

Stuhl-DNA-Tests zur Früherkennung des kolorektalen Karzinoms Systematische Übersichtsarbeit unter Verwendung des HTA Core Model® for Rapid Relative Effectiveness Assessment

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

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Wir bitten um Beachtung

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Abkürzungsverzeichnis

APL	Advanced precancerous lesions
CRC	Colorectal cancer
DNA	Invasive deoxyribonucleic acid
EUnetHTA	Europäisches Netzwerk für HealthTechnology Assessment
FIT	Fäkaler immunochemischer Test, engl.: Fecal immunochemical test
gFOBT	Guajakbasierter Stuhlbluttest, engl.: Guaiac based fecal occult blood test
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HTA	Health Technology Assessment
KRK	Kolorektaler Krebs
M2-PK	Pyruvate Kinase Isoenzyme Typ M2, engl.: Pyruvate Kinase Isoenzyme Type M2
PICOS	Population–Intervention–Comparison–Outcome–Study designs
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2

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 MEDLINE, 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 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 respectively gFOBT, 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 advanced 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 evaluating the effectiveness of this screening option in a European context.

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 immunochemischen Test (FIT)) und eine Studie einen kombinierten DNA-Stuhltest (ColoAlert®, im Vergleich zu einem guajakbasierten 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.

Scientific Article

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.³⁷ 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.^{17, 26, 27, 35} 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.^{20, 25, 30}

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.^{3, 11, 31, 40, 41} 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.^{28, 39}

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.⁵ (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.^{1, 2, 5, 22, 23, 29, 38} 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 actually 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).

The manufacturer website (www.cologuardtest.com/faq/cost, accessed on 18 June 2020) gives a price of US\$ 649 for Cologuard®, which converts to ~€ 578 (as of June 2020). From the manufacturer's online shop (<https://coloalert.de/12-online-shop> for Germany and <https://www.medsalus.eu/shop-produkte> for Austria, both accessed on 19 June 2020) two product types of ColoAlert® are available: 'ColoAlert Basic' with a price of currently € 119.95 in Germany and € 139.95 in Austria and 'ColoAlert Plus' (including, according to the manufacturer's website, determination of hemoglobin/haptoglobin complex) costing € 169.95 in Germany and € 189.95 in Austria. Austrian prices exclude value added tax. As of 2019 stool DNA testing was not reimbursed in European countries.

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.

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 ³⁴ and German ¹² guidelines, American Cancer Society Guideline for CRC Screening ⁴³).
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–study design.

Source: Stürzlinger et al.³⁶

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 report³⁶, 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 4.2¹⁶ (including potential ethical, organisational, social and legal issues), and additional questions according to the HTA Core Model® Version 3.0¹⁵, 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 elsewhere³⁶.

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 study¹⁴ with an abstract publication from 2016¹³ was published as a full-text article and was added to the study pool being the only study on ColoAlert®. We searched for ongoing studies in clinical trial registries (ClinicalTrials.gov, World Health Organization 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 (see 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-2⁴²), 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®.

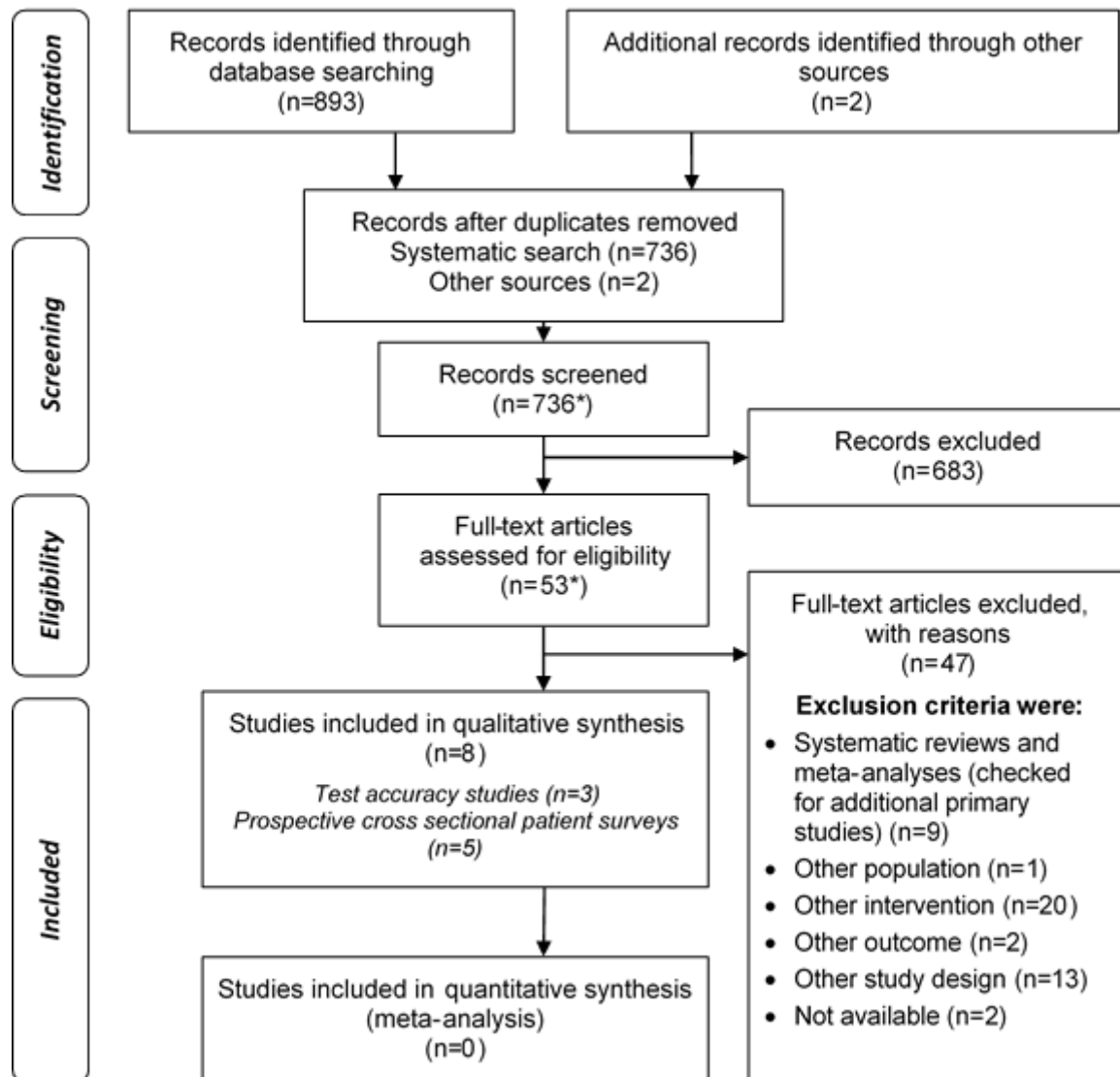
Patients or healthy individuals were involved during the scoping phase via interviews (telephone or face to face). Five persons, fulfilling the criteria for a CRC screening population experienced with DNA stool testing, gFOBt, FIT or colonoscopy, were identified, either by personal communication or via a physician's office. A standardised open questionnaire was used asking them about their experiences and preferences regarding screening tests³⁶. 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®^{7, 19} and one study assessed ColoAlert®¹⁴ (see table 2). Five published patient surveys^{4, 8, 24, 32, 33} investigating patient perceptions and preferences of CRC screening tests including stool DNA testing were identified via systematic literature search, but only one of them investigated one of the currently available tests²⁴ (Cologuard®). 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.

Figure 1: PRISMA flow chart of the study selection process



*Excluding studies added through other sources.

Source: Stürzlinger et al.³⁶

Study characteristics

Imperiale et al.¹⁹ 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.⁷ 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.¹⁹. Recruitment took place in 20 gastroenterology offices in Southern Germany from November 2008 to September 2014. Dollinger et al.¹⁴ compared in a preclinical case cohort study a combined DNA stool assay [ColoAlert® combined with a gFOBT and a 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.

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 ¹⁹	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	<ul style="list-style-type: none"> 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 ⁷	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	<ul style="list-style-type: none"> 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. ¹⁹)
Dollinger et al., 2018 ¹⁴	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	<ul style="list-style-type: none"> 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. USA = United States of America.






















Source: Stürzlinger et al.³⁶



Five prospective cross-sectional patient surveys from USA^{4, 8, 24, 32, 33} were performed in (asymptomatic) screening populations, some of these study populations with and some without previous CRC screening experience. Four of these studies^{4, 8, 32, 33} referred to a USA precursor test (PreGen-Plus®) of Cologuard®, which is no longer available⁶. Only one survey²⁴ investigated Cologuard®, comparing colonoscopy with DNA stool testing (for further details see the full assessment Report ³⁶).

Risk of bias for test accuracy studies

For the two studies investigating Cologuard®^{7, 19} we noted a risk of bias regarding patient selection (see table 3), no other concerns arose. We noted a considerable risk of bias as well as applicability concerns for the study investigating ColoAlert®¹⁴ (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 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 <i>et al.</i> 2014 ¹⁹ (Cologuard)	 ^a						
Brenner <i>et al.</i> 2017 ⁷ (Cologuard)	 ^b						
Dollinger <i>et al.</i> 2018 ¹⁴ (ColoAlert®)	 ^c				 ^d	 ^e	

 low risk;  high risk. CRC = Colorectal cancer. FIT = fecal immunochemical test gFOBT = guaiac based fecal occult blood test M2-PK = Pyruvate Kinase Isoenzyme Type M2

Notes:

^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.*¹⁹ 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.*³⁶

Patient interviews

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

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.

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.³⁶

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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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

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

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.

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.³⁶

1.1.1.1 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).

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 <i>et al.</i> 2014 ¹⁹						
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 <i>et al.</i> 2017 ⁷						
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		

Table 6 - continued

Dollinger <i>et al.</i> 2018 ¹⁴						
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 process³⁶, 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.*³⁶

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.³⁶).

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.³⁶).

Organisational aspects

Most stool tests can be ordered via the Internet or bought in a pharmacy. Cologuard® is available by prescription only^{9,10}. Users can administer stool tests at home, but specimens (mostly) have to be sent to a specialised 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^{7,19}) and one¹⁴ investigating ColoAlert®. The certainty of evidence was moderate to high for Cologuard® results and low to very low for ColoAlert® results.³⁶ Besides serious concerns about patient selection (see 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.³⁶

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.^{18,21} 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.¹⁴, 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 study¹⁹ 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 assessment³⁶, but not reported in this article.

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® (though both tests are more expensive than the non-invasive comparators gFOBT, FIT or M2-PK). 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.

References

1. Allameh, Z.; Davari, M.; Emami, MH. (2011): Sensitivity and Specificity of Colorectal Cancer Mass Screening Methods: A Systematic Review of the Literature. In: Iran J Cancer Prev 4/2: 88-105
2. Asselineau, J; Paye, A; Bessède, E; Perez, P; Proust-Lima, C (2018): Different latent class models were used and evaluated for assessing the accuracy of campylobacter diagnostic tests: overcoming imperfect reference standards? Epidemiology and Infection. 146/1556:1564
3. Bailey, James R.; Aggarwal, Ashish; Imperiale, Thomas F. (2016): Colorectal Cancer Screening: Stool DNA and Other Noninvasive Modalities. In: Gut And Liver 10/2:204-211
4. Berger, Barry M.; Schroy, Paul C., 3rd; Rosenberg, Jennifer L.; Lai-Goldman, Myla; Eisenberg, Marcia; Brown, Trisha; Rochelle, Robert B.; Billings, Paul R. (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. In: Clinical Colorectal Cancer 5/5:338-343
5. Bernard, F. ; Barkun, AN.; Martel, M.; Von Renteln, D. (2018): Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. In: World J Gastroenterol 24/1: 124-138
6. Blue Regence (2018): Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening. Medical Policy Manual Genetic Testing, Policy No 12,
7. Brenner, H.; Chen, H. (2017): Fecal occult blood versus DNA testing: Indirect comparison in a colorectal cancer screening population. In: Clinical Epidemiology 9377-384
8. Calderwood, Audrey H.; Wasan, Sharheel K.; Heeren, Timothy C.; Schroy, Paul C., 3rd (2011): Patient and Provider Preferences for Colorectal Cancer Screening: How Does CT Colonography Compare to Other Modalities? In: International Journal Of Cancer Prevention 4/4:307-338
9. Cologuard (2019): Discussion Guide. Let's talk. Hg. v. Exact Sciences Corporation.
10. Cologuard (2019): How to get Cologuard [Online]. <https://www.cologuardtest.com/how-to-get-cologuard> [Zugriff am 02.07.2019]
11. Danalıoğlu, Ahmet (2014): Can "DNA-based stool tests" replace colonoscopy in screening for colon cancer? In: The Turkish Journal Of Gastroenterology: The Official Journal Of Turkish Society Of Gastroenterology 25/1:122-123
12. DKG Krebsgesellschaft; Deutsche Krebshilfe; AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) (2017): Leitlinienprogramm Onkologie. S3-Leitlinie Kolorektales Karzinom. Langversion 2.0.
13. Dollinger, M.; Hiemer, S.; Behl, S.; T., Schinköthe.; Fleig, W. (2016): Frühdetektion kolorektaler Karzinome: Multizentrische Phase II-Studie zur Validierung eines neuen DNA-basierten Stuhltest. In: Der Internist S53-S53
14. Dollinger MM, Behl S, Fleig WE (2018): Early Detection of Colorectal Cancer: a Multi-Center Pre-Clinical Case Cohort Study for Validation of a Combined DNA Stool Test In: Clin Lab 64 (10): 1719-30. Epub 2018/10/20.
15. European Network for Health Technology Assessment (2016): Joint Action on HTA 2012-2015: HTA Core Model for Rapid Relative Effectiveness.
16. European Network for Health Technology Assessment (2016): Joint Action on HTA 2012-2015: HTA core model; version 3.0
17. Fleming, M.; Ravula, S.; Tatishchev, S. F.; Wang, H.; (2012): Colorectal carcinoma: Pathologic aspects.21
18. Garcia, Montse (2015): Addressing overuse and overdiagnosis in colorectal cancer screening for average-risk individuals. In: Colorectal Cancer 4/1:27-35
19. Imperiale, TF; Ransohoff, DF.; Itzkowitz, SH., Levin, TR; Lavin, P; Lidgard, GP; Ahlquist, DA; Berger, BM (2014): Multitarget stool DNA testing for colorectal-cancer screening. In: The New England Journal Of Medicine 370/14:1287-1297
20. Jefferson, T.; Cerbo, M.; Vicari, N. (2014): Fecal Immunochemical Test (FIT) versus guaiac-based fecal occult blood test (FOBT) for colorectal cancer screening [Core HTA],. Hg. v. Agenas - Agenzia nazionale per i servizi sanitari regionali
21. Kalager, Mette; Wieszcz, Paulina; Lansdorp-Vogelaar, Iris; Corley, Douglas A.; Bretthauer, Michael; Kaminski, Michal F. (2018): Overdiagnosis in Colorectal Cancer Screening: Time to Acknowledge a Blind Spot. In: Gastroenterology 155/3:592-595
22. Lauby Secretan B.; Vilahur, N.; Bianchini, F.; Guha, N.; Straif, K. (2018): The IARC Perspective on Colorectal Cancer Screening. In: N Engl J Med 378/18: 1734-1740

23. Lin, J. S.; Piper, M. A.; Perdue, L. A.; Rutter, C. M.; Webber, E. M.; O'Connor, E.; Smith, N.; Whitlock, E. P. (2016): Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. In: *JAMA* 315/23:2576-2594
24. Matthew V. Abola, Todd F. Fennimore, Marcia M. Chen, Zhengyi Chen, Ashutosh K. Sheth, Gregory Cooper, Li Li (2015): Stool DNA-based versus colonoscopy-based colorectal cancer screening: Patient perceptions and preferences. In: *Family Medicine and Community Health* 2015;3(3) 2-8
25. MS, Cappell (2005): From Colonic Polyps to Colon Cancer: Pathophysiology, Clinical Presentation, and Diagnosis. In: *Clin Lab Med* 25 135-177
26. Nikolaou, Stella; Qiu, Shengyang; Fiorentino, Francesca; Rasheed, Shahnawaz; Tekkis, Paris; Kontovounisios, Christos (2018): Systematic review of blood diagnostic markers in colorectal cancer. In: *Techniques In Coloproctology*
27. Phalguni, Angaja; Seaman, Helen; Routh, Kristina; Halloran, Stephen; Simpson, Sue (2015): Tests detecting biomarkers for screening of colorectal cancer: What is on the horizon? In: *GMS Health Technology Assessment* 11Doc01-Doc01
28. Ponti, A.; Antilla, A.; Ronco, G.; Senore, C. (2017): Against Cancer. Cancer Screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening. Hg. v. European Commission.
29. Reitsma, JB; Rutjes, AW; Khan, KS; Coomarasamy, A; Bossuyt, PM (2009): A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. In: *J Clin Epidemiol* 62/8: 797-806
30. Rex, Douglas K.; Boland, C. Richard; Dominitz, Jason A.; Giardiello, Francis M.; Johnson, David A.; Kaltenbach, Tonya; Levin, Theodore R.; Lieberman, David; Robertson, Douglas J. (2017): Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. In: *Gastroenterology* 153/1:307-323
31. Schreuders, Eline H.; Grobbee, Esmée J.; Spaander, Manon C. W.; Kuipers, Ernst J. (2016): Advances in Fecal Tests for Colorectal Cancer Screening. In: *Current Treatment Options In Gastroenterology* 14/1:152-162
32. Schroy, Paul C., 3rd; Heeren, Timothy C. (2005): Patient perceptions of stool-based DNA testing for colorectal cancer screening. In: *American Journal Of Preventive Medicine* 28/2:208-214
33. Schroy, Paul C., 3rd; Lal, Subodh; Glick, Julie T.; Robinson, Patricia A.; Zamor, Philippe; Heeren, Timothy C. (2007): Patient preferences for colorectal cancer screening: how does stool DNA testing fare? In: *The American Journal Of Managed Care* 13/7:393-400
34. Segnan, N.; Patnick, J.; von Karsa, L. (2010): European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Hg. v. European Commission
35. Sofic, A., et al. (2010): CT colonography in detection of colorectal carcinoma. In: *Radiology And Oncology* 44/1: 19-23
36. Stürzlinger, H.; Conrads-Frank, A.; Eisenmann, A.; Ivansits, S.; Jahn, B.; Janzic, A.; Kostnapfel, T.; Mencej Bedrac, S.; Mühlberger, N.; Rochau, U.; Siebert, U.; Schnell-Inderst, P.; Sroczynski, G.(2019): Stool DNA testing for early detection of colorectal cancer. Joint Assessment. Vienna: EUnetHTA
37. Torre, L. A.; Bray, F.; Ferlay, J.; Lortet-Tieulent, J.; Ahmedin, J.; (2015): Global Cancer Statistics, 2012. In: *CA CANCER J CLIN* 65 87-108
38. van Rijn, JC.; Reitsma, JB.; Stoker, J., et al. (2006): Polyp miss rate determined by tandem colonoscopy: a systematic review. In: *Am J Gastroenterol* 101/2: 343-350
39. Von Karsa, L.; Patnick, J.; Segnan, N.; Atkin, W.; Halloran, S., et al. (2013): European guidelines for quality assurance in colorectal cancer screening and diagnosis: Overview and introduction to the full Supplement publication. In: *Endoscopy* 45/1: 51-59
40. Waldmann, Elisabeth; Regula, Jaroslaw; Ferlitsch, Monika (2015): How can screening colonoscopy be optimized? In: *Digestive Diseases (Basel, Switzerland)* 33/1:19-27
41. Wang, Xi; Kuang, Ye-Ye; Hu, Xiao-Tong (2014): Advances in epigenetic biomarker research in colorectal cancer. In: *World Journal Of Gastroenterology* 20/15:4276-4287

42. Whiting, Penny F.; Rutjes, Anne W.S.; Westwood, Marie E.; Mallett, Susan; Deeks, Jonathan J.; Reitsma, Johannes B.; Leeflang, Mariska M.G.; Sterne, Jonathan, A.C.; Bossuyt, Patrick M.M.; Group*, QUADAS-2 (2011): QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. In: American College of Physicians 155/8: 529-536
43. Wolf, A. M. D.; Fontham, E. T. H.; Church, T. R.; Flowers, C. R.; Guerra, C. E.; LaMonte, S. J.; Etzioni, R.; McKenna, M. T.; Oeffinger, K. C.; Shih, Y. T.; Walter, L. C.; Andrews, K. S.; Brawley, O. W.; Brooks, D.; Fedewa, S. A.; Manassaram-Baptiste, D.; Siegel, R. L.; Wender, R. C.; Smith, R. A. (2018): Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. In: CA Cancer J Clin

Conflict of interest

--> see full report³⁶ (published on the EunetHTA website), page 3

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Die systematische Bewertung medizinischer Prozesse und Verfahren, *Health Technology Assessment* (HTA), ist mittlerweile integrierter Bestandteil der Gesundheitspolitik. HTA hat sich als wirksames Mittel zur Sicherung der Qualität und Wirtschaftlichkeit im deutschen Gesundheitswesen etabliert.

Seit Einrichtung der Deutschen Agentur für HTA des DIMDI (DAHTA@DIMDI) im Jahr 2000 gehören die Entwicklung und Bereitstellung von Informationssystemen, speziellen Datenbanken und HTA-Berichten zu den Aufgaben des DIMDI.

Das DIMDI wurde gemäß Artikel 16a des Medizinprodukte-EU-Anpassungsgesetzes am 26. Mai 2020 in das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) eingegliedert.

Im Rahmen der Forschungsförderung beauftragte das DIMDI qualifizierte Wissenschaftlerinnen und Wissenschaftler mit der Erstellung von HTA-Berichten, die Aussagen machen zu Nutzen, Risiko, Kosten und Auswirkungen medizinischer Verfahren und Technologien mit Bezug zur gesundheitlichen Versorgung der Bevölkerung. Dabei fallen unter den Begriff Technologie sowohl Medikamente als auch Instrumente, Geräte, Prozeduren, Verfahren sowie Organisationsstrukturen. Vorrang haben dabei Themen, für die gesundheitspolitischer Entscheidungsbedarf besteht.