Stool DNA testing for early detection of colorectal cancer: systematic review using the HTA Core Model® for Rapid Relative Effectiveness Assessment

Systematische Übersichtsarbeit unter Verwendung des HTA Core Model® for Rapid Relative Effectiveness Assessment

Abstract

Background: Stool DNA testing for early detection of colorectal cancer (CRC) is a non-invasive technology with the potential to supplement established CRC screening tests. The aim of this health technology assessment was to evaluate effectiveness and safety of currently CE-marked stool DNA tests, compared to other CRC tests in CRC screening strategies in an asymptomatic screening population.

Methods: The assessment was carried out following the guidelines of the European Network for Health Technology Assessment (EUnetHTA). This included a systematic literature search in MED-LINE, Cochrane and EMBASE in 2018. Manufacturers were asked to provide additional data. Five patient interviews helped assessing potential ethical or social aspects and patients' experiences and preferences. We assessed the risk of bias using QUADAS-2, and the quality of the body of evidence using GRADE.

Results: We identified three test accuracy studies, two of which investigated a multitarget stool DNA test (Cologuard®, compared fecal immunochemical test (FIT)) and one a combined DNA stool assay (ColoAlert®, compared to guaiac-based fecal occult blood test (gFOBT), Pyruvate Kinase Isoenzyme Type M2 (M2-PK) and combined gFOBT/M2-PK). We found five published surveys on patient satisfaction. No primary study investigating screening effects on CRC incidence or on overall mortality was found. Both stool DNA tests showed in direct comparison higher sensitivity for the detection of CRC and (advanced) adenoma compared to FIT, or gFOBT, respectively, but had lower specificity. However, these comparative results may depend on the exact type of FIT used. The reported test failure rates were higher for stool DNA testing than for FIT. The certainty of evidence was moderate to high for Cologuard® studies, and low to very low for the ColoAlert® study which refers to a former version of the product and yielded no direct evidence on the test accuracy for ad-vanced versus non-advanced adenoma.

Conclusions: ColoAlert® is the only stool DNA test currently sold in Europe and is available at a lower price than Cologuard®, but reliable evidence is lacking. A screening study including the current product version of ColoAlert® and suitable comparators would, therefore, help evaluate the effectiveness of this screening option in a European context.

Keywords: colorectal neoplasms, multitarget stool DNA test, colorectal cancer screening, sensitivity, specificity, test performance

Heidi Stürzlinger[1]
Annette Conrads-Frank[2]
Alexander Eisenmann[1]
Sarah Invansits[1]
Beate Jahn[2]
Andrej Janzic[3]
Marjetka Jelenc[4]
Tatja Kostnapfel[4]
Simona Mencej Bedrac[3]
Nikolai Mühlberger[2]
Uwe Siebert[2]
Gaby Sroczynski[2]
European Network for Health Technology Assessment (EUnetHTA)

1 Austrian Public Health Institute (GOEG), Vienna, Austria

2 Department of Public Health, Health Services Research and Health Technology Assessment, UMIT TIROL – University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria

3 Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP), Ljubljana, Slovenia

4 National Institute of Public Health (NIJZ), Ljubljana, Slovenia

Zusammenfassung

Hintergrund: Stuhl-DNA-Tests zur Früherkennung des kolorektalen Karzinoms (KRK) sind nicht-invasiv und können etablierte KRK-Screening-Verfahren ergänzen. Ziel dieses Health Technology Assessment war die Untersuchung der Wirksamkeit und Sicherheit von CE-zertifizierten Stuhl-DNA-Tests im Vergleich zu anderen Tests für ein Screening einer asymptomatischen KRK-Screening-Population.

Methodik: Das Assessment wurde nach den Richtlinien des Europäischen Netzwerks für Health Technology Assessment (EUnetHTA) durchgeführt und schloss eine systematische Literaturrecherche in MEDLINE, Cochrane und EMBASE ein, durchgeführt 2018. Die Hersteller wurden bezüglich der Übermittlung von weiteren Daten kontaktiert. Fünf Patienteninterviews halfen in der Einschätzung möglicher ethischer oder sozialer Aspekte sowie von Patientenerfahrungen und -präferenzen. Wir bewerteten das Verzerrungsrisiko mit QUADAS-2 und verwendeten GRADE, um die Qualität der Evidenz zu bewerten.

Ergebnisse: Wir identifizierten drei Studien zur Testgenauigkeit; zwei untersuchten einen Multitarget-Stuhl-DNA-Test (Cologuard®, im Vergleich zu einem fäkalen immunchemischen Test (FIT)) und eine Studie einen kombinierten DNA-Stuhltest (ColoAlert®, im Vergleich zu einem guajak-basierten Stuhlbluttest (gFOBT), Pyruvate Kinase Isoenzyme Typ M2 (M2-PK) und kombiniertem gFOBT/M2-PK). Wir fanden fünf publizierte Erhebungen zur Patientenzufriedenheit, jedoch keine Primärstudien zu den Auswirkungen eines Screenings mit den beiden Tests auf KRK oder die Gesamtmortalität. Beide Stuhl-DNA-Tests zeigten im direkten Vergleich eine höhere Sensitivität für den Nachweis von KRK und (fortgeschrittenen) Adenomen als FIT beziehungsweise gFOBT, wiesen aber eine geringere Spezifität auf. Diese Ergebnisse könnten jedoch vom genauen Typ des jeweils verwendeten FIT abhängen. Die berichteten Testausfallraten waren beim Stuhl-DNA-Test höher als beim FIT. Die Stärke der Evidenz war moderat bis hoch für die Cologuard®-Studien und niedrig bis sehr niedrig für die ColoAlert®-Studie, die sich auf eine frühere, nicht mehr am Markt befindliche Version des Produkts bezieht und die in den Ergebnissen zur Testgenauigkeit nicht zwischen fortgeschrittenen und nicht-fortgeschrittenen Adenomen differenzierte.

Schlussfolgerungen: ColoAlert® ist der einzige derzeit in Europa am Markt befindliche Stuhl-DNA-Test und ist zu einem niedrigeren Preis als Cologuard® erhältlich, jedoch fehlt zuverlässige Evidenz. Eine Screening-Studie mit Implementierung der aktuellen Produktversion von ColoAlert® und geeigneten Komparatoren würde daher helfen, diese Screening-Option im europäischen Kontext zu evaluieren.

Schlüsselwörter: kolorektales Karzinom, Stuhl-DNA-Test, Darmkrebs-Screening, Sensitivität, Spezifität, Testgüte

Introduction

Colorectal cancer (CRC) is – worldwide and in developed countries – the second most commonly diagnosed cancer in females and the third in males. It is also a leading cause of cancer-related deaths within developed countries [1]. CRC typically develops in pre-existing benign polyps following genetic transformations. In most of the cases, colorectal carcinoma manifest as adenocarcinoma originating from epithelial cells of the colorectal mucosa. In the early stage of disease, many patients have no or non-specific symptoms [2], [3], [4], [5]. Symptoms become more common and prominent during late stages of CRC and include abdominal or back pain, rectal bleeding, iron deficiency anemia, and/or melena, altered bowel habits and shape, weight loss, diarrhea or constipation, nausea and vomiting, malaise, anorexia, and abdominal distention [6], [7], [8].

Due to the natural history of disease with slow progression from a premalignant polyp to cancer and the high incidence and associated mortality, CRC is suitable for population screening [9], [10], [11], [12], [13]. The Council of EU Recommendation recommends CRC screening in a target average-risk population between 50 and 74 years of age. Screening modalities include fecal occult blood testing, either guaiac-based (gFOBT) or immunochemical (FIT). With gFOBT or FIT, most of the established screening programs start between 50 and 60 years of age, with a two-year screening interval. A ten-year interval or more is recommended for screening with endoscopic screening methods, that is flexible sigmoidoscopy or total colonoscopy. It is recommended to continue screening up to the age of 70 to 75 years [14], [15].

With regard to test performance characteristics, FIT is seen as superior to gFOBT. According to guidelines, combining flexible sigmoidoscopy with a stool-based test yields better results than either test alone [16]. (Total) colonoscopy is considered the reference standard for the detection of CRC, allowing an examination of the complete colon (albeit it might overlook small tumours). It is used both as a primary screening tool and as a follow-up for patients who have tested positive [16], [17], [18], [19], [20], [21], [22]. Colonoscopy participation rates, however, often are not seen as sufficient, whereas non-invasive screening tests might yield higher compliance.

Non-invasive deoxyribonucleic acid (DNA) stool tests have been developed for early screening and prevention of CRC. The expected benefit is that they might be superior to the other non-invasive screening tests in terms of test accuracy and comparable in terms of patient compliance. They are usually combined with FIT or gFOBT and are designed for detection of tumour DNA in the stool. Two stool DNA tests in Europe have a CE-mark as of 2018, ColoAlert® (PharmGenomics) and Cologuard® (Exact Sciences). Only ColoAlert® is currently sold in Europe. It is a combination of two tests:

1. a FIT (test in fecal occult blood detecting globin by immunochemical reactions), and
2. a DNA test detecting three molecular genetic markers in stool DNA: mutations in BRAF and KRAS, and quantification of human DNA (hDNA).

In June 2020, the manufacturer website [23] gave a price of 649 USD for Cologuard® (around 578 EUR as of June 2020). Since an update the manufacturer website no longer publishes a price in the FAQs [24] but directly refers to reimbursement of the product [25].

In 2022 from the manufacturer's online shops in Germany and Austria 'ColoAlert Basic' can be ordered at a price of € 139.95 EUR in Austria [26] and 'ColoAlert Stuhltest' can be ordered at a price of € 159.95 EUR in Germany [27]. The Austrian price excludes value added tax and shipping costs.

Research question

The aim of the study was to assess the effectiveness and safety of stool DNA testing for early detection of colorectal cancer compared to other tests and to assess potential ethical, organisational, social and legal issues. Detailed research questions (see Methods section) also included patient satisfaction with the test. Table 1 shows the defined PICOS (Population, Intervention, Comparison, Outcomes, Study designs) criteria.

Methods

Methodological framework

Methods followed the guidelines of the European Network for Health Technology Assessment (EUnetHTA) for Rapid Relative Effectiveness Assessments and are described in detail in the full assessment report [28], which is available from the website of EUnetHTA. Detailed research questions were formulated according to the HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 [29] (including potential ethical, organisational, social and legal issues), and additional questions according to the HTA Core Model® Version 3.0 [30], Application for Screening Technologies, were added if applicable. To assess the short- and long-term benefits as well as unintended harms of stool DNA screening strategies in comparison to strategies using alternative tests (e.g. colonoscopy, FIT) a benefit-harm analysis applying a decision-analytic model was conducted in addition. This analysis is described elsewhere [28].

Literature search and selection

We conducted a systematic literature search in MEDLINE, the Cochrane Library and EMBASE in August 2018. In October 2018, a primary study [31] with an abstract publication from 2016 [32] was published as a full-text article and was added to the study pool as the only study on ColoAlert®. We searched for ongoing studies in clinical trial registries (ClinicalTrials.gov, World Health Organiza-

Table 1: PICOS

Description	Project scope
Population	Asymptomatic, predominantly healthy persons aged 45 years or older, who do not belong to a high-risk group for the development of CRC (Rationale: European [47] and German [48] guidelines, American Cancer Society Guideline for CRC Screening [49])
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) that have a European CE mark
Comparison	Colonoscopy (which also is the reference standard for test accuracy studies), (Flexible) Sigmoidoscopy, gFOBT, FIT, M2-PK test, SEPTIN9 test, CT colonography
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, 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, NNH • Other outcomes: test performance (test failure and uncertain results rate), health-related quality of life, handling problems carrying out the test and/or taking the specimen, patient adherence (patient preference), cost of test (intervention)
Study design	• Effectiveness: diagnostic accuracy studies, randomised controlled trials, prospective controlled studies, systematic reviews, meta-analyses • Safety: randomised controlled trials, prospective studies with or without a control group, qualitative studies for the psychological harm outcome, systematic reviews, meta-analyses • Other outcomes: qualitative studies, such as patient surveys

CRC = colorectal cancer; CT = computed tomography; DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; gFOBT = guaiac-(based) fecal occult blood test; M2-PK = Pyruvate Kinase Isoenzyme Type M2; NNH = number needed to harm; NNS = number needed to screen; PICOS = Population, Intervention, Comparison, Outcomes and Study design
Source: Stürzlinger et al. [28]

tion International Clinical Trials Registry Platform and the EU Clinical Trials Register) with an update search in March 2019. We performed a manual search in addition to the systematic search.

Two of the authors screened abstracts independently from each other for inclusion and exclusion, based on the predefined PICOS criteria (Table 1). The same criteria were applied for the full text screening of selected abstracts, performed by the same two authors independently from each other, with cases of dissent being discussed between them. We restricted language to English or German. We checked all relevant systematic reviews and meta-analyses for additional primary studies not identified by the systematic search and screened all abstracts for literature that might be relevant for epidemiologic and technology issues.

Data extraction and quality assessment

One author extracted all relevant data of the included test accuracy studies. Results were checked by another author. We assessed risk of bias by using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2 [33]), carried out by two authors independently of each other, with discrepancies resolved by consensus. We additionally assessed the quality of the body of evidence using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

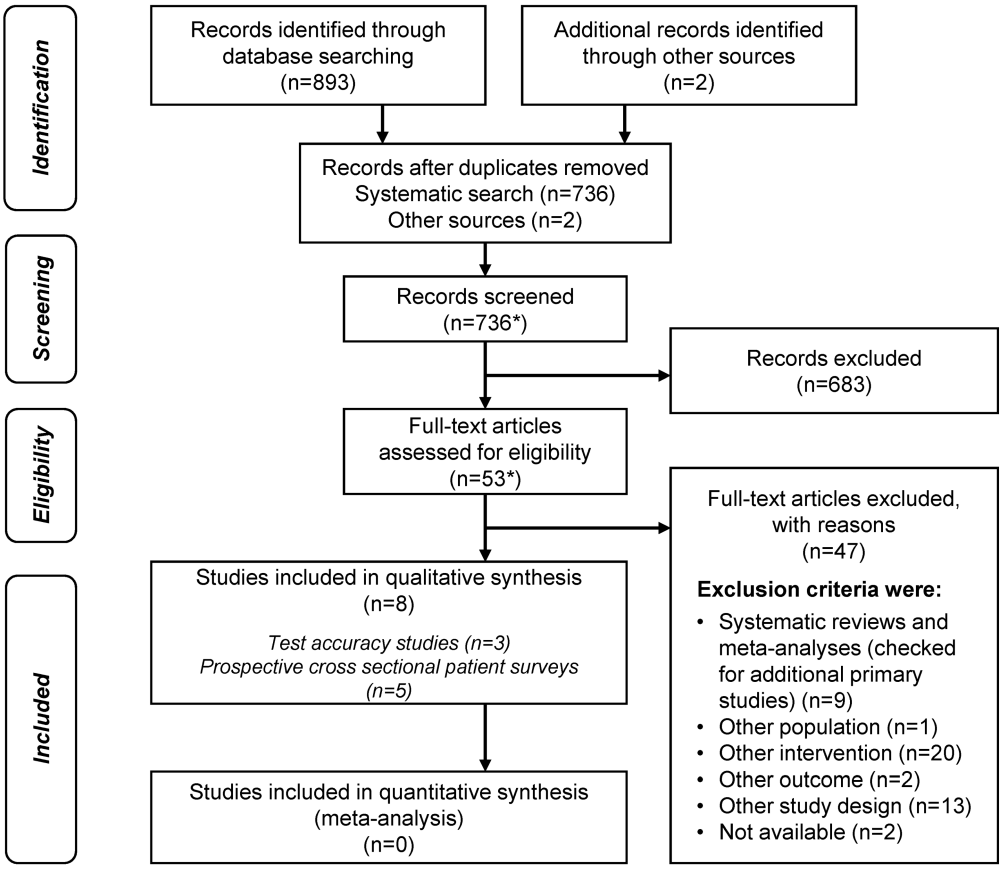
Stakeholder involvement

Manufacturers of the two tests were contacted regarding contribution of data. One gave a (positive) reply and submitted device-specific information via the EUnetHTA submission file as well as answers on further queries regarding the manufacturer-sponsored study on ColoAlert®. Patients or healthy individuals were involved during the scoping phase via interviews (telephone or face to face). Five persons, fulfilling the criteria for a CRC screening population experienced with DNA stool testing, gFOBT, FIT or colonoscopy, were identified, either by personal communication or via a physician's office. A standardised open questionnaire was used asking them about their experiences and preferences regarding screening tests [28]. We used information from patient involvement for assessing the relevance of potential ethical and social aspects and for answering research questions related to patient aspects (e.g. satisfaction with the test).

Results

Search results

Figure 1 shows the study selection process. Out of the eight included studies, three investigated test accuracy; two of them assessed Cologuard® [34], [35] and one study assessed ColoAlert® [31] (Table 2). Five published patient surveys [36], [37], [38], [39], [40] investigating patient perceptions and preferences of CRC screening tests in-



* Excluding studies added through other sources; source: Stürzlinger et al. [28]

Figure 1: PRISMA flow chart of the study selection process

cluding stool DNA testing were identified via systematic literature search, but only one of them investigated one of the currently available tests (Cologuard®) [36]. They were used to complement the results from the patient interviews. No primary study was identified assessing the effectiveness of DNA stool tests on CRC incidence, CRC mortality, overall mortality or health-related quality of life.

Study characteristics

Imperiale et al. [35] conducted a cross-sectional screening study across 90 sites throughout the USA and Canada with recruitment lasting from June 2011 through November 2012. They compared the Cologuard® DNA stool test with a FIT [OC FIT-CHEK® (Polymedco)]. In a prospective screening cohort study, Brenner et al. [34] assessed the diagnostic performance of another FIT [FOB Gold® (Sentinel Diagnostics)] and – with adjusted cut-off – compared it with performance data of Cologuard®, as reported by Imperiale et al. [35]. Recruitment took place in 20 gastroenterology offices in Southern Germany from November 2008 to September 2014. Dollinger et al. [31] compared in a preclinical case cohort study a combined DNA stool assay [ColoAlert® combined with a gFOBT and an hDNA quantification test (threshold 15 ng/µL)] with a single gFOBT (ColoScreen-ES®, Helena Biosciences), a single tumour Pyruvate Kinase Isoenzyme Type M2 (M2-PK) test (ScheBo Biotech AG) and a combined gFOBT/M2-PK assay. They recruited patients from 16 different sites in Germany from August 2005 to May 2007. Detailed study characteristics can be found in Table 2.

Five prospective cross-sectional patient surveys from USA [36], [37], [38], [39], [40] were performed in (asymptomatic) screening populations, some of these study populations with and some without previous CRC screening experience. Four of these studies [37], [38], [39], [40] referred to a USA precursor test (PreGen-Plus®) of Cologuard®, which is no longer available [41]. Only one survey [36] investigated Cologuard®, comparing colonoscopy with DNA stool testing (for further details see the full assessment Report [28]).

Risk of bias for test accuracy studies

For the two studies investigating Cologuard® [34], [35], we noted a risk of bias regarding patient selection (Table 3), no other concerns arose. We noted a considerable risk of bias as well as applicability concerns for the study investigating ColoAlert® [31] (Table 3). Concerns were high that the study population did not match well with the research question of this assessment. Moreover, the stool DNA assay evaluated in the study was different from the currently available product regarding several components.

Table 2: Main characteristics of test accuracy studies included for efficacy and safety

Author, year	**Study type**	**No. of patients fully evaluated** (No. of patients enrolled)	**Country/ies of recruitment**	**Participants (inclusion criteria)**	**Intervention(s)**	**Main endpoints**
Imperiale et al., 2014 [35]	Prospective screening cross-sectional study	9,989 (12,776)	USA, Canada	Asymptomatic persons aged 50 to 84 at average risk for CRC scheduled for screening colonoscopy. Enrolment weighted toward persons ≥65 years of age to increase prevalence of CRC	• 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 [34]	Prospective screening cohort study	3,494 (4,203)	Germany; recruitment for Cologuard® study (Imperiale et al. 2014) in USA and Canada	Participants of screening colonoscopy, no previous diseases of colon	• 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. [35])
Dollinger et al., 2018 [31]	Preclinical case cohort study	521 (734)	Germany	Patients aged 38–85 before elective or screening colonoscopy or before surgery in case of recent diagnosis of CRC	• Colonoscopy (screening or 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

CRC = colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood testing; hDNA = human deoxyribose nucleic acid
Source: Stürzlinger et al. [28]

Table 3: 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 [35] (Cologuard)	☹[a]	☺	☺	☺	☺	☺	☺
Brenner et al. 2017 [34] (Cologuard)	☹[b]	☺	☺	☺	☺	☺	☺
Dollinger et al. 2018 [31] (ColoAlert®)	☹[c]	☺	☺	☹	☹[d]	☹[e]	☺

☺ low risk, ☹ high risk, CRC = colectoral cancer, FIT = fecal immunochemical test, gFOBT = guaiac-based fecal occult blood test, M2-PK = Pyruvate Kinase Isoenzyme Type M2

[a] Patient enrolment was intentionally weighted toward persons 65 years of age or older to increase CRC prevalence within the study population which seems not consistent with a consecutive patient recruitment.

[b] As performance data of Cologuard® were taken from Imperiale et al. [35], the risk of bias regarding patient selection was rated accordingly.

[c] It was not clear whether patient enrolment was consecutive and whether inappropriate exclusions were avoided. The analysed 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).

[d] For drop-outs, 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.

[e] The combined stool assay evaluated in this study incorporates a gFOBT, whereas the CE-marked ColoAlert® stool DNA test includes a FIT.

Source: Stürzlinger et al. [28]

Patient interviews

Five individuals (three female/two male) at the age of 56 to 65 were included. All of them were living in Austria. Summarised results are shown in Table 4.

Effectiveness outcomes

Table 5 details test accuracy results for the detection of CRC and of adenoma, which are divided into advanced precancerous lesions (APL) and Non-APL. For the detection of CRC, Cologuard® showed a sensitivity of 92.3% (compared with 73.8% and 96.7% for OC FIT-CHEK® and FOB Gold®, respectively) and 46.4% for the detection of CRC or APL (compared with 27.7% and 51.1% for OC FIT-CHEK® and FOB Gold®, respectively). The specificity for the detection of CRC was 84.4% (compared with 93.4% and 83.0% for OC FIT-CHEK® and FOB Gold®, respectively) and 86.6% for the detection of CRC or APL (compared with 94.9% and 86.5% for OC FIT-CHEK® and FOB Gold®, respectively). For ColoAlert® the sensitivity to detect CRC was 84.6% (compared with 68.0% and 82.9% for gFOBT and M2-PK, respectively). The sensitivity for this test was 35.5% for the detection of CRC or (any) adenoma (compared with 22.3% and 54.7% for gFOBT and M2-PK, respectively), without discriminating APL from Non-APL. Its specificity was 87.0% for the detection of CRC (compared with 95.5% and 58.7% for gFOBT and M2-PK, respectively) and 88.4% for the detection of CRC or adenoma (compared with 95.8% and 60.1% for gFOBT and M2-PK, respectively). Calculations of positive and negative predictive values as well as of number needed to screen can be found in the full report [28].

Safety outcomes

No reports of adverse events or user-dependent harms of DNA stool tests were found (or mentioned) within the identified primary evidence. We also found no studies that directly investigated the consequences of false positive or false negative test results from the viewpoint of patient safety [28].

Other outcomes

Test failures include tests that have not been submitted or that are unevaluable or unusable. The test failure rates were 6.25% for Cologuard® and 0.31% for OC FIT-CHEK® (Table 6). For the study including ColoAlert® only a combined failure rate of all stool tests investigated was available, which amounted to 17.74% (Table 6).

Handling problems carrying out the test and/or taking the specimen were reported by four of the five persons interviewed for this study. Difficulties with having bowel movements were reported once. Results of the five identified published patient surveys do not hint at major handling problems for the majority of patients (for details see Stürzlinger et al. [28]).

Regarding patient preferences, four of the five interviewees said they would rather do the experienced stool test (FIT in two persons and gFOBT in the two other) than colonoscopy (three of them had already undergone a colonoscopy). One person, who was experienced in all of the four tests, appeared to be indifferent. Rather inconsistent results on screening test preferences were found within the five identified published patient surveys (for details see Stürzlinger et al. [28]).

Table 4: Main results from the five patient interviews

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

DNA = deoxyribonucleic acid; FIT = fecal immunochemical test; gFOBT = guaiac-(based) fecal occult blood test
Source: Stürzlinger et al. [28]

Table 5: 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 [35], DNA stool test (Cologuard®, Exact Sciences)										
Colonoscopy findings	65	757	822	3,715	2893	1,817	6,274	9,167	9,924	4,457
Positive (n)	60	321	381	879	498	278	733	1,231	1,552	455
Negative (n)	5	436	441	2,836	2,395	1539	5,541	7,936	8,372	4,002
% 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 [35], FIT (OC FIT-CHEK®, Polymedco)										
Positive	48	180	228	448	220	90	252	472	652	162
Negative	17	577	594	3267	2673	1,727	6,022	8,695	9,272	4,295
% 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 [34], FIT (FOB Gold®, Sentinel Diagnostics; adjusted cutoff 8.4 µg hemoglobin/g faces)										
Colonoscopy findings	30	359	389	1077	688	n.r.	2,417	3,105	3,464	n.r.
Positive (n)	29	170	199	333	134		n.r.	419	589	
Negative (n)	1	189	190	744	554		n.r.	2,686	2,875	
% 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 [31], Combined DNA stool assay [ColoAlert®, PharmGenomics; gFOBT and DNA quantification test (threshold 15 ng/µL)]										
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)

Table 5: Test accuracy data – sensitivity and specificity (Continued)

	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)
Dollinger *et al.* 2018 [31], 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 [31], 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 [31], 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
Source: Stürzlinger et al. 2019 [28]

Table 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 [35]						
12,776	1,760: 464 withdrew consent 1,168 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	9,989
			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 [34]						
4,203	225 32 with history of CRC or IBD 193 had colonoscopy in the preceding 5 years	3,978	Colonoscopy (reference standard)	484 (12.17%)	432 inadequate bowel preparation 52 incomplete colonoscopy	3,494
			FIT (FOB Gold®)	Not reported		
Dollinger et al. 2018 [31]						
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 manufacturer fact check process [28], 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.

CRC = colorectal carcinoma; FIT = fecal immunochemical test; gFOBT = guaiac-(based) fecal occult blood test; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome

Source: Stürzlinger et al. [28]

Organisational aspects

Most stool tests can be ordered via the Internet or bought in a pharmacy. Cologuard® is available by prescription only [42], [43]. Users can administer stool tests at home, but specimens (mostly) have to be sent to a specialiced laboratory for analysis.
No (further) relevant ethical, social or legal aspects were identified.

Discussion

Of the two CE-marked DNA stool tests, ColoAlert® is the most recent product, being authorised in 2016. It is the only DNA stool test currently sold on the European market.
In our systematic literature search we identified three test accuracy studies, two on Cologuard® (both referring to the same Cologuard® study population [34], [35]) and one [31] investigating ColoAlert®. The certainty of evidence was moderate to high for Cologuard® results and low to very low for ColoAlert® results [28]. Besides serious concerns about patient selection (Table 3), recruitment of the study dates back to 2005 to 2007 and a former version of the test was used that differs in several components from the currently available product. Also the study did not report information on the exact proportion of test failures in the DNA assay alone compared with the other stool tests [28].
The test accuracy (against the reference standard) of CRC triage screening tests cannot easily be depicted as one value for sensitivity and one for specificity. Not all precancerous lesions – if not removed – progress to clinically symptomatic cancer [44], [45]. Thus triage screening tests should yield a positive test result in persons with CRC and, preferably, also in persons with advanced adenomas (which can be removed by polypectomy and should be followed by shorter surveillance intervals thereafter). On the one hand, it might be debated if they should also yield a positive result (and, thus, reference to colonoscopy) in cases of non-advanced adenomas. On the other hand, with regard to specificity, either the proportion of negative test results in all persons without CRC or (any) adenoma, or the proportion of negative test results in all persons without CRC or advanced adenoma, is of interest. This differentiation, however, was not reported in the study by Dollinger et al. [31], making it difficult to interpret and compare the test accuracy results. For the detection of CRC, ColoAlert® yielded a lower sensitivity than Cologuard®, and, on the other hand, correctly detected a higher proportion of completely healthy persons (Table 5). Remarkably, the test accuracy results of FIT differed largely, depending on brand and cut-off value. Though this was not a focus of this assessment, it might be a relevant issue for comparison. There was no direct comparison between ColoAlert® and FIT. Lastly, also test failure rates are a relevant issue for judging test accuracy. Test failures can partly be compensated by collecting a second specimen, although this is associated with increased time effort and potential costs. Only in one study [35], test failure rates were completely reported, and were highest for stool DNA testing, followed by colonoscopy, and FIT.
Results of this HTA are limited by the fact that not all PICO-comparators were investigated within the identified studies, which also is connected to the very small number of studies available for the CE-marked products. Also, the incorporation of patient views was limited by the difficulty of finding patients that had stool DNA test experience. Patient surveys found in the literature mostly referred to a precursor test of Cologuard®.
In our systematic literature search, we did not identify studies on long-term effects of stool DNA tests on mortality and morbidity, which might be due to the short time period DNA tests are on the market. With regard to adverse events or direct user-dependent harms, no major findings were reported. Undoubtedly, there will be consequences from false positive and false negative test results as undetected adenomas, on the one hand might progress further and false positive results, on the other hand, lead to unnecessary colonoscopies. Moreover, positive test results mostly lead to immediate worry and all of the test procedures, but namely colonoscopies, imply some kind of immediate burden to the person tested. The benefit-harm tradeoff of respective screening strategies was investigated within a decision-analytic modeling done for this assessment [28], but not reported in this article.
Finally, the literature search for this HTA was done in 2018. An update systematic rapid review published in 2021 [46] which was based on the original literature search of our report [28] found two further studies on Cologuard® and concluded that these newer studies confirm the existing results regarding diagnostic test accuracy, with additional (favourable) results on the specificity of Cologuard® for detecting CRC in persons 45 to 49 years old [46].

Conclusions

Overall, stool DNA tests showed higher sensitivity for the detection of CRC and (advanced) adenoma than FIT or gFOBT, but lower specificity. The results depended to a degree on the exact type of FIT used. The reported test failure rate of stool DNA tests was higher than that of FIT. ColoAlert® is the only stool DNA test currently sold in Europe and is available at a lower price than Cologuard®. Reliable evidence on ColoAlert® is lacking, however. A cross-sectional screening study including the current product version, as well as FIT as additional comparator, would therefore help in evaluating this screening option in a European context. In terms of the comparator tests, especially FIT, it would be desirable to carefully select the brand and especially the cut-off value and provide some rationale for those choices. Also, (directly) addressing the effectiveness of DNA stool tests on morbidity, mortality

and health-related quality of life, by conducting prospective (randomised) controlled trials, should be considered.

Abbreviations

- APL: Advanced precancerous lesions
- CRC: Colorectal cancer
- DNA: Invasive deoxyribonucleic acid
- EUnetHTA: European Network for Health Technology Assessment
- FIT: Fecal immunochemical test
- gFOBT: Guaiac-based fecal occult blood test
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- HTA: Health technology assessment
- M2-PK: Pyruvate Kinase Isoenzyme Type M2
- PICOS: Population, Intervention, Comparison, Outcomes and Study designs
- QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2

Notes

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Competing interests

See full report [28] (published on the EunetHTA website), page 3.

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Corresponding author:
Heidi Stürzlinger
Gesundheit Österreich GmbH, Stubenring 6, 1010 Wien, Austria
heidi.stuerzlinger@goeg.at

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