth, Gregory Cooper, Li Li. Stool DNA-based versus colonoscopy-based colorectal cancer screening: Patient perceptions and preferences. Family Medicine and Community Health. 2015;2015;3(3): 2-8.
[8] Schroy PC, 3rd, Lal S, Glick JT, Robinson PA, Zamor P, Heeren TC. Patient preferences for colorectal cancer screening: how does stool DNA testing fare? The American Journal Of Managed Care. 2007;13(7): 393-400.
[9] Berger BM, Schroy PC, 3rd, Rosenberg JL, Lai-Goldman M, Eisenberg M, Brown T, et al. Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests. Clinical Colorectal Cancer. 2006;5(5): 338-43.
[10] Calderwood AH, Wasan SK, Heeren TC, Schroy PC, 3rd. Patient and Provider Preferences for Colorectal Cancer Screening: How Does CT Colonography Compare to Other Modalities? International Journal Of Cancer Prevention. 2011;4(4): 307-38.
[11] Schroy PC, 3rd, Heeren TC. Patient perceptions of stool-based DNA testing for colorectal cancer screening. American Journal Of Preventive Medicine. 2005;28(2): 208-14.
[12] Cologuard. How to get Cologuard. https://www.cologuardtest.com/how-to-get-cologuard2019 [02.07.2019], accessed 02.07.2019.
[13] Cologuard. Discussion Guide. Let's talk. 2019.
[14] Ponti A, Antilla A, Ronco G, Senore C. Against Cancer. Cancer Screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening. 2017.
[15] Segnan N, Patnick J, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. European Commission Ed. Ort|: Verlag|; Jahr|. Seitenzahl p|.
[16] DKG Krebsgesellschaft, Deutsche Krebshilfe, AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften). Leitlinienprogramm Onkologie. S3-Leitlinie Kolorektales Karzinom. Langversion 2.0. 2017.
[17] Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018.
[18] European Network for Health Technology Assessment. Joint Action on HTA 2012-2015: HTA core model; version 3.0 2016.
[19] European Network for Health Technology Assessment. Joint Action on HTA 2012-2015: HTA Core Model for Rapid Relative Effectiveness. 2016.
[20] Zauber AG. Cost-Effectiveness of Colonoscopy. Gastrointestinal endoscopy clinics of North America. 2010;20(4): 751-70.

[21] Knudsen AB, Zauber AG, Rutter CM, Naber SK, Doria-Rose VP, Pabiniak C, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA. 2016;315(23): 2595-609. Epub 2016/06/16.
[22] Ladabaum U, Alvarez-Osorio L, Rösch T, Brueggenjuergen B. Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. Endoscopy International Open. 2014;2(2): E96-E104.
[23] Berger BM, Schroy PC, 3rd, Dinh TA. Screening for Colorectal Cancer Using a Multitarget Stool DNA Test: Modeling the Effect of the Intertest Interval on Clinical Effectiveness. Clin Colorectal Cancer. 2016;15(3): e65-74. Epub 2016/01/23.
[24] Patel SS, Kilgore ML. Cost Effectiveness of Colorectal Cancer Screening Strategies. Cancer Control. 2015;22(2): 248-58. Epub 2015/06/13.
[25] Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care?: Springer; 2003.
[26] Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-Transition Modeling:A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–3. Medical Decision Making. 2012;32(5): 690-700.
[27] Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012;15(6): 812-20. Epub 2012/09/25.
[28] Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health. 2012;15(6): 796-803. Epub 2012/09/25.
[29] Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Med Decis Making. 2012;32(5): 667-77. Epub 2012/09/20.
[30] Drummond MF, Schwartz JS, Jonsson B, Luce BR, Neumann PJ, Siebert U, et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008;24(3): 244-58; discussion 362-8. Epub 2008/07/08.
[31] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Bmj. 2013;346: f1049. Epub 2013/03/27.
[32] EUnetHTA. Methods for health economic evaluations – A guideline based on current practices in Europe. 2016. Available online from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Methods%20for%20health%20economic%20evaluations%20A%20guideline%20based%20on%20current%20practices%20in%20Europe_Guideline_Final%20May%202015.pdf [Accessed on December 28, 2017].
[33] Hassan C, Quintero E, Dumonceau JM, Regula J, Brandao C, Chaussade S, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2013;45(10): 842-51. Epub 2013/09/14.
[34] Cancer Intervention and Surveillance Modeling Network (CISNET). Colorectal cancer models overview. Available online from: https://resources.cisnet.cancer.gov/registry/site-summary/colorectal/ [Accessed on December 28, 2017].
[35] Union POotE. European guidelines for quality assurance in colorectal cancer screening and diagnosis. 2010.
[36] Austrian Society of Gastroenterology and Hepatology ÖGfGuH-Ö. LEITLINIE Qualitätsgesicherte Vorsorgekoloskopie. 2010. Available from http://www.oeggh.at/zertifikat/pdf/2010/Leitlinie%2029%2009%202010_Version%201.5.pdf [Accessed on December 28, 2017].
[37] Statistics Austria. Personal communication. 2017.
[38] Statistics Austria. Sterbetafeln. Jährliche Sterbetafeln 1947 bis 2016 für Österreich. Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/bevoelkerung/sterbetafeln/index.html [Accessed on December 27, 2017].

[39] Brenner H, Jansen L, Ulrich A, Chang-Claude J, Hoffmeister M. Survival of patients with symptom- and screening-detected colorectal cancer. Oncotarget. 2016;7(28): 44695-704. Epub 2016/05/24.
[40] Corporation ES. Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer (DeeP-C). Available online from: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1311194/suppl_file/nejmoa1311194_protocol.pdf [Accessed on March 4, 2019].
[41] Gies A, Cuk K, Schrotz-King P, Brenner H. Direct Comparison of Diagnostic Performance of 9 Quantitative Fecal Immunochemical Tests for Colorectal Cancer Screening. Gastroenterology. 2018;154(1): 93-104. Epub 2017/09/30.
[42] Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology. 2011;259(2): 393-405. Epub 2011/03/19.
[43] (CISNET) CIaSMN. Screening for Colorectal Cancer, NCI- National Cancer Institute. Available online from: https://cisnet.cancer.gov/projections/colorectal/screening.php [Accessed on March 4, 2019].
[44] Holme Ø, Garborg K, Bretthauer M, Løberg M, Kalager M, Adami HO. Current status of screening for colorectal cancer. Annals of Oncology. 2013;24(8): 1963-72.
[45] Eddy D, Hollingworth W, Caro J, Tsevat J, McDonald KM, Wong J, et al. Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Value in Health. 2012;15: 843-50.
[46] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012;32(5): 733-43. Epub 2012/09/20.
[47] Phalguni A, Seaman H, Routh K, Halloran S, Simpson S. Tests detecting biomarkers for screening of colorectal cancer: What is on the horizon? GMS Health Technology Assessment. 2015;11: Doc01-Doc.
[48] Exact Sciences. Exact Sciences Provides Update on Strong Launch Trajectory of Cologuard®. https://www.exactsciences.com/newsroom/update-on-strong-launch-trajectory-of-cologuard%C2%AE2015 [27.03.2019], accessed 27.03.2019.
[49] Berger BM, Levin B, Hilsden RJ. Multitarget stool DNA for colorectal cancer screening: A review and commentary on the United States Preventive Services Draft Guidelines. World Journal Of Gastrointestinal Oncology. 2016;8(5): 450-8.
[50] Cologuard. Analyzing Stool DNA Based on Breakthrough sDNATechnology. https://www.cologuardtest.com/hcp/the-science 2019 [27.03.2019], accessed 27.03.2019.
[51] Parks, Philip, Weiser E. Cologuard®: A Call to Action in Colorectal Cancer Screening. 2018.
[52] Patera N, Schumacher I. Screening for Colorectal Cancer. Part 1: Screening Tests and Program Design
[53] Wasserkort R, Kalmar A, Valcz G, Spisak S, Krispin M, Toth K, et al. Aberrant septin 9 DNA methylation in colorectal cancer is restricted to a single CpG isalnd. BMC Cancer. 2013;13(398): 3-11.
[54] Wilbacher I, Scheffel S. CRC Screening mit M2-PK Stuhltest. Im Vergleich zu gFOBT und FIT. 2015.
[55] Molnár B, Tóth K, Barták BK, Tulassay Z. Plasma methylated septin 9: a colorectal cancer screening marker. Expert Review Of Molecular Diagnostics. 2015;15(2): 171-84.
[56] Rengucci C, De Maio G, Menghi M, Calistri D. Stool DNA Integrity Method for Colorectal Cancer Detection. Methods In Molecular Biology (Clifton, NJ). 2018;1765: 193-202.
[57] Suehiro Y, Hashimoto S, Higaki S, Fujii I, Suzuki C, Hoshida T, et al. Blood free-circulating DNA testing by highly sensitive methylation assay to diagnose colorectal neoplasias. Oncotarget. 2018;9(24): 16974-87.
[58] Skally M, Hanly P, Sharp L. Cost effectiveness of fecal DNA screening for colorectal cancer: a systematic review and quality appraisal of the literature. Applied Health Economics And Health Policy. 2013;11(3): 181-92.
[59] Young GP, Bosch LJW. Fecal tests: From blood to molecular markers. Current Colorectal Cancer Reports. 2011;7(1): 62-70.

[60] SY. G. The Current Guidelines and Recommended Protocols for Screening Colorectal Cancer. Biomedical & Pharmacology Journal. 2016;9(3): 957-966.
[61] Wang X, et al. Advances in epigenetic biomarker research in colorectal cancer. World Journal Of Gastroenterology. 2014;20(15): 4276-4287.
[62] MS C. From Colonic Polyps to Colon Cancer: Pathophysiology, Clinical Presentation, and Diagnosis. Clin Lab Med. 2005;25: 135-177.
[63] Rex DK, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2017;153(1): 307-323.
[64] Sofic A, et al. CT colonography in detection of colorectal carcinoma. Radiology And Oncology. 2010;44(1): 19-23.
[65] Taunk P, Calderwood AH. Colorectal cancer: Screening and surveillance recommendations. Journal of Clinical Outcomes Management. 2015;22(3): 130-142.
[66] Waldmann E, et al. How can screening colonoscopy be optimized? Digestive Diseases (Basel, Switzerland). 2015;33(1): 19-27.
[67] Wolf AMD, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA: A Cancer Journal For Clinicians. 2018.
[68] Guraya SY. The current guidelines and recommended protocols for screening colorectal cancer. Biomedical and Pharmacology Journal. 2016;9(3): 957-66.
[69] Hviding K, Juvet LK, Vines D, Fretheim A. Colorectal Cancer Screening – Effect on Mortality and Incidence Rate of Colorectal Cancer: Overview of Documentation and International Recommendations. 2008.
[70] Kormi SMA, Ardehkhani S, Kerachian MA. New insights into colorectal cancer screening and early detection tests. Colorectal Cancer. 2017;6(2): 63-8.
[71] Lauby Secretan B., Vilahur N, Bianchini F, Guha N, Straif K. The IARC Perspective on Colorectal Cancer Screening. N Engl J Med. 2018;378(18): 1734-1740.
[72] Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. Annals Of Internal Medicine. United States: American College of Physicians--American Society of Internal Medicine; 2010. p. 368-77.
[73] Ketwaroo GA, Sawhney MS. Quality measures and quality improvements in colonoscopy. Current Opinion. Gastroenterology. 2015;31(1): 56-61.
[74] Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., García FAR, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23): 2564-75.
[75] Lieberman D. Colorectal cancer screening: practice guidelines. Digestive Diseases (Basel, Switzerland). 2012;30 Suppl 2: 34-8.
[76] Stintzing S. Management of colorectal cancer. F1000Prime Reports. 2014;6(108).
[77] Edward Giovanucci, Walter CW. Dietary factors and risk of colon cancer. 2009;1994: 452. Journal Annals of Medicine.
[78] Dominik D. Alexander, Doulas L. Weed, Paula E. Miller, Mohammed MA. Red Meat and Colorectal Cancer: A Quantitative Update on the State of the Epidemiologic Science. Pub Med. 2015.
[79] Adam M. Bernstein, Mingyang Song, Xuehong Zhang, An Pan, Molin Wang, Charles S. Fuchs, et al. Processed and Unprocessed Red Meat and Risk of Colorectal Cancer: Analysis by Tumor Location and Modification by Time. 2015.
[80] Dominik D. Alexander, Douglas L. Weed, Paula E. Miller, Mohamed MA. Red Meat and Colorectal Cancer: A Quantitative Update on the State of the Epidemiologic Science. 2015: 543.
[81] Ferrer-Mayorga G, Larriba M, Crespo P, Muñoz A. Mechanisms of action of vitamin D in colon cancer. Journal of Steroid Biochemistry and Molecular Biology. 2019;185: 1-6.
[82] Sang-Min Jeon, Shin E-A. Exploring vitamin D metabolism and function in cancer. 2008;2018.
[83] Hall MJ, Manne SL, Myers RE, Keenan EM, Balshem AM, Weinberg DS. Predictors of patient uptake of colorectal cancer gene environment risk assessment. Genome Medicine. 2012;4(11): 92-.
[84] Hardiman KM. Update on Sporadic Colorectal Cancer Genetics. Clinics In Colon And Rectal Surgery. 2018;31(3): 147-52.

[85] Kanthan R, Senger JL, Kanthan SC. Fecal molecular markers for colorectal cancer screening. Gastroenterology Research and Practice. 2012;(no pagination)(184343).
[86] Nikolaou S, Qiu S, Fiorentino F, Rasheed S, Tekkis P, Kontovounisios C. Systematic review of blood diagnostic markers in colorectal cancer. Techniques In Coloproctology. 2018.
[87] Sweetser S, Ahlquist DA. Multi-Target Stool DNA Test: Is the Future Here? Current Gastroenterology Reports. 2016;18(6): 30-.
[88] Li Y, Song L, Gong Y, He B. Detection of colorectal cancer by DNA methylation biomarker SEPT9: past, present and future. Biomarkers In Medicine. 2014;8(5): 755-69.
[89] Wang X, Kuang Y-Y, Hu X-T. Advances in epigenetic biomarker research in colorectal cancer. World Journal Of Gastroenterology. 2014;20(15): 4276-87.
[90] Bosch LJW, Carvalho B, Fijneman RJA, Jimenez CR, Pinedo HM, van Engeland M, et al. Molecular tests for colorectal cancer screening. Clinical Colorectal Cancer. 2011;10(1): 8-23.
[91] Cappell MS. From colonic polyps to colon cancer: pathophysiology, clinical presentation, screening and colonoscopic therapy. Minerva Gastroenterologica E Dietologica. 2007;53(4): 351-73.
[92] Jefferson T, Cerbo M, Vicari N. Fecal Immunochemical Test (FIT) versus guaiac-based fecal occult blood test (FOBT) for colorectal cancer screening [Core HTA],. Agenas - Agenzia nazionale per i servizi sanitari regionali Ed. Ort|: Verlag|; Jahr|. Seitenzahl p|.
[93] Glaser A, Fraser L, Corner J, et al. Patient-reported outcomes of cancer survivors in England 1–5 years after diagnosis: a cross-sectional survey. BMJ Open. 2013;3: e002317-.
[94] Wilson T, Alexander D, Kind P. Measurement of health-related quality of life in the early follow-up of colon and rectal cancer. Dis Colon Rectum. 2006;49(11): 1692-1702.
[95] Trentham-Dietz A, Remington P, Moinpour C, Hampton J, Sapp A, Newcomb P. Health-related quality of life in female long-term colorectal cancer survivors. Oncologist. 2003;8(4): 342-349.
[96] Jansen L, Koch L, Brenner H, Arndt V. Quality of life among long-term (≥5 years) colorectal cancer survivors - systematic review. Eur J Cancer. 2010;46(16): 2879-. Epub 2888.
[97] Marventano S, Prieto-Flores M, Sanz-Barbero B, Martín-García S, Fernandez-Mayoralas G, et al. Quality of life in older people with dementia: a multilevel study of individual attributes and residential care center characteristics. Geriatr Gerontol Int. 2015;15(1): 104-110.
[98] Schreuders EH, Grobbee EJ, Spaander MCW, Kuipers EJ. Advances in Fecal Tests for Colorectal Cancer Screening. Current Treatment Options In Gastroenterology. 2016;14(1): 152-62.
[99] Waldmann E, Regula J, Ferlitsch M. How can screening colonoscopy be optimized? Digestive Diseases (Basel, Switzerland). 2015;33(1): 19-27.
[100] Bailey JR, Aggarwal A, Imperiale TF. Colorectal Cancer Screening: Stool DNA and Other Noninvasive Modalities. Gut And Liver. 2016;10(2): 204-11.
[101] Danalıoğlu A. Can "DNA-based stool tests" replace colonoscopy in screening for colon cancer? The Turkish Journal Of Gastroenterology: The Official Journal Of Turkish Society Of Gastroenterology. 2014;25(1): 122-3.
[102] Capellá G. Is fecal DNA testing superior to fecal occult-blood testing for colorectal cancer screening? Nature Clinical Practice Oncology. 2005;2(5): 234-5.
[103] Ridge JR, Statz S. Exact Sciences' experience with the FDA and CMS parallel review program. Expert Review Of Molecular Diagnostics. 2015;15(9): 1117-24.
[104] Wilking N, Hofmarcher T, Lindgren P, Jönsson B. The burden and direct cost of cancer in Europe (EU-28). Journal of Clinical Oncolog. 2016;34(15): 6618-6618.
[105] Ned RM, Melillo S, Marrone M. Fecal DNA testing for Colorectal Cancer Screening: the ColoSure™ test. PLoS Currents. 2011;3: RRN1220-RRN.
[106] Świderska M, et al. . The diagnostics of colorectal cancer. Contemp Oncol (Pozn). 2014;18(1): 1-6.
[107] Bernard F, Barkun A, Martel M, Von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. World J Gastroenterol. 2018;24(1): 124-138.

[108] Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Group CAADobotEGW. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013;24(6): vi64-vi72.
[109] van Cutsem E, Cervantes A, Group NBADobotEGW. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2014;25(3): iii1-iii9.
[110] Glynne-Jones R, Wyrwicz L, Tiret E, Ro C, Cervantes A, Committee ADobotEG. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017;28(4): iv22-iv40.
[111] Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA: A Cancer Journal For Clinicians. 2018.
[112] The council of the European Union. Council Recommendation of 2 December 2003 on Cancer Screening. (2003/878/EC) Official Journal of the European Union,. 2003;327: 34-38.
[113] Leitlinienprogramm-Onkologie. Leitlinienprogramm Onkologie. S3-Leitlinie Kolorektales Karzinom, Langversion 2.0, 2017. AWMF Registrierungsnummer: 021/007OL. http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/ 2017 [26.09.2018], accessed 26.09.2018.
[114] Eurostat. Population on 1st January by age, sex and type of projection [Datafile]. http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=proj_15npms&lang=en2018 [November 2018], accessed November 2018.
[115] Prince M, Lester L, Chiniwala R, Berger B. Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. World Journal Of Gastroenterology. 2017;23(3): 464-71.
[116] Ahlquist DA. Multi-target stool DNA test: a new high bar for noninvasive screening. Digestive Diseases And Sciences. 2015;60(3): 623-33.
[117] Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, et al. Screening for Colorectal Cancer: A Systematic Review for the U.S. Preventive Services Task Force. 2016.
[118] van Rijn J, Reitsma J, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101(2): 343-350.
[119] Allameh Z, Davari M, Emami M. Sensitivity and Specificity of Colorectal Cancer Mass Screening Methods: A Systematic Review of the Literature. Iran J Cancer Prev. 2011;4(2): 88-105.
[120] Asselineau J, Paye A, Bessède E, Perez P, Proust-Lima C. Different latent class models were used and evaluated for assessing the accuracy of campylobacter diag-nostic tests: overcoming imperfect reference standards? Epidemiology and Infection. 2018;146(1556): 1564.
[121] Reitsma J, Rutjes A, Khan K, Coomarasamy A, Bossuyt P. A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. J Clin Epidemiol. 2009;62(8): 797-806.
[122] Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. The New England Journal Of Medicine. 2004;351(26): 2704-14.
[123] Blue Regence. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening. 2018.
[124] EUnetHTA. Meta-analysis of Diagnostic Test Accuracy Studies. Guideline. EUnetHTA JA2 WP7. 2014.
[125] Johnson DH, Kisiel JB, Burger KN, Mahoney DW, Devens ME, Ahlquist DA, et al. Multitarget stool DNA test: clinical performance and impact on yield and quality of colonoscopy for colorectal cancer screening. Gastrointestinal Endoscopy. 2017;85(3): 657-65.e1.
[126] Fröschl B, Antony K, Ivansits S. Übersicht nationaler Kolonkrebs-Screening-Programme. Available from https://www.researchgate.net/publication/316683925_Ubersicht_nationaler_Kolonkrebs-Screening-Programme [Accessed on December 27, 2017]. 2017.
[127] Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev. 2011;33: 88-100. Epub 2011/06/03.

[128] Barzi A, Lenz H-J, Quinn DI, Sadeghi S. Comparative effectiveness of screening strategies for colorectal cancer. Cancer. 2017;123(9): 1516-27.
[129] Bretthauer M, Kaminski MF, Loberg M, Zauber AG, Regula J, Kuipers EJ, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med. 2016;176(7): 894-902. Epub 2016/05/24.
[130] Guiriguet C, Pera G, Castells A, Toran P, Grau J, Rivero I, et al. Impact of comorbid conditions on participation in an organised colorectal cancer screening programme: a cross-sectional study. BMC Cancer. 2017;17(1): 524. Epub 2017/08/09.
[131] Hassan C, Giorgi Rossi P, Camilloni L, Rex DK, Jimenez-Cendales B, Ferroni E, et al. Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. Aliment Pharmacol Ther. 2012;36(10): 929-40. Epub 2012/10/06.
[132] Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Prev Med. 2012;55(2): 87-92. Epub 2012/05/29.
[133] Von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: Overview and introduction to the full Supplement publication. Endoscopy. 2013;45(1): 51-59.
[134] Leitlinienprogramm-Onkologie. Leitlinienprogramm Onkologie. S3-Leitlinie Kolorektales Karzinom, Langversion 2.1, 2019. AWMF Registrierungsnummer: 021/007OL. http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/ 2019 [29.03.2019], accessed 29.03.2019.
[135] Zauber A, Knudsen A, Rutter C, Lansdorp-Vogelaar I, Kuntz K. Evaluating the benefits and harms of colorectal cancer screening strategies: a collaborative modeling approach. Available from: https://www.uspreventiveservicestaskforce.org/Home/GetFile/1/16540/cisnet-draft-modeling-report/pdf [Accessed on December 27, 2017]. AHRQ Publication. 2015(14-05203).
[136] Goede SL, van Roon AHC, Reijerink JCIY, van Vuuren AJ, Lansdorp-Vogelaar I, Habbema JDF, et al. Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. Gut. 2013;62(5): 727-34.
[137] Reumkens A, Rondagh EJ, Bakker CM, Winkens B, Masclee AA, Sanduleanu S. Post-Colonoscopy Complications: A Systematic Review, Time Trends, and Meta-Analysis of Population-Based Studies. Am J Gastroenterol. 2016;111(8): 1092-101. Epub 2016/06/15.
[138] Bundo M, Jahn B, Arvandi M, Sroczynski G, Siebert U, editors. Adenoma Miss Rate of Conventional Colonoscopy: a Systematic Review and Meta-Analysis [forthcoming poster presentation] EbM-Kongress 2018; 2018; Graz, Austria.
[139] Austrian Colonoscopy Registry. Personal communication. 2017.

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Table A1: Search strategy for Medline (23 March 2018)

Number	Search Terms	Results
S20	S4 AND S19	View Results (645)
S19	S15 OR S18	View Results (7,166)
S18	S16 OR S17	View Results (14)
S17	cologuard	View Results (13)
S16	colo-alert	View Results (1)
S15	S8 AND S14	View Results (7,161)
S14	S9 OR S10 OR S11 OR S12 OR S13	View Results (969,788)
S13	TI deoxyribonucleic acid	View Results (6,329)
S12	AB deoxyribonucleic acid	View Results (8,960)
S11	TI dna	View Results (283,708)
S10	AB dna	View Results (885,823)
S9	(MM "DNA")	View Results (126,979)
S8	S5 OR S6 OR S7	View Results (133,116)
S7	TI stool OR feces OR faeces OR fecal OR faecal	View Results (27,898)
S6	AB stool OR feces OR faeces OR fecal OR faecal	View Results (120,610)
S5	(MM "Feces")	View Results (24,073)
S4	S1 OR S2 OR S3	View Results (216,536)
S3	TI (colorectal OR colonic OR rectal OR rectum OR colon) AND (neoplasm* OR tumor* OR carcinoma* OR cancer*)	View Results (109,911)
S2	AB (colorectal OR colonic OR rectal OR rectum OR colon) AND (neoplasm* OR tumor* OR carcinoma* OR cancer*)	View Results (187,556)
S1	(MM "Colorectal Neoplasms")	View Results (66,807)

Table A2: Search strategy for Embase (27 March 2018)

Number	Search Terms	Results
1	(colorectal or colonic or rectal or rectum or colon).ab,ti.	478261
2	(neoplasm* or tumor* or carcinoma* or cancer*).ab,ti.	3367730
3	feces/	46829
4	(stool or feces or faeces or fecal or faecal).ab,ti.	155866
5	DNA/	356366
6	(DNA or deoxyribonucleic acid).ab,ti.	1089393
7	colorectal cancer/	122949
8	colo-alert.af.	1
9	cologuard.af.	39
10	1 and 2	305466

Number	Search Terms	Results
11	7 or 10	331753
12	3 or 4	168690
13	5 or 6	1161963
14	8 or 9	40
15	12 and 13	9709
16	14 or 15	9729
17	11 and 16	1059
18	limit 17 to exclude medline journals	96

Table A3: Search strategy for Embase (27 March 2018)

Number	Search Terms	Results
S20	S4 AND S19	View Results (27)
S19	S15 OR S18	View Results (152)
S18	S16 OR S17	View Results (2)
S17	cologuard	View Results (0)
S16	colo-alert	View Results (2)
S15	S8 AND S14	View Results (150)
S14	S9 OR S10 OR S11 OR S12 OR S13	View Results (6,971)
S13	TI deoxyribonucleic acid	View Results (23)
S12	AB deoxyribonucleic acid	View Results (129)
S11	TI dna	View Results (1,597)
S10	AB dna	View Results (6,536)
S9	(MH "DNA")	View Results (11)
S8	S5 OR S6 OR S7	View Results (8,923)
S7	TI stool OR feces OR faeces OR fecal OR faecal	View Results (6,978)
S6	AB stool OR feces OR faeces OR fecal OR faecal	View Results (8,895)
S5	(MH "Feces")	View Results (234)
S4	S1 OR S2 OR S3	View Results (11,328)
S3	TI (colorectal OR colonic OR rectal OR rectum OR colon) AND TI (neoplasm* OR tumor* OR carcinoma* OR cancer*)	View Results (7,468)
S2	AB (colorectal OR colonic OR rectal OR rectum OR colon) AND (neoplasm* OR tumor* OR carcinoma* OR cancer*)	View Results (8,976)
S1	(MH "Colorectal Neoplasms")	View Results (1,098)

Table A4: Search strategy for ClinicalTrials.gov (12 March 2019)

Number	Search Terms	Results
#1	(cologuard OR colo-alert) OR ((deoxyribonucleic acid OR dna) AND (stool OR feces OR faeces OR fecal OR faecal))	
#2	(colorectal OR colonic OR rectal OR rectum OR colon) AND (neoplasm OR tumor OR carcinoma OR cancer)	
#3	#1 AND #2	
	Applied Filters: Adult (18–64), Older Adult (65+)	56

Table A5: Search strategy for EU Clinical Trials Register (12 March 2019)

Number	Search Terms	Results
#1	(cologuard OR colo-alert) OR ((deoxyribonucleic acid OR dna) AND (stool OR feces OR faeces OR fecal OR faecal))	2

Table A6: Search strategy for WHO ICTRP (12 March 2019)

Number	Search Terms	Results
#1	(colorectal OR colonic OR rectal OR rectum OR colon) AND (neoplasm OR tumor OR carcinoma OR cancer)	
#2	(cologuard OR colo-alert) OR ((deoxyribonucleic acid OR dna) AND (stool OR feces OR faeces OR fecal OR faecal))	
#3	#1 AND #2	9

DESCRIPTION OF THE EVIDENCE USED

Guidelines for screening

Table A7: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
American College of Gastroenterology: **ACG guidelines**	2009	North America	Preferred screening test: colonoscopy, repeated every 10 years, starting at age 50 (strong recommendation, moderate-quality evidence). Preferred detection test: annual FIT (strong recommendation, moderate-quality evidence). Alternatives: - - annual Hemoccult Sensa (gFOBT) (strong recommendation, moderate-quality evidence) - - sDNA testing every 3 years (weak recommendation, moderate-quality evidence)	See left column
American College of Physicians: **ACP guidelines**	2015	North America	Screening for individuals between 50 to 75 years, using one of four suggested modalities: - -'high-sensitivity FOBT' or FIT (annually) - - FS every 5 years, colonoscopy every 10 years - - a combination of 'high-sensitivity' FOBT/FIT (every 3 years) and FS (every 5 years) Individuals 75 years or older and people with a life expectancy less than ten years should not undergo screening.	
US Preventive Services Task Force **USPSTF guidelines**	2016	North America	Screening average-risk individuals from age 50 to 75 (grade A recommendation). For individuals between 76 to 85 years, screening is defined as a personal decision (grade C recommendation). Individuals should be allowed to choose their preferred screening options: - annual high sensitivity gFOBT,	50 to 75 (grade A recommendation). 76 to 85 (grade C)

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			- annual FIT, - sDNA test every 1 to 3 years, - FS every 5 years, - colonoscopy every 10 years, - CT colonography every 5 years, - a combination of FS every 10 years with annual FIT.	
Canadian Task Force on Preventive Health Care: **CTFPHC guidelines**	2016	North America	Screening individuals aged 60 to 74: - using gFOBT or FIT every two years, - FS every 10 years (strong recommendation, low to moderate-quality evidence). Individuals aged 50 to 59 can get screened, using the same modalities (weak recommendation, moderate-quality evidence). Recommends against colonoscopy for screening (weak recommendation; low-quality evidence), based on the lack of high-quality evidence proving its efficacy when compared to other screening tests.	See left column
National Comprehensive Cancer Network: **NCCN guidelines**	2017	North America	Screening average-risk individuals starting at age 50. For individuals aged 76 to 85: recommended as an individual decision. Screening recommendations include: - colonoscopy every 10 years (category 2A), - annual high sensitivity gFOBT (category 1) or FIT (category 2A), - stool DNA test every 3 years (category 2A), - FS every 5 to 10 years (category 1),	high-level evidence (category 1) low-level evidence (category 2A).

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			- FS every 5 to 10 years combined with gFOBT/FIT at year 3 (category 2A), - CT colonography every 5 years (category 2A).	
American College of Gastroenterology, the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy: **United States Multi-Society Task Force: CRC guidelines**	2017	North America	Screening average-risk individuals starting at age 50 (strong recommendation; high-quality evidence). Screening should be interrupted at age 75 in individuals with negative prior screening or when life expectancy does not exceed 10 years (weak recommendation) Distinguishes cancer detection (colonoscopy, sigmoidoscopy, CT-colonography, capsule endoscopy) from cancer prevention (FOBT, genetic stool tests). Colonoscopy repeated every 10 years (grade B recommendation; 3b level of evidence). A positive FOBT needs to be followed up with a complete colonoscopy, any annual FOBT should be completed before the associated FS in order to avoid unnecessary FS. Genetic stool tests are not recommended for CRC screening, because of insufficient data. Radiologic screening modalities (CT and MR-colonography) are not recommended, but could be used in case of an incomplete colonoscopy in an individual requesting a complete colon examination.	Colonoscopy (grade B recommendation; 3b) Genetic stool tests (grade B recommendation; respectively 3b and 4 levels of evidence) Radiologic screening modalities (grade B recommendation; 3b level of evidence)
American Cancer Society. **(Guideline Update**)	2018	North America	Recommends that adults aged 45 years and older with an average risk of CRC undergo regular screening (with a high-sensitivity stool based test or a structural (visual) examination). All positive results on non-colonoscopy screening tests should be followed up with timely colonoscopy. Regular screening in adults aged 50 years and older is a strong recommendation. Qualified recommendations:	See left column

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			1) average risk adults with a life expectancy of more than 10 years continue CRC screening through the age of 75 years; 2) clinicians individualize CRC screening decisions for individuals aged 76 through 85 years based on patient preferences and life expectancy; 3) clinicians discourage individuals older than 85 years from continuing CRC screening. The options for CRC screening are: - fecal immunochemical test annually; - high-sensitivity, guaiac-based fecal occult blood test annually; - multitarget stool DNA test every 3 years; - colonoscopy every 10 years; - computed tomography colonography every 5 years; - flexible sigmoidoscopy every 5 years.	
European Colorectal Cancer **Screening Guidelines Working Group**	2013	Europe	Screening individuals between ages 50 and 74. FOBT is mentioned as the only screening method approved throughout the European Union. Most commonly used modalities in Europe are FOBT, FS and colonoscopy. gFOBT and FIT are effective, but it is suggested that quantitative FIT is superior. FOBTs should be repeated on an annual or biennial basis or, at the very least every three years if FIT is used. Current evidence supports 10 year surveillance if colonoscopy is used, suggesting that interval extension to 20 years might be appropriate. FS is discussed as potential screening test, but no screening interval is clearly defined; the authors suggest using the	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			same interval as for colonoscopy screening. FOBT with FS, CT colonography, stool DNA testing and capsule endoscopy are not recommended.	
German Guideline Program in Oncology (GGPO), Evidence-based Guideline for Colorectal Cancer, Version 2.1	2019	Germany	There exists a variety of FIT modalities offered in Germany with greatly varying specificities and sensitivities, making it difficult to favour FIT as a blanket statement over gFOBT. However, a given FIT test could replace gFOBT if its given specificity has been shown to be greater than 90%, while also exhibiting a high sensitivity (grade 0 recommendation; 3a level of evidence). Genetic stool tests were not recommended for CRC screening, because of insufficient data (grade B recommendation; respectively 3b and 4 levels of evidence). Radiologic screening modalities such as CT and MR-colonography were not recommended, but could be used in case of an incomplete colonoscopy in an individual requesting a complete colon examination (grade B recommendation; 3b level of evidence).	See left column
Spanish Society of Medical Oncology: **SEOM clinical guidelines for diagnosis and treatment of metastatic colorectal cancer**	2015	Europe	Screening for average-risk individuals between ages 50 and 74. Biennial FOBT is recommended based on high-quality evidence (grade A) with FIT considered as the preferred test. As alternative to FIT, annual or biennial high-sensitivity gFOBT, FS repeated every 5 years or colonoscopy repeated every 10 years can be used (grade B quality of evidence). Recommends against using a combination of FS and gFOBT. It also recommends against the use of CT colonography until sufficient data become available (grade B quality of evidence).	FOBT (grade A) FS, every 5 years or colonoscopy, every 10 years (grade B quality of evidence).
Scottish Intercollegiate Guidelines Network - Healthcare Improvement Scotland	2016	Europe	For screening quantitative FIT is recommended. FS is an efficacious screening test (more so than FIT), but its effectiveness is unproven - neither are colonoscopy nor CT colonography. The guideline does not specify an age range nor surveillance intervals following a negative FIT.	quantitative FIT (grade A recommendation).

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
European Commission **Multidisciplinary, evidence-based guidelines for quality assurance in CRC screening and diagnosis**	2013	Europe	In the European Union the age range recommended by the Council of the EU is 50–74 years for men and women. For screening FIT and gFOBT are recommended. **Endoscopy in the Diagnostics of Polyps and Colorectal Cancer** If a colonoscopy was incomplete due to a stenosing tumor, an additional preoperative CT colonography can be performed. In case of a positive FOBT/FIT test, suspicion of a tumor, or sigmoidoscopic evidence of neoplastic polyps, a full colonoscopy has to be performed. If a colonoscopy was incomplete due to other causes (e. g. adhesions), a CT colonography should be performed. **pT1 Cancer** After complete removal (R0) of low-risk (pT1, low-grade (G1, G2, L0)) cancer, endoscopic surveillance examinations of the local resection site should be performed after six months. Complete colonoscopy should be performed after three years. **Polyp Management (Follow-Up)** After removal of small single, non-neoplastic polyps, no endoscopic surveillance should be performed. Adjuvant therapy should not be omitted solely for reasons of age. For patients with R0 resected stage III colon cancer, adjuvant chemotherapy shall be carried out.	

Abbreviations: ACG -American College of Gastroenterology, FS -flexible sigmoidoscopy, CT - computed tomography , FIT - Fecal immunochemical test, gFOBT - Fecal Occult Blood Test (guaiac), ACP -American College of Physicians, USPSTF - US Preventive Services Task Force, - Canadian Task Force on Preventive Health Care, NCCN - National Comprehensive Cancer Network, MR - magnetic resonance, SEOM- Spanish Society of Medical Oncology, GGPO - German Guideline Program in Oncology.

Sources: Bernard *et al.* [107], Wolf *et al.* [17], Von Karsa *et al.* [133], Segnan *et al.* [15], DKG *et al.* [134], Lin *et al.* [117].

Evidence tables of test accuracy studies included for clinical effectiveness and safety

Table A8: Evidence table – Imperiale *et al.* 2014

Author(s), year of publication	Thomas F. Imperiale, David F. Ransohoff, Steven H. Itzkowitz, *et al.* 2014 [2]
Study objective	Comparison of a noninvasive, multitarget stool DNA test (Cologuard®) with a fecal immunochemical test (FIT) in persons at average risk for colorectal cancer
Country/ies of recruitment	USA, Canada
Setting	90 sites throughout USA and Canada, including private-practice and academic settings
Data collection period	June 2011 through November 2012
Diagnostic test (index test) and cut off	Multitarget stool DNA test (Cologuard®); consists of molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, and β-actin (a reference gene for human DNA quantity), as well as an immunochemical assay for human hemoglobin. Quantitative measurements of each marker were incorporated into a validated, prespecified logistic-regression algorithm, with a value ≥183 indicating that the test result was positive
Comparator test(s) and cut off	FIT (OC FIT-CHEK®, Polymedco); stool samples with >100 ng of hemoglobin per milliliter of buffer were considered to be positive
Reference standard and type of quality assurance	Histologically confirmed screening colonoscopy; quality assurance: colonoscopists were required to describe the extent of the examination, document cecal visualization, rate the quality of preparation (on a modified Aronchick scale), and record the size and location of lesions. The biopsy and surgical specimens underwent histopathological analysis at the laboratory typically used by each study site. Polyps with high grade dysplasia or 25% or more villous elements in adenomas measuring less than 1 cm, as well as sessile serrated or hyperplastic polyps measuring1 cm or larger, were re-reviewed centrally by a gastrointestinal pathologist for confirmation, with diagnostic disagreements resolved by consensus of at least two central pathologists.
Study design	prospective screening cross sectional study
Sponsoring	Exact Sciences
Conflict of interest	no conflict of interest reported
n of pat. enrolled (age, gender)	12776 (n. r.)
n of pat. could not be evaluated	1760
n of pat. could be evaluated	11016
n excluded due to test failure (%)	total: 1027 (9.32%), colonoscopy: 304 (2.76%), DNA stool test: 689 (6.25%), FIT: 34 (0.31%)
n of pat. fully evaluated	9989
Patients eligibility criteria	
inclusion criteria	asymptomatic persons between the ages of 50 and 84 years who were considered to be at average risk for colorectal cancer and who were scheduled to undergo screening colonoscopy. Enrolment was weighted toward persons 65 years of age or older in order to increase the prevalence of cancer.

Author(s), year of publication	**Thomas F. Imperiale, David F. Ransohoff, Steven H. Itzkowitz, *et al.* 2014 [2]**	
exclusion criteria	participants who had a personal history of colorectal neoplasia, digestive cancer, or inflammatory bowel disease; had undergone colonoscopy within the previous 9 years or a barium enema, computed tomographic colonography, or sigmoidoscopy within the previous 5 years; had positive results on fecal blood testing within the previous 6 months; had undergone colorectal resection for any reason other than sigmoid diverticula; had overt rectal bleeding within the previous 30 days; had a personal or family history of colorectal cancer; had participated in any interventional clinical study within the previous 30 days; or were unable or unwilling to provide written informed consent	
Evaluable group	age, mean (SD)	64.2 (8.41)
	gender (male); no. (%)	4625 (46.3%)
Non-evaluable group	age, mean (SD)	65.4 (8.50)*
	gender (male); no. (%)	1.282 (46.6)
Outcomes (test accuracy)		
CRC (any stage)	Multitarget stool DNA test (Cologuard®)	FIT (OC FIT-CHEK®, Polymedco)
n	4522	4522
true pos.	60	48
false pos.	455	162
false neg.	5	17
true neg.	4002	4295
sensitivity% (95% CI)	92.3 (80.3-97.5)	73.8 (61.5-84.0)
specificity% (95% CI)	89.8 (88.9-90.7)	96.4 (95.9-96.9)
PPV (95% CI)	0.037 (0.029–0.048)	0.068 (0.051–0.090)
NPV (95% CI)	0.999 (0.998–1.00)	0.998 (0.997–0.999)
NNS to detect CRC (95% CI)	166 (130-217)	208 (156-266)
APL (include advanced adenomas and sessile serrated polyps measuring ≥1cm)		
n	9924	9924
true pos.	321	180
false pos.	1231	472
false neg.	436	577
true neg.	7936	8695
sensitivity% (95% CI)	42.4 (38.9-46.0)	23.8 (61.5-84.0)
specificity% (95% CI)	86.6 (85.9-87.2)	94.9 (94.4-95.3)
PPV (95% CI)	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.
NNS to detect APL (95% CI)	13 (12-14)	55 (48-65)
Other outcomes		
psychological harms from false-neg. and false-pos. test results	n.r.	n.r.
health related quality of life	n.r.	n.r.

Author(s), year of publication	Thomas F. Imperiale, David F. Ransohoff, Steven H. Itzkowitz, *et al.* 2014 [2]	
handling problems carrying out the test/taking the specimen	474 stool samples that could not be evaluated owing to leakage in shipping or repeat specimen not received before colonoscopy 213 technical failure owing to insufficient DNA (low β-actin), hemoglobin sample volume, stool supernatant for target capture, or material for repeat assay 2 missing samples	34 samples excluded because of insufficient hemoglobin sample
patient adherence (patient preferences)	n.r.	n.r.
cost of the test	n.r.	n.r.

* significant

Abbreviations: APL=advanced precancerous lesion/s, CI=confidence interval, CRC=colorectal cancer, FIT=fecal immunochemical test, n=number, neg.=negative, NNS=Number needed to screen, NPP=negative predictive value, n. r.=not reported, pat.=patient/s, pos.=positive, PPV=positive predictive value, SD=standard deviation,%=percent

Source: Imperiale *et al.* 2014

Table A9: Evidence table – Dollinger *et al.* 2018

Author(s), year of publication	Matthias M. Dollinger, Susanna Behl, Wolfgang E. Fleig, 2018
Study objective	To investigate if a non-invasive stool assay can offer sufficient sensitivity and specificity to supplement colonoscopy-based screening.
Country/ies of recruitment	Germany
Setting	16 different centers (no further details reported)
Data collection period	n.r.
Diagnostic test (index test) and cut off	Combined DNA stool assay (ColoAlert®) includes: ▪ molecular assays for detection of gene mutations in KRAS (codon 12 and 13) and BRAF (codon 600) ▪ quantification of human DNA (hDNA); (pos. test result cutoff concentrations: ≥ 5 and ≥ 15 ng of hDNA per µL of total DNA extracted) ▪ standard gFOBT (ColoScreen-ES®, Helena Biosciences, USA) Combined DNA stool assay was pos. if at least 1 of the 4 markers were pos.; and neg. if none of the 4 testing systems came up as pos.
Comparator test(s) and cut off	▪ gFOBT (ColoScreen-ES®, Helena Biosciences, USA), cut off following manufacturer's specifications ▪ M2-PK assay (ScheBo Biotech AG, Germany), cut off following manufacturer's specifications ▪ Combined gFOBT and M2-PK assay; >test result was neg. if both tests were neg., and as pos. if at least 1 of the 2 tests was pos.
Reference standard and type of quality assurance	histologically confirmed screening colonoscopy; (no further information regarding type of quality assurance reported)
Study design	pre-clinical case cohort study
Sponsoring	Nordiag ASA (Norway)
Conflict of interest	no conflict of interest reported
n of pat. enrolled (age, gender)	734 (n.r.)

Author(s), year of publication	**Matthias M. Dollinger, Susanna Behl, Wolfgang E. Fleig, 2018**				
n of pat. could not be evaluated	7				
n of pat. could be evaluated	727				
n excluded due to test failure (%)	total: 161 (22.15%); colonoscopy: 32 (4.40%), all stool tests together: 129 (17,74%)				
n of pat. fully evaluated	566 (521, when patients with IBS and IBD excluded)				
Patients eligibility criteria					
inclusion criteria	Patients aged 38 to 85 prior to elective or screening colonoscopy or prior to surgery in case of a recent diagnosis of CRC. Patients prior to colonoscopy were included if the procedure was indicated independently of the inclusion in the study, either because of clinical symptoms, within the scope of cancer prevention (surveillance colonoscopy) or to check on previously diagnosed pathological findings (e.g., planned polypectomy in patients who had recently undergone a diagnostic colonoscopy); same applies to patients with planned polypectomy.				
exclusion criteria	Patients with known hereditary risk for developing CRC (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer), patients who had a second tumor or malignant illness identified in the previous five years, and patients with impaired coagulation and/or patients taking anticoagulant therapeutics. Other contraindications prohibiting colonoscopy or surgery were also considered. Furthermore, IBD and IBS patient groups were explicitly excluded from the calculations of all related statistics, as these patients clinically disqualify for such a screening test as most of all commercially available CRC tests frequently deliver false positive rates as results and using them is not recommended.				
Evaluable group	age, mean (SD)	61,5 (8,5)			
	gender (male); no. (%)	246 (47,2%)			
Non-evaluable group	age, mean (SD)	n.r.			
	gender (male); no. (%)	n.r			
Outcomes (test accuracy)					
CRC (any stage)	combined DNA test (hDNA 5ng/µL)	combined DNA test (hDNA 15ng/µL)	gFOBT	M2-PK	gFOBT+ M2-PK
n	304	304	302	276	303
true pos.	44	44	34	34	46
false pos.	25	21	9	92	96
false neg.	8	8	16	7	5
true neg.	227	231	243	143	156
sensitivity% (95% CI)	84.8 (71.9-93.1)	84.8 (71.9-93.1)	68.0 (53.3- 80.5)	82.9 (67.9- 92.8)	90.2 (78.6- 96.7)
specificity% (95% CI)	90.11 (85.7-93.5)	91.7 (87.5-94.8)	96.4 (93.3-98.4)	60.9 (54.3-67.1)	61.9 (55.6-67.9)
PPV (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
NNS to detect CRC (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
CRC or adenoma					

Author(s), year of publication	Matthias M. Dollinger, Susanna Behl, Wolfgang E. Fleig, 2018				
n	521	521	519	472	520
true pos.	67	66	41	87	103
false pos.	43	39	14	125	134
false neg.	119	120	143	72	82
true neg.	292	296	321	188	201
sensitivity% (95% CI)	36.0 (29.1-43.4)	35.5 (28.6-42.8)	22.3 (16.5- 29.0)	54.7 (46.6-62.6)	55.7 (48.2- 63.0)
specificity% (95% CI)	87.2 (83.1-90.6)	88.4 (84.4-91.6)	95.8 (93.1-97.7)	60.1 (54.4- 65.5)	60.0 (54.5- 65.3)
PPV (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
NNS to detect APL (95% CI)	n.r.	n.r.	n.r.	n.r.	n.r.
Other outcomes					
psychological harms from false-neg. and false-pos. test results	n.r.	n.r.	n.r.	n.r.	n.r.
health related quality of life	n.r.	n.r.	n.r.	n.r.	n.r.
handling problems carrying out the test/taking the specimen	n.r.	n.r.	n.r.	n.r.	n.r.
patient adherence (patient preferences)	n.r.	n.r.	n.r.	n.r.	n.r.
cost of the test	n.r.	n.r.	n.r.	n.r.	n.r.

Abbreviations: CI=confidence interval, CRC=colorectal cancer, gFOBT=Guaiac (based) fecal occult blood testing, IBD=inflammatory bowel disease, hDNA=human DNA, IBS=Irritable bowel syndrome, n=number, neg.=negative, NNS=Number needed to screen, NPP=negative predictive value, n.r.=not reported, pat.=patient/s, pos.=positive, PPV=positive predictive value, SD=standard deviation,%=percent

Source: Dollinger *et al.* 2018

Table A10: Evidence table – Brenner *et al.* 2017

Author(s), year of publication	Hermann Brenner, Hongda Chen, 2017
Study objective	To assess diagnostic performance of a quantitative FIT in an independent study among participants of screening colonoscopy and to compare it with the previously reported performance of a multitarget stool DNA test (MSDT, Cologuard®).
Country/ies of recruitment	Germany; recruitment for Cologuard study (Imperiale *et al.* 2014) in USA and Canada
Setting	Gastroenterology practices
Data collection period	November 2008 to September 2014
Diagnostic test (index test) and cut off	FIT (FOB Gold®; Sentinel Diagnostics, Milano, Italy) 2 cut offs for hemoglobin (hb) per g feces used: - as recommended by the manufacturer, i.e. 17 µg hb/g feces - 8.5 µg hb/g feces (to yield same specificity as reported for Cologuard® by Imperiale *et al.* 2014)
Comparator test(s) and cut off	performance data of Cologuard®, as reported by Imperiale et a. 2014

Author(s), year of publication	**Hermann Brenner, Hongda Chen, 2017**	
Reference standard and type of quality assurance	histologically confirmed screening colonoscopy; clinical data extracted in a standardized manner, by trained research assistants who, like the endoscopists, are blinded with respect to results of blood or stool tests.	
Study design	Prospective screening cohort study	
Sponsoring	grant from German Research Council (BLITZ study DFG, grant No. BR1704/16-1); Co-author H. Chen partly supported by the China Scholarship Council (CSC).	
Conflict of interest	no conflict of interest reported	
n of pat. enrolled (age, gender)	4203 (n.r.)	
n of pat. could not be evaluated	225 (32 history of CRC or IBD,193 colonoscopy in preceding 5 years)	
n of pat. could be evaluated	3978	
n excluded due to test failure (%)	484 (12.17%, 432 inadequate bowel preparation and 52 incomplete colonoscopy); not reported for FIT	
n of pat. fully evaluated	3494	
Patients eligibility criteria		
inclusion criteria	participants of screening colonoscopy, no previous diseases of the colon	
exclusion criteria	History of CRC or inflammatory bowel disease, colonoscopy in the preceding 5 years, inadequate bowel preparation before colonoscopy, incomplete colonoscopy	
Evaluable group (FIT)	age, mean (SD)	62.1
	gender (male); no. (%)	1737 (49.7)
Non-evaluable group	age, mean (SD)	n.r.
	gender (male); no. (%)	n.r.
Outcomes (test accuracy)		
CRC (any stage)	FIT, original cut off 17 µg hb/g	FIT, adjusted cut off 8.4 µg hb/g
n		
true pos.	29	29
false pos.	n.r.	n.r.
false neg.	1	1
true neg.	n.r.	n.r.
sensitivity% (95% CI)	96.7 (82.8-99.9)	96.7 (82.8-99.9)
specificity% (95% CI)	n.r.	n.r.
PPV (95% CI)	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.
NNS to detect CRC (95% CI)	n.r.	n.r.
APL		
n		
true pos.	121	170
false pos.	n.r.	n.r.
false neg.	235	189

Author(s), year of publication	Hermann Brenner, Hongda Chen, 2017	
true neg.	n.r.	n.r.
sensitivity% (95% CI)	33.7 (28.8-38.9)	47.4 (42.1-52.7)
specificity% (95% CI)	n.r.	n.r.
PPV (95% CI)	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.
NNS to detect APL (95% CI)	n.r.	n.r.
CRC or APL		
n		
true pos.	150	199
false pos.	225	419
false neg.	239	190
true neg.	2880	2686
sensitivity% (95% CI)	38.6 (33.7-43.6)	51.1(46.1-56.2)
specificity% (95% CI)	92.8 (91.8-93.4)	86.5 (85.3-87.7)
PPV (95% CI)	n.r.	n.r.
NPV (95% CI)	n.r.	n.r.
NNS to detect APL (95% CI)	n.r.	n.r.
Other outcomes		
psychological harms from false-neg. and false-pos. test results	n.r.	
health related quality of life	n.r.	
handling problems carrying out the test/taking the specimen	n.r.	
patient adherence (patient preferences)	n.r.	
cost of the test	costs for FIT (FOB Gold®) approximately 20-fold lower than for Cologuard®	

Abbreviations: APL=advanced precancerous lesion/s, CI=confidence interval, CRC=colorectal cancer, FIT=fecal immunochemical test, n=number, neg.=negative, NNS=Number needed to screen, NPP=negative predictive value, n. r.=not reported, pat.=patient/s, pos.=positive, PPV=positive predictive value, SD=standard deviation,%=percent

Source: Brenner *et al.* 2017

List of ongoing and planned studies

Table A11: List of ongoing studies with a stool DNA test

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02419716	July 2020	Observational	2404	Cologuard®	Colonoscopy (reference standard), no further comparator	Average risk patients 50 years and older	Primary endpoint: PPV and NPV at year 3 (in subjects with repeat DNA test after negative DNA test in year 1) Other endpoints include: CRC incidence; the distribution of colorectal epithelial lesions among test positive subjects in year 1 and 3; adherence to repeat Cologuard at year 3; compliance to colonoscopy following a positive Cologuard result; cross-over to alternative screening methodologies; test failure rate; adverse event rate
NCT03705013	May 2023	Observational study of sub-populations from NCT02419716	100	Cologuard®	Colonoscopy (reference standard), no further comparator	Four sub-populations: positive first Cologuard test and negative colonoscopy or no colonoscopy and positive 3-year follow-up Cologuard test and negative colonoscopy or no colonoscopy.	The number of subjects with discordant results that can be attributed to intercurrent disease
NCT03728348	July 2019	Observational	942	Cologuard®	Colonoscopy (reference standard), no further comparator	Subjects 45-49 years of age who are at average risk for development of CRC	Primary endpoint: to confirm the specificity of Cologuard®, in an average risk population aged 45 to 49 Other endpoints include: sensitivity for CRC and advanced adenoma; the distribution of colorectal epithelial lesions among test positive subjects; test failure rate
NCT01647776	March 2019	Observational	1600	Stool DNA (obviously Cologuard®)	Colonoscopy (reference standard) with biopsies of rectal and colon mucosa	Average-risk patients undergoing colonoscopy at screening endoscopy centers in the University Hospitals of Cleveland system, aged 30 to 80 years	Primary endpoint: stool DNA feasibility and compliance; efficacy of stool DNA testing for the detection of advanced adenomas

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Other endpoints include: concordance/discordance between tissue and stool DNA aberrant methylation markers; persistence of positive stool DNA testing after removal of advanced adenomas; frequency of missed or occult colonic and upper gastrointestinal neoplasia in patients with initially normal colonoscopies and persistently positive stool DNA testing
ChiCTR1800020071	Unclear. Last refreshment in December 2018	Observational (test accuracy study)	148	Stool multi-target DNA and microRNA-135b (combined)	Colonoscopy (reference standard) and pathology	Patients who finished a colonoscopy, aged 27 to 84 years (not clear if a screening population is included)	Not reported within the register
ChiCTR1800019552	Unclear. Last refreshment in November 2018	Observational (test accuracy study)	50	DNA methylation biomarkers	Colonoscopy (reference standard)	Individuals to be considered at average risk of colorectal cancer, aged 40-75	Test accuracy

Abbreviations: CRC=colorectal cancer, DNA=Deoxyribonucleic acid, NPV=negative predictive value, PPV=positive predictive value, RNA=ribonucleic acid

Sources: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (WHO ICTRP), EU Clinical Trials Register

Risk of bias tables

Table A12: Risk of bias – test accuracy studies

Trial/Authors	Risk of Bias				Applicability concerns		
	Patient selection (Domain 1)	Index test (Domain 2)	Reference standard (Domain 3)	Flow and timing (Domain 4)	Patient selection (Domain 1)	Index test (Domain 2)	Reference standard (Domain 3)
Imperiale *et al.* 2014 (Cologuard®)	U patient enrolment intentionally weighted towards persons ≥65 years of age, no consistent consecutive patient recruitment	L	L	L	L	L	L
Brenner *et al.* 2017 (Cologuard® data from Imperiale *et al.* 2014 compared to FIT)	U performance data of Cologuard® taken from Imperiale *et al.* 2014 (explanation for unclear risk see above)	L	L	L	L	L	L
Dollinger *et al.* 2018 (ColoAlert®)	H unclear, weather patient enrolment was consecutive and whether inappropriate exclusions have been avoided	L	L	H no adequate description of patient flow, insufficient information on excluded patients	H study population does not represent an average screening population (CRC and APL prevalence, patients <40 years of age)	H stool assay evaluated incorporates a gFOBT, whereas the CE-marked ColoAlert® stool DNA test includes a FIT instead	L

Abbreviations: APL=advanced precancerous lesion(s), CRC=Colorectal cancer, L=Low risk, H=High risk, U=Unclear risk

Sources: Imperiale *et al.* 2014, Brenner *et al.* 2017, Dollinger *et al.* 2018

Table A13: GRADE assessment of test accuracy outcomes of two studies: DNA stool testing (Cologuard®) versus FIT

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives 1) patients with CRC 2) patients with CRC or APL **False negatives** 1) patients incorrectly classified as not having CRC 2) patients incorrectly classified as not having CRC or APL	2 studies 1) 65+30 patients 2) 822+389 patients	cross-sectional (cohort type accuracy study)	not serious*	not serious	serious**	not serious	none***	⊕⊕⊕◯ MODERATE
True negatives 1) patients without CRC 2) patients without CRC or APL **False positives** 1) patients incorrectly classified as having CRC 2) patients incorrectly classified as having CRC or APL	2 studies 1) 9924+3464 patients 2) 9167+3105 patients	cross-sectional (cohort type accuracy study)	not serious*	not serious	not serious**	not serious	none***	⊕⊕⊕⊕ HIGH

* rated as not serious as there were no concerns about risk of bias (using QUADAS 2) except that the screening population was intentionally weighted toward persons 65 years of age or older in order to increase prevalence of CRC within the study population, ** inconsistency rated as serious as sensitivity with FIT was lower than DNA stool test in one study and higher in the other – although different brands were used (which might be an explanation) no consistent conclusions can be drawn; no inconsistency with specificity as the FIT cutoff was intentionally adjusted in such a way that it yielded the same specificity as reported for the DNA stool test, *** no publication bias was to be suspected or could be detected

Abbreviations: APL=advanced precancerous lesions, CoE=Certainty of evidence, CRC=colorectal cancer, FIT=Fecal immunochemical test.

Sources: Imperiale *et al.* 2014 [2], Brenner *et al.* 2017 [6].

Table A14: GRADE assessment of test accuracy outcomes of one study: DNA stool testing (ColoAlert®) versus gFOBT/versus M2-PK/versus gFOBT + M2-PK

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives 1) patients with CRC 2) patients with CRC or adenoma **False negatives** 1) patients incorrectly classified as not having CRC 2) patients incorrectly classified as not having CRC or adenoma	1 study 1) 52 patients 2) 186 patients	case-control type accuracy study (case cohort study)	serious*	serious**	not serious***	serious****	none*****	⊕◯◯◯ VERY LOW
True negatives 1) patients without CRC 2) patients without CRC or adenoma **False positives** 1) patients incorrectly classified as having CRC 2) patients incorrectly classified as having CRC or adenoma	1 study 1) 469 patients 2) 335 patients	case-control type accuracy study (case cohort study)	serious*	serious**	not serious***	not serious	none*****	⊕⊕◯◯ LOW

* unclear, weather patient enrolment was consecutive and whether inappropriate exclusions have been avoided; no adequate description of patient flow, insufficient information on excluded patients, ** combined stool assay evaluated in the included study incorporates a gFOBT, whereas the CE-marked ColoAlert® stool DNA test includes a FIT instead; study population does not represent an average CRC screening population, *** no inconsistency, als only one study, **** study includes an atypical high proportion of CRC cases which leads to an overestimated sensitivity of detecting 'CRC or adenoma', ***** no publication bias was to be suspected or could be detected

Abbreviations: CoE=Certainty of evidence, CRC=colorectal cancer, gFOBT=Guaiac (based) faecal occult blood test

Sources: Dollinger *et al.* [3].

Applicability tables

Table A15: Summary table characterizing the applicability of the body of studies

Domain	Description of applicability of evidence
Population	The study population in the two included studies on Cologuard® was asymptomatic persons between the ages of 50 and 84 years who were to be considered at average risk for CRC. Although in one study patient enrolment was intentionally weighted toward persons over 65 years of age in order to increase CRC prevalence within the study population, the study population might not differ from the target population for CRC screening. So no substantial concern about the applicability of the Cologuard study results on this aspect is noticed. However, the population of the ColoAlert® study does not represent an average CRC screening population, as by study design, CRC and APL prevalences are substantially higher than those reported for the target CRC screening population. Additionally patients under 40 years of age are included in the ColoAlert® study, which also differs from the target CRC screening population. Therefore concerns about the applicability regarding the population of the ColoAlert® study are stated.
Diagnostic (index) tests	The included studies assessed two multitarget/combined DNA stool assays (ColoAlert® and Cologuard®), which are both CE-marked tests in Europe. Cologuard® is also available on the USA market, approved by the FDA, and reimbursed by Medicare. In the USA Cologuard® is in routine use for non-invasive CRC screening. The reported study results for Cologuard® are rated as being applicable for routine use. Regarding the applicability of the ColoAlert® test concerns are noted as the combined stool assay evaluated in the included study incorporates a gFOBT, whereas the CE-marked ColoAlert® stool DNA test includes a FIT instead.
Reference standard	The appropriate reference standard for screening CRC (and APL) is histologically confirmed colonoscopy. All included studies used histologically confirmed colonoscopy as the reference test, so there is no concern about the applicability regarding this aspect.
Comparators	The comparators assessed in the included studies are FIT, gFOBT, and the M2-PK assay. In particular FIT and gFOBT are those diagnostic tests, which are in routine use for CRC screening in most European countries. There are no concerns about the applicability of the study results of these comparators.
Outcomes	The most frequently reported outcomes from the included studies are test accuracy data (i.e. positive and negative test results, sensitivity, and specificity), reflecting relevant outcomes for CRC screening tests. However, other relevant outcomes, e.g. positive and negative predictive values and number needed to screen to detect CRC or APL, have been reported in only one of the three included studies. Results on harms of the screenings tests assessed are lacking in all of the included studies and are not mentioned as primary or secondary outcomes.
Setting	The assessed screening tests have been carried out in medical practices as well as in academic centers, stool specimen have been taken by the patients at their private places. This reflects the settings in which the assessed screening tests typically will be used.

Abbreviations: APL=advanced precancerous lesion/s, CRC=colorectal cancer, FIT=fecal immunochemical test, gFOBT=Guaiac (based) fecal occult blood testing, M2-PK=M2 pyruvate kinase

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A16: Regulatory status

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
European countries	Organization in charge of giving CE mark in each country	yes	Cologuard®: non-invasive DNA colorectal cancer screening test ColoAlert®: two of the product components are CE-IVD certified. The complete product has a CE mark as patient kit.	ColoAlert® shall not be used by patients with known irritable bowel syndrome and inflammatory bowel disease disorders.	Cologuard®: 2014 (by FDA through a pilot parallel review program), date of CE mark unknown, probably 2014 ColoAlert®: 2016	Cologuard®: not launched in European countries ColoAlert®: launched in 2016	DE/CA33/PHG/2015/2/1 (ColoAlert® patient kit) Others n.a.

Abbreviations: DNA=Deoxyribonucleic acid, FDA=Food and Drug Administration, IVD=In vitro diagnostics.

Sources: Exact Sciences [48], PharmGenomics [1], Ridge *et al.* 2015 [103].

Table A17: Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Stool DNA tests are not reimbursed in European countries.		

Abbreviations: DNA=Deoxyribonucleic acid

Sources: PharmGenomics [1], survey among EUnetHTA-partners

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1. Ethical	Relevance*
Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No**
Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No**
Organisational	Relevance*
Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organizational changes?	Yes
An increased usage of DNA stool testing might result in a higher demand for laboratories that have the relevant knowledge/experience (e.g. in 2018 there was only one laboratory for analysing ColoAlert®). Moreover, the (diagnostic) colonoscopy rate might change.	
Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organizationally relevant?	Yes
See above.	
Social	Relevance*
Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
Legal	Relevance*
Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

* If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.

** All forms of genetic technologies can potentially raise ethical issues. However, the technologies in questions do not seem to present any new specific ethical challenges.

APPENDIX 4: MISCELLANEOUS

Table A18: Documentation of queries to study authors in the assessment report

Study	Content of query	Reply received yes/no	Content of reply
Dollinger *et al.* 2018 (communication with study sponsor)	▪ Explanations for the reasons of excluded patients	yes	▪ Missing reasons were given
	▪ Inquiry about availability of results for advanced and non-advanced adenomas separately	yes	▪ Results not available
	▪ Inquiry about the exact dates of study recruitment ▪ Inquiry about the current definition of hDNA thresholds and algorithm ▪ Inquiry if colonoscopy was performed blinded to the index test(s)	yes	▪ Dates/answers were given accordingly
	▪ Inquiry how many gFOBT, how many M2-PK and how many of the DNA-assays were missing or unusable ▪ Inquiry how sufficient quality of colonoscopy was ensured	yes	▪ No clear reply on these questions
	▪ Inquiry about the costs of ColoAlert®	yes	▪ Price is defined by local partners independently. Manufacturer recommends to not exceed the German prices largely, though.

Table A19: Standardized patient questionnaire

1. What do you know about screening of colorectal cancer in your country?
2. What kind of tests do you know?
a. ☐ Colonoscopy b. ☐ DNA-blood-stool-test c. ☐ FIT d. ☐ gFOBT } Blood stool tests
3. What kind of test did you already do?
a. ☐ Colonoscopy b. ☐ DNA-blood-stool-test c. ☐ FIT d. ☐ gFOBT } Blood stool tests
4. Did you have the option to choose the test? If so, why did you decide to do:
a. ☐ Colonoscopy b. ☐ DNA-blood-stool-test c. ☐ FIT d. ☐ gFOBT } Blood stool tests
5. Did your GP offer you the option of a colonoscopy?
6. Do you have particular risk factors for CRC?
Colonoscopy
1. When did you have a colonoscopy?
2. How often did you have a colonoscopy?
3. Why did you decide to do a colonoscopy?
4. How were the preparations for the examination?
5. Did you feel any pain? Did you use anesthesia?
6. Were there any complications?
7. Would you do it again?
Blood-stool-tests
1. Do you know what kind of stool test you used for examination? (multiple answers are possible)
☐ Colonoscopy ☐ DNA-blood-stool-test ☐ FIT ☐ gFOBT

2. Why did you decide for your chosen option?
3. Why did you decide against the other options? Is there a reason why you decided against a colonoscopy?
4. How often did you submit a stool-blood test?
5. Could you explain how you collected your most recent stool sample?
6. Did they give you any information on how to collect the stool sample?
7. When you were given the stool collection kit, did your worry about how to collect the stool sample?
8. When you collected the sample did you find it easier or harder than you had expected? Why?
9. Why do you think some patients don't return stool samples?

BENEFIT-HARM-MODELING

Validation

Following the ISPOR-SMDM good modeling practice recommendations, the model was validated internally and externally on several levels: (1) face validity (i.e., by clinical experts, modeling experts), (2) internal validation (e.g., debugging, consistency and plausibility checks) and (3) external validation.

External validation was performed with epidemiological data from Statistics Austria [37] on cumulative cancer mortality at age 75 and data from the literature. As a result, the calibrated natural history model predicts a cumulative CRC related mortality of 1.74% at the age of 75. Statistics Austria reports a cumulative mortality of 1.97% for the years 1995-1999 [37] when there was no CRC screening established in Austria. The relative difference of -4.28% is reasonable according to the Austrian expert panel.

Model calibration

Calibration parameters were transition probabilities from adenoma to advanced adenoma, advanced adenoma to preclinical UICC stage I and from preclinical UICC stage I to stage II, III and IV as well as probabilities of being symptomatic (from any preclinical stage).

The transition probabilities were estimated in three steps. First, epidemiological data were determined from published literature serving as starting parameter sets for the start of adenoma growth and data from Statistics Austria for calibration targets. Second, the model was calibrated in a hierarchical fashion using optimization algorithms. Third, a final parameter adjustment was performed to meet target distribution for all cancer stages.

The cumulative incidence of colorectal cancer at age 75 (i.e., the risk to develop cancer by the age of 75) was the primary calibration target. Secondary targets were age-specific lifetime incidence and the cancer stage distribution (detected UICC I-IV cases). These target parameters were derived from an unscreened population in Austria (1995-1999) [37]. Age-specific lifetime incidence was given in 5-year age groups with a peak at age 70-75.

It was assumed that cancer cases reported as death certificate only (DCO cases) are severe cases and therefore, they were proportionally distributed among UICC III-IV stages. Cases with undefined cancer stages were proportionally distributed among UICC I-IV cases. Stage distribution from the

US Surveillance, Epidemiology, and End Results Program (SEER) database and other modeling studies were applied for plausibility checks [135].

Table A20: Natural history model parameters and screening adverse effects

Transition From	To	Age (years)	Annual probability (annual rate)	Source
No lesion	Adenoma	0-19	0.00200*	Goede *et al.* 2013 [136]
		20-29	0.00400*	
		30-39	0.00600*	
		40-44	0.02400*	
		45-49	0.02900*	
		50-54	0.03000*	
		55-59	0.03400*	
		60-64	0.04100*	
		65-69	0.04700*	
		70-74	0.05700*	
		75-79	0.03800*	
		80-84	0.03600*	
		85-120	0.01000*	
Adenoma	Advanced adenoma		0.016273	calibrated
Advanced adenoma	UICC I undetected		0.027150	calibrated
UICC I undetected	UICC II undetected		0.500000	calibrated
UICC II undetected	UICC III undetected		0.600000	calibrated
UICC III undetected	UICC IV undetected		0.700000	calibrated
UICC I undetected	UICC I detected by symptoms		0.105000	calibrated
UICC II undetected	UICC II detected by symptoms		0.205000	calibrated
UICC III undetected	UICC III detected by symptoms		0.450000	calibrated
UICC IV undetected	UICC IV detected by symptoms		1.000000	calibrated
Screening adverse effects				
Death from colonoscopy			0.002900	Reumkens *et al.* 2016 [137]
Hospitalization			0.000420	Austrian Colonoscopy Registry (personal communication, 2017)

* Calibrated to autopsy studies.
Calibrated - to cumulative and age-specific incidence of colorectal cancer and UICC stage distribution of incident cases in Austria - Statistics Austria 1995-1999 [37].

Abbreviations: UICC - Union for International Cancer Control classification.

Age-specific adenoma incidence was derived from a calibration study of the MISCAN CRC screening model for the Netherlands [136]. In this study, observed adenoma prevalence data estimated from international autopsy studies and Dutch epidemiological target data were used [136].

In the second step performing an automated calibration, the calibration parameters were first fitted to the cumulative cancer incidence at age 75 and age-specific lifetime-risk was checked. Thereafter, the algorithm was adapted using a weighted set of two target parameters (cumulative incidence, UICC stage distribution) as a goodness-of-fit measure.

In the third step (non-automated), marginal adjustments were performed to obtain stage distribution of UICC II-IV cancer cases.

Screening test accuracy values applied in benefit-harm analysis

Table A21: Screening test accuracy data

Test	Value	Source
Colonoscopy		
Sensitivity for non-advanced adenomas	69.0%	Bundo *et al.* 2017 [138]*
Sensitivity for advanced adenomas	86.7%	Bundo *et al.* 2017 [138]*
Sensitivity for cancer	94.7%	Pickhardt *et al.* 2003 [42]
Specificity	100.0%	NCI [43], Garborg *et al.* 2013 [44]
ColoAlert®		
Sensitivity for non-advanced adenomas	12.60%	Recalculated from Dollinger *et al.* 2018 [3]
Sensitivity for advanced adenomas	31.03%	Recalculated from Dollinger *et al.* 2018 [3]
Sensitivity for cancer	84.62%	Dollinger *et al.* 2018 [3]
Specificity	91.7%	Dollinger *et al.* 2018 [3]
Cologuard®		_ENREF_27
Sensitivity for non-advanced adenomas	17.21%	Imperiale *et al.* 2014 [2]
Sensitivity for advanced adenomas	42.40%	Imperiale *et al.* 2014 [2]
Sensitivity for cancer	92.31%	Imperiale *et al.* 2014 [2]
Specificity	89.80%	Imperiale *et al.* 2014 [2]
FIT		_ENREF_27
Sensitivity for adenomas	7.60%	Imperiale *et al.* 2014 [2]
Sensitivity for advanced adenomas	23.80%	Imperiale *et al.* 2014 [2]
Sensitivity for cancer	73.80%	Imperiale *et al.* 2014 [2]
Specificity	96.4%	Imperiale *et al.* 2014 [2]

Abbreviations: FIT - fecal immunochemical test, NCI – National Cancer Institute.

* Sensitivity for non-advanced and advanced adenomas is calculated per patient. Therefore, the missed non-advanced adenoma rate (41.44%) and missed advanced adenoma rate (18.1%) was determined from a meta-analysis (11 tandem colonoscopy studies; 1314 patients) [138]. The sensitivity of colonoscopy for adenomas (69.0%) and for advanced adenomas (86.7%) per patient were consequently based on the number of adenomas per patient. Distributions of adenomas in Austrian individuals were applied [139].

Colorectal cancer survival and mortality data

Table A22: Relative survival probability for patients with symptomatic-detected colorectal cancer

Year post first diagnosis	Relative survival probability for symptomatic-detected colorectal cancer patients with first CRC diagnosis			
	UICC I	**UICC II**	**UICC III**	**UICC IV**
1-year	0.915	0.892	0.851	0.470
2-year	0.980	0.961	0.888	0.615
3-year	0.983	0.967	0.905	0.645
4-year	0.978	0.964	0.911	0.721
5-year	0.991	0.966	0.939	0.806
6-year	0.993	0.972	0.950	0.840
7-year	0.994	0.977	0.959	0.869
8-year	0.995	0.981	0.966	0.896
9-year	0.996	0.985	0.973	0.920
10-year	0.997	0.989	0.980	0.942
11-year	0.998	0.992	0.985	0.963
12-year	0.999	0.995	0.991	0.982
13-year	1.000	0.997	0.995	1.000
14-year	1.000	1.000	1.000	1.000

Recalculated based on averaged relative survival probabilities from Statistics Austria 2010-2014 for first diagnosis (ICD 10 C18 - malignant neoplasm of colon, ICD 10 C19 - malignant neoplasm of rectosigmoid junction, ICD 10 C20 - malignant neoplasm of rectum) including screen and non-screen detected patients.
Abbreviations: CRC - colorectal cancer, UICC - Union for International Cancer Control classification.

Table A23: Relative survival probability for patients with screen-detected colorectal cancer

Year post first diagnosis	Relative survival probability for screen-detected colorectal cancer patients with first CRC diagnosis			
	UICC I	**UICC II**	**UICC III**	**UICC IV**
1-year	0.975	0.967	0.948	0.675
2-year	0.994	0.989	0.961	0.777
3-year	0.995	0.990	0.968	0.796
4-year	0.994	0.989	0.970	0.843
5-year	0.997	0.990	0.979	0.894
6-year	0.998	0.992	0.983	0.913
7-year	0.998	0.993	0.986	0.930
8-year	0.999	0.994	0.989	0.944
9-year	0.999	0.996	0.991	0.958
10-year	0.999	0.997	0.993	0.970
11-year	1.000	0.998	0.995	0.981
12-year	1.000	0.998	0.997	0.991
13-year	1.000	0.999	0.999	1.000
14-year	1.000	1.000	1.000	1.000

Recalculated based on averaged relative survival probabilities from Statistics Austria 2010-2014 for first diagnosis (ICD 10 C18 - malignant neoplasm of colon, ICD 10 C19 - malignant neoplasm of rectosigmoid junction, ICD 10 C20 - malignant neoplasm of rectum) including screen and non-screen detected patients.
Abbreviations: CRC - colorectal cancer, UICC - Union for International Cancer Control classification.

Table A24: Background mortality of the general population in Austria 2016 (Statistics Austria)

Age [years]	Prob. of death in age interval	Age [years] continued	Prob. of death in age interval	Age [years] continued	Prob. of death in age interval
0	0.00307	41	0.00099	82	0.054750
1	0.00028	42	0.00087	83	0.062720
2	0.00014	43	0.00102	84	0.069350
3	0.00012	44	0.00144	85	0.080300
4	0.00005	45	0.00132	86	0.092230
5	0.00012	46	0.00154	87	0.104170
6	0.00002	47	0.00159	88	0.119310
7	0.00011	48	0.00198	89	0.128990
8	0.00006	49	0.00221	90	0.147420
9	0.00010	50	0.00232	91	0.168440
10	0.00007	51	0.00234	92	0.191490
11	0.00008	52	0.00271	93	0.215040
12	0.00010	53	0.00318	94	0.219660
13	0.00007	54	0.00367	95	0.247870
14	0.00007	55	0.00367	96	0.271770
15	0.00018	56	0.00464	97	0.299200
16	0.00023	57	0.00532	98	0.322160
17	0.00024	58	0.00539	99	0.373920
18	0.00040	59	0.00611	100	0.398363
19	0.00043	60	0.00640	101	0.434346
20	0.00049	61	0.00714	102	0.472143
21	0.00037	62	0.00838	103	0.511532
22	0.00039	63	0.00915	104	0.552216
23	0.00027	64	0.00928	105	0.593823
24	0.00027	65	0.01050	106	0.635898
25	0.00036	66	0.01164	107	0.677919
26	0.00042	67	0.01284	108	0.719299
27	0.00028	68	0.01430	109	0.759412
28	0.00049	69	0.01565	110	0.797617
29	0.00036	70	0.01647	111	0.833290
30	0.00041	71	0.01793	112	0.865870
31	0.00057	72	0.01889	113	0.894894
32	0.00050	73	0.02133	114	0.920040
33	0.00056	74	0.02245	115	0.941155
34	0.00054	75	0.02417	116	0.958277
35	0.00057	76	0.02674	117	0.971626
36	0.00069	77	0.02983	118	0.981586
37	0.00066	78	0.03247	119	0.988661

Age [years]	Prob. of death in age interval	Age [years] continued	Prob. of death in age interval	Age [years] continued	Prob. of death in age interval
38	0.00068	79	0.03610	120	0.993417
39	0.00069	80	0.04172		
40	0.00087	81	0.04679		

*Probabilities for age groups > 99 years were extrapolated.