HTA Austria
Austrian Institute for
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GmbH

Stool DNA testing for colorectal cancer (CRC) screening

Policy Brief

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Systematic Review

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Content

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List of abbreviations

AE – adverse events;

AMSTAR-II – Assessing the methodological quality of systematic reviews;

CRC – colorectal cancer;

DTA – diagnostic test accuracy

EUnetHTA – European Network for Health Technology Assessment;

FIT – faecal immunochemical test;

gFOBT - guaiac based faecal occult blood test;

GRADE – grading of recommendations assessment development and evaluation;

HTA – health technology assessment;

KRAS – Kirsten rat sarcoma 2 viral oncogene homologue;

M2-PK – pyruvate kinase isoenzyme type M2

MeSH – Medical subject headings;

MT-sDNA – multi-target stool DNA;

NDRG4 – N-Myc Downstream Regulated Gene 4;

NRCT – non-randomised controlled trial;

PICO – population, intervention, control, outcome;

QUADAS-II – Quality Assessment of Diagnostic Accuracy Studies II;

RCT – randomised controlled trial;

Executive Summary

Introduction

colorectal carcinoma, early detection essential

Colorectal Carcinoma (CRC) is the third most frequent cancer type, with an incidence and prevalence of approximately 4,800 and 40,000 cases respectively each year in Austria. Multi-target stool DNA (MT-sDNA) testing is a novel non-invasive screening test that may be able to supplement or replace established stool tests by analysing (stool-based) tumour DNA. In this policy brief, the latest available evidence with regard to the clinical benefits and harms of MT-sDNA tests is summarized.

DNA stool test as a new, non-invasive test: Cologuard®, ColoAlert®.

Methods

update EUnetHTA Report 2019

The quality of a recent EUnetHTA report published in 2019 was critically appraised using the AMSTAR-II checklist. Further, an update systematic rapid review was conducted: a systematic literature search was conducted in three databases (8/2018-5/2021) using the search strategy deployed in the EUnetHTA report. A qualitative synthesis of the evidence was conducted with a focus on effectiveness/safety and diagnostic test accuracy.

Results

evidence: no RCTs/NRCTs on efficacy/safety.

1 modeling analysis from 2019 (based on 3 studies)

and 2 new studies updating the evidence on diagnostic accuracy

The current available evidence consists of five diagnostic test accuracy observational studies (three studies in EUnetHTA report and two newly identified studies). Hence, there is currently no direct evidence evaluating the clinical effectiveness and safety of the screening device under investigation. Indirect evidence from the EUnetHTA report (benefit-harm analysis considering a lifetime time horizon) showed the following results based on a cohort of 1,000 individuals (comparison: no screening; screening interval: 50 to 74 year olds; based on test accuracy data from two studies and assumptions regarding test frequency tailored to the Austrian system):

- **Life years gained:** 394 with colonoscopy, 385 with Cologuard®, 365 with FIT, and 358 with ColoAlert®.
- **Colorectal cancer-related deaths prevented**: 31 with colonoscopy, 30 with Cologuard®, 28 with FIT, and 27 with ColoAlert®.
- **Number of Colonoscopies:** 904 with FIT, 1,053 with ColoAlert®, 1,292 with Cologuard® and 2,777 with colonoscopy

colonoscopy most effective strategy

higher sensitivity and lower specificity compared to immunological stool blood tests (FIT)

Diagnostic test accuracy data from the five currently available studies consistently indicates that the sensitivity of MT-sDNA tests in an average screening population is higher than sensitivities of FIT, yet with a lower specificity. For patients aged 45 to 49 years only, one study found considerably high specificity, although no direct comparison was conducted within this study.

Conclusion

evidence insufficient to demonstrate clear population-based clinical added benefit

The current evidence is insufficient to demonstrate superiority of MT-sDNA testing compared with other conventional screening methods. Based on diagnostic test accuracy data, modelling analysis shows that MT-sDNA with Cologuard® could be an option among other screening strategies such as FIT or

colonoscopy, although 10-yearly colonoscopy is still the most effective strategy. There is still high uncertainty with regard to the use of MT-sDNA with ColoAlert®.

indirect evidence: Cologuard® as an option consideration of costs, patient preference & adherence necessary

More high quality evidence derived from randomised controlled trials is needed to clearly show whether a screening strategy with MT-sDNA yields clinically relevant benefits in terms of reduced CRC mortality. It is suffice to say that adherence, patient preferences and costs and cost-effectiveness further need to be considered in decision making. The screening strategy as such (opportunistic vs. organized) plays a further pivotal role in reducing the burden of CRC that should lastly be prioritised. Next to clinical trials, further decision-analytic evaluations would be necessary to demonstrate an acceptable benefit-harm ratio and cost-effectiveness of screening strategies with varying test time intervals, combination of tests, start and end ages.

Zusammenfassung

Einleitung

Das kolorektale Karzinom (CRC) ist die dritthäufigste Krebsart mit einer Inzidenz und Prävalenz von etwa 4.800 bzw. 40.000 Fällen pro Jahr. Der DNA-Stuhltest ist ein neuartiger, nicht-invasiver Screeningtest, der die etablierten Stuhltests durch die Analyse der Tumor-DNA (im Stuhl) ergänzen oder ersetzen könnte. In diesem Bericht wird die verfügbare Evidenz hinsichtlich des klinischen Nutzens und Schadens von DNA-Stuhltests beschrieben.

kolorektales Karzinom, Früherkennung wesentlich

DNA-Stuhltest als neuer, nicht-invasiver Test: Cologuard®, ColoAlert®

Methoden

Die Qualität eines aktuellen (2019 veröffentlichten) EUnetHTA-Berichts wurde anhand der AMSTAR-II-Checkliste bewertet. Darauf aufbauend wurde eine systematische Literatursuche in drei Datenbanken (8/2018-5/2021) – unter Verwendung der im EUnetHTA-Bericht verwendeten Suchstrategie – durchgeführt. Die Datenextraktion und Qualitätsbewertung der identifizierten Studien wurden von einer Person durchgeführt. Die Evidenz wurde narrativ beschrieben.

Update EUnetHTA Report 2019

Ergebnisse

Die derzeit verfügbare Evidenz besteht aus fünf Beobachtungsstudien zur diagnostischen Testgenauigkeit (drei Studien aus EUnetHTA Report 2019 und zwei neu identifizierte Studien). Daher gibt es derzeit keine direkte Evidenz zur Bewertung der klinischen Wirksamkeit und Sicherheit des untersuchten Screening-Instruments.

Evidenz: keine RCTs/NRCTs zu Wirksamkeit/Sicherheit

Indirekte Evidenz aus dem EUnetHTA-Bericht 2019 (entscheidungsanalytisches Markov-Modell) deutet darauf hin, dass die 10-jährliche Koloskopie – im Vergleich zu anderen Teststrategien (Cologuard®: 3-jährlich; ColoAlert®: 3-jährlich; FIT: 2-jährlich) – die wirksamste Strategie ist (allerdings mit der größten Belastung für die gescreenten Individuen). Auf Basis einer Screening-Kohorte von 1.000 Personen sind die Ergebnisse der Modellierung (im Vergleich zu keinem Screening; basierend auf Testgenauigkeitsdaten von zwei Studien und Österreichspezifische Annahmen) wie folgt:

1 Modellierung aus 2019 (basierend auf 3 Studien)

und 2 neue Studien zur Aktualisierung der Erkenntnisse über die diagnostische Genauigkeit

Koloskopie effektivste Strategie

- **Gewonnene Lebensjahre:** 394 mit Koloskopie, 385 mit Cologuard®, 365 mit fäkal immunologischen Tests (FIT), und 358 mit ColoAlert®
- **verhinderte Darmkrebs-bedingte Todesfälle**: 31 durch Koloskopie, 30 durch Cologuard®, 28 durch FIT und 27 durch ColoAlert®
- **Koloskopien**: 904 mit FIT, 1.053 mit ColoAlert®, 1.292 mit Cologuard® und 2.777 mit Koloskopie

Die Daten zur diagnostischen Genauigkeit der Tests aus den fünf derzeit verfügbaren Studien deuten übereinstimmend darauf hin, dass die Sensitivität von DNA-Stuhltests in einer durchschnittlichen Screening-Population höher ist als die von FIT. Die Spezifität ist dagegen bei DNA-Stuhltests (im Vergleich zu FIT) niedriger. Für Patient*innen im Alter von 45 bis 49 Jahren wurde in einer nicht-komparativen Studie jedoch eine hohe Spezifität gemessen.

höhere Sensitivität und geringere Spezifität im Vergleich zu immunologischen Stuhlbluttests (FIT)

Schlussfolgerung

Evidenz unzureichend, um eindeutige populationsbezogene Effekte nachweisen zu können

Die Evidenz ist unzureichend, um eine Überlegenheit der DNA-Stuhltests im Vergleich zu anderen herkömmlichen Screening-Verfahren zu belegen. Auf der Grundlage der Daten zur diagnostischen Testgenauigkeit zeigt eine umfassende Modellierung jedoch, dass der DNA-Stuhltest mit Cologuard® eine alternative Option neben anderen Screening-Strategien sein könnte, obwohl die 10-jährliche Koloskopie nach wie vor die effektivste Strategie ist.

indirekte Evidenz: Cologuard® als Option

Berücksichtigung der Kosteneffektivität, Patient*innenpräferenz & Adhärenz notwendig

(Randomisierte) Kontrollstudien sind notwendig, um eruieren zu können, ob der standardmäßige Einsatz der DNA-Stuhltests mit einem klinisch relevanten bevölkerungsbezogenen Nutzen (Verringerung der Sterblichkeit bei Darmkrebs) einhergeht. Es ist darauf hinzuweisen, dass die Adhärenz sowie die Präferenzen der Patient*innen ebenfalls einen wesentlichen Einfluss auf den bevölkerungsweiten Nutzen eines Darmkrebsscreenings haben. Ebenso spielt die Screening-Strategie als solche (opportunistisch vs. organisiert) eine weitere zentrale Rolle bei der Verringerung der Gesundheitslast durch Darmkrebs. Gesundheitsökonomische Evaluationen und weitere entscheidungsanalytische Modellierungen (Nutzen-Schaden-Verhältnis) sind – neben weiterer klinischer Forschung – zielführend. Dabei sollten unterschiedliche Testzeitintervalle, Testkombinationen sowie Screening-Perioden (Anfangs- und Endalter) adäquat berücksichtigt werden.

1 Introduction[1]

Technical Characteristics of MT-sDNA and anticipated benefit

DNA-Stuhltest: neuer, nicht-invasiver Test zur Darmkrebsfrüherkennung: Cologuard® ColoAlert®

Multi-target stool DNA (MT-sDNA) testing is a novel non-invasive screening test that may be able to supplement or replace established stool tests such as guaiac based faecal occult blood test (gFOBT) to detect colorectal carcinoma (CRC) by analysing (stool-based) tumour DNA. For the diagnosis of CRC, there are currently numerous types of tests available, with colonoscopy representing the gold standard hereby. While colonoscopy evaluates the gastrointestinal tract completely, it is also an invasive procedure (similar to sigmoidoscopy). Additionally, there are several non-invasive screening methods that can be used for the early detection of CRC. These consider, for instance, components of (haemo)globin in the stool or (additionally) DNA (e.g., aberrantly methylated BMP3/NDRG4 promoter regions, mutant KRAS). Table 1-1 gives a broad overview of MT-sDNA tests and other tests available for CRC screening.

Table 1-1: Features of MT-sDNA tests and comparators

Type of Screening test/ Name of test	Invasive (Yes, No)	Main features
Colonoscopy/ NA	Yes	Direct visual examination of entire colon and rectum with removal of polyps
flexible Sigmoidoscopy/ NA	Yes	Visual examination of rectum and lower third of colon by insertion of a flexible tube into colon
Guaiac fecal occult blood test (gFOBT)/ NA	No	Detection of pseudoperoxidase activity of heme component of hemoglobin
Fecal immunochemical test (FIT)/ NA[2]	No	Detection of presence of globin by immunochemical reactions
Stool DNA test + FIT/ Cologuard® (Exact Sciences)	No	Detection of aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, ACTB (reference gene for hDNA quantity), FIT
Stool DNA test + FIT/ ColoAlert® (PharmGenomics)	No	Mutant KRAS, mutant BRAF, quantification of hDNA, FIT
M2-PK/ e.g., Schebo®(Biotech AG)	No	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: [1, 2]

[1] For a more nuanced description of technical characteristics of MT-sDNA tests to diagnose, and health problem regarding, CRC, the reader is referred to initial EUnetHTA report.

[2] There are numerous FIT producers on the market.

Health problem and current use of MT-sDNA test in Austria

Darmkrebs: dritthäufigste Krebsart in Österreich Früherkennung wesentlich, weil oft asymptomatisch

CRC is the third most frequent cancer type, with an incidence and prevalence of approximately 4,800 and 40,000 cases respectively each year in Austria [3]. Most patients suffering from CRC are asymptomatic and, hence, early detection is primordial to reduce the mortality-risk associated with CRC [4-6]: While approximately 90% of patients survive 5 years post-diagnosis of localised CRC, CRC-patients with distant metastases (which are also often asymptomatic) have an estimated 5-year survival of only 10% [7]. Besides, adenomas can be removed before they progress to cancer[8].

Österreich: 10-jährliche Koloskopie, Okkult-Bluttest und fäkal-immunochemischer Test (regional)

In Austria, the non-population-based options for total 10-yearly colonoscopy and annual gFOBT exists for individuals aged 50 years and above. In one state of Austria (Burgenland), organized population based faecal immunochemical test (FIT) exists for individuals aged 40 to 80 years [2, 9].

Available knowledge and need for policy brief

EUnetHTA Report 2019 nur indirekte Evidenz

A recent European Network for Health Technology Assessment (EUnetHTA) report 2019 [2] assessed the evidence regarding an additional benefit of adopting MT-sDNA tests into diverse screening pathways. In this assessment, no direct evidence derived from randomised controlled trials was identified, although three diagnostic accuracy studies and five patient surveys were included. Based on decision-analytic modelling which incorporated indirect evidence, stool DNA testing showed a promising benefit–harm balance when different screening strategies were compared, although these results are only applicable to one of two currently available DNA stool tests (Cologuard®) [10]

Update der Evidenz 2018-2021

In the absence of direct evidence regarding a clinical benefit of MT-sDNA tests, it is still uncertain whether this screening test (as add-on of the existing screening pathway or potential replacement of gFOBT) yields additional population-based benefits in terms of a reduced disease burden of CRC.

2 Scope

2.1 PICO question

PIKO-Fragen

What is the latest evidence on the diagnostic test accuracy of MT-sDNA testing as an add-on or replacement of existing screening tests in different screening pathways in healthy individuals aged 45 or older?

Is a screening pathway with MT-sDNA testing more effective than, and at least as safe as, a conventional screening pathway in terms of reducing CRC related mortality and potential harms?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 2-1. For the update review, studies with high risk of bias and retrospective studies were additionally excluded.

Table 2-1: Inclusion criteria

Population	Asymptomatic, predominantly healthy persons aged 45 years or older, who do not belong to a high-risk group for the development of CRC (e.g., individuals with a family history of CRC, carriers for hereditary CRC, people found to have five colorectal adenomas, and patients with inflammatory bowel disease)
Intervention	Standard screening pathway with a stool test for the detection of altered DNA from cancerous and precancerous lesions of the colonic mucosa (also in addition to occult blood testing). Product names: ColoAlert® (PharmGenomics), Cologuard® DNA test (Exact Sciences)
Control	Conventional screening pathway that may or may not include one of the following: ■ Colonoscopy (which also is the reference standard for test accuracy studies) ■ (Flexible) Sigmoidoscopy ■ gFOBT ■ FIT ■ M2-PK test ■ SEPTIN9 test ■ CT colonography
Outcomes	
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 ■ handling problems carrying out the test and/or taking the specimen
Study design	
Effectiveness	■ diagnostic accuracy studies, ■ randomized controlled trials, prospective controlled studies
Safety	■ randomized controlled trials, prospective studies with or without a control group, qualitative studies for the psychological harm outcome

Slightly adapted from [2][3]

Abbreviations: CRC=colorectal cancer; CT=computed tomography; DNA=deoxyribonucleic acid; FIT=fecal immunochemical test; gFOBT=guaiac (based) fecal occult blood test.

[3] In the EUnetHTA report, one can find further evidence on patient adherence (patient preference) and costs of the test.

3 Methods

This policy brief represents an evidence synthesis based on a recent EUnetHTA report 2019 [2] and an update of the evidence of the screening test under investigation.

Update Rapid Review

3.1 Systematic literature search

The systematic literature search was conducted on the 06.05.2021 in the following databases:

systematische Literatursuche in drei Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library

The systematic search was limited to the years 2018 to 2021,updating the evidence of the EUnetHTA report 2019 [2]. After deduplication, overall 608 citations were included. The specific search strategy employed can be found in the Appendix (see “Literature search strategies”).

Zeitraum: 2018-2021

Furthermore, a hand-search in the reference list of one recent systematic review [11] was conducted to strengthen the systematic search and eventually identify potentially further eligible studies: no further studies were hereby identified.

insgesamt 608 Publikationen identifiziert

3.2 Flow chart of study selection

Overall 608 hits were identified. The references were screened by one researcher. The selection process is displayed in Figure 3-1.

Literaturauswahl

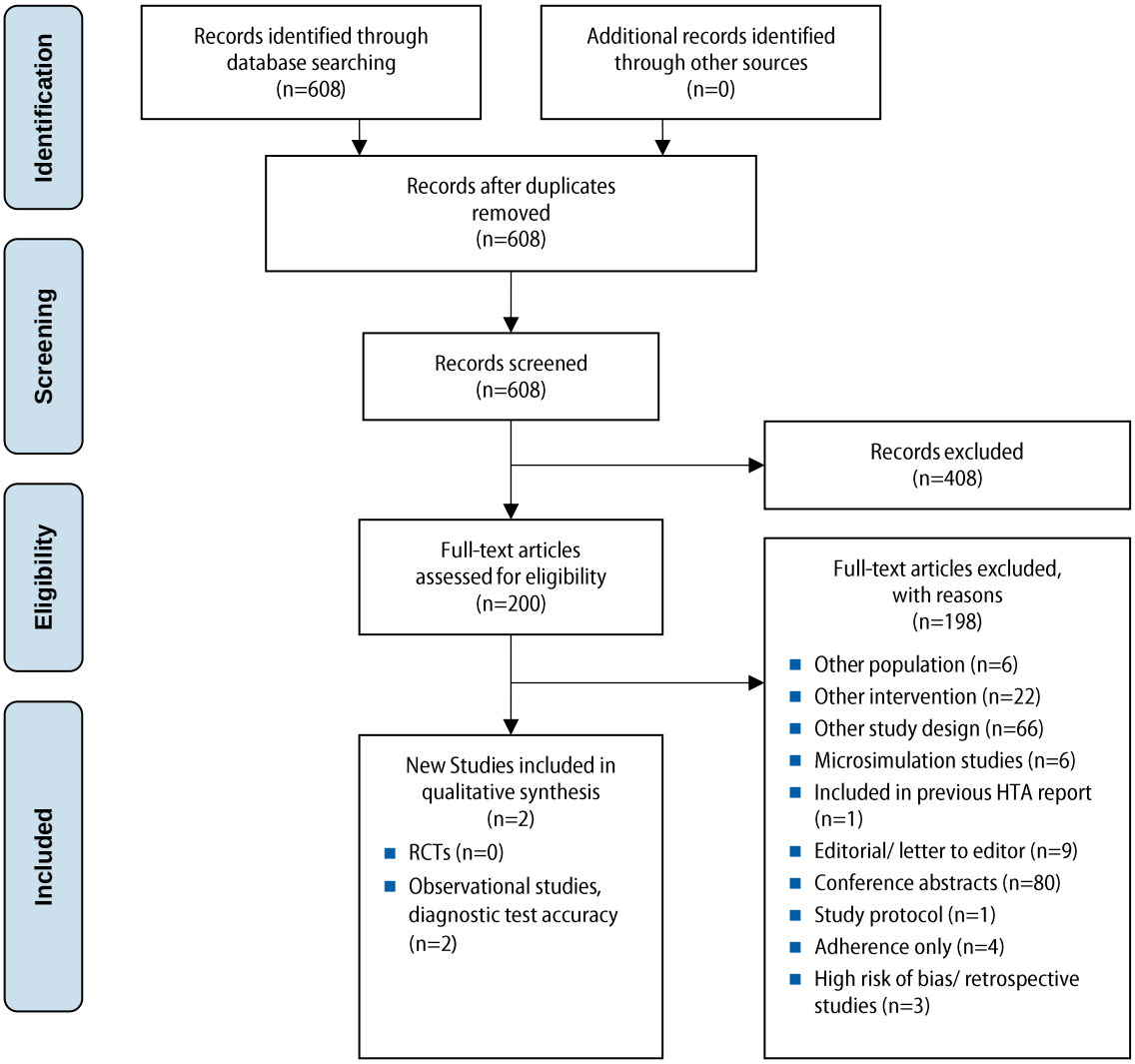

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.3 Analysis

Qualitätsbeurteilung und Extraktion durch 1 Person

The methodological quality of the EUnetHTA report 2019 [2] was assessed with the AMSTAR-II tool [12]. Relevant data from eligible primary studies were systematically extracted into data-extraction tables. One person (GG) extracted the data and assessed the risk of bias using the QUADAS-II instrument [13].

GRADEpro für Darstellung der diagnostischen Genauigkeitsdaten

For the detection of CRC solely, GRADEpro[4] was used to calculate the consequences of the diagnostic test accuracy results across studies (true positives, false negatives, true negatives, false positives) per 1.000 tested patients based on prevalence data as defined in the EUnetHTA report 2019 [2].

3.4 Synthesis

qualitative Evidenzsynthese

A qualitative synthesis of the evidence was performed: The evidence was narratively described, with reference to the EUnetHTA report 2019 [2] and data-extraction tables of the studies identified within the update rapid review (see Table A - 1).

[4]Grading of recommendations assessment development and evaluation (GRADE; https://gdt.gradepro.org/, assessed on 01.08.2021).

4 Clinical Effectiveness and Safety of MT-sDNA tests

4.1 Outcomes

The following outcomes were selected for the update evidence synthesis with regard to the evaluation of **effectiveness** of MT-sDNA:

Wirksamkeit: Darmkrebsmortalität, Gesamtmortalität, Darmkrebsinzidenz

- CRC mortality
- Overall mortality
- CRC incidence

The following outcomes were selected for the update evidence synthesis with regard to the evaluation of **diagnostic test accuracy** of MT-sDNA:

Endpunkte: diagnostische Genauigkeit (Sensitivität Spezifizität, etc.)

- Sensitivity and specificity for CRC
- Sensitivity and specificity for precancerous lesions
- Positive and negative predictive value
- Number needed to screen to detect CRC
- NNS to detect advanced adenoma

The following outcomes were selected for the update evidence synthesis with regard to the evaluation of **safety** of MT-sDNA:

Sicherheit: (Folgen von) falsch-positiven/ falsch-negativen Testergebnissen, etc.

- 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

4.2 Included studies

One EUnetHTA report 2019 [2] that included three observational studies [14-16] and further two observational studies [10, 17] updating the evidence were included in this review. The EUnetHTA report 2019 included studies on the use of the Cologuard® test (vs. FIT test) [14, 15] and ColoAlert® test (vs. gFOBT) [16]. The newly identified studies evaluated the use of Cologuard® [15, 17].

3 Studien aus EUnetHTA Report 2019 zu Cologuard® oder ColoAlert®

und 2 neue Studien zu Cologuard®

Study characteristics

Of all eligible primary studies, two were conducted as cross sectional screening studies [14, 17], two further studies were prospective screening cohort studies [10, 16] and the remaining study was a preclinical multicentre case cohort study [15].

zur diagnostischen Testgenauigkeit

Index tests and reference standards

Cologuard® (vs. FIT) in 4 Studien ColoAlert® vs. gFOBT und M2-PK in 1 Studie

Of all studies, three studies [10, 14, 17] used MT-sDNA using the Cologuard® test as an index test, and two of these studies [10, 14] compared these results to FIT results. Another study [16] used a newer version of the FIT test as the index test to indirectly make comparisons to Cologuard® data from a prior published study [14]. The remaining study chose MT-sDNA with the ColoAlert® test as the index test and compared it to the gFOBT and pyruvate kinase isoenzyme type M2 (M2-PK) test.

Koloskopie als Referenzstandard in allen Studien

All studies [10, 14-17] selected colonoscopy as the reference standard.

Setting and outcomes measured

Setting: Privatpraxen oder Gastroenterologische Praxen

The setting were private practices or gastroenterology practices in three studies [14-16] and not reported in the remaining two studies [10, 17].

None of the primary studies assessed patient-relevant outcomes directly. Instead, diagnostic test accuracy outcomes were assessed by the included observational studies [10, 14-17].

Endpunkte: diagnostische Genauigkeit

The EUnetHTA report 2019 [2] assessed patient-relevant endpoints indirectly through a markov model using diagnostic test accuracy data.

Patient characteristics

Alter der Patient*innen: Cologuard®/4 Studien: 45-84 J. ColoAlert®/1 Studie: 38-85 J.

For Cologuard®, all participants in primary studies were asymptomatic and between 45 to 84 years old [10, 14, 16, 17]. One study [14], however, was intentionally weighted toward individuals who were older or at least 65 years in order to increase the prevalence of CRC. Another study [17] included, conversely, average risk individuals aged between 45 and 49 years.

For ColoAlert®, the only available study [15] included individuals aged 38 to 85 years, which does not represent an average CRC screening population.

Methodological Quality/ Risk of bias assessment

methodische Qualität: hoch in EUnetHTA report 2019 und 4 Primärstudien und niedrig in 1 Studie (zu ColoAlert®)

The systematic review conducted as a EUnetHTA assessment 2019 [2] reached a high quality according to the AMSTAR-II assessment (see Table A - 1 in the appendix).

The risk of bias in primary studies included in the EUnetHTA report was judged to be low in two studies [14, 16] and high in the remaining study [15]. The risk of bias of included primary studies identified in the update assessment was low in both studies [10, 17].

Full risk of bias assessment can be found in the appendix[5] (see Table A - 2 and Table A - 3).

[5] Of note is that studies with high risk of bias/ retrospective studies were excluded in the update of the evidence.

Funding

The EUnetHTA report 2019 [2] and one primary study [16] were financed through public academic funding, whilst the remaining studies were industry-financed studies [10, 14, 15, 17].

Finanzierung durch Industrie in 4 (von 5) Primärstudien

Study characteristics and results of included new studies [10, 17] are displayed in Table A - 1. For more information (evidence tables) with regard to eligible studies [14-16] published prior to 2018, the reader is referred to the EUnetHTA report 2019 [2].

4.3 Results

Table 4-1: Study characteristics of the EUnetHTA report 2019 [2]

First author, year	Stürzlinger, 2019 [10]
Methodological quality (AMSTAR-II)	High
N of included studies/ study design	3/ diagnostic test accuracy cohort or case control studies
Index tests included	Cologuard®/2 studies and ColoAlert®/ 1 study
Reference standards	Colonoscopy
RoB in included studies	Low (Cologuard® studies) to high (ColoAlert® study)
Setting	Private practices or gastroenterology practices
Countries of included studies	USA, Canada, Germany
Information on modelling analysis	
Modelling design	Decision-analytic Markov state-transition cohort model
Screening strategies considered in analysis	(1) No screening; (2) FIT (age, 50–74 years; screening interval, biennial); (3) Stool DNA testing using Cologuard® (age, 50–74 years; screening interval, 3 years); (4) Stool DNA testing using ColoAlert® (age, 50–74 years; screening interval, 3 years); and (5) Colonoscopy (COL) (age, 50–74 years; screening interval, 10 years).

Clinical Effectiveness and safety

Effectiveness of MT-sDNA tests

Wirksamkeit: keine direkte Evidenz Modellierung zeigt:

Neither the EUnetHTA report 2019 [2], nor the studies identified in the update review, assessed the clinical utility of MT-sDNA tests directly. The EUnetHTA report 2019 [2] conducted a Markov model based on two diagnostic test accuracy studies. In the reporting of results of the benefit-harm analysis, the screening test always refers to the time intervals as to be seen in Table 4-1.

Koloskopie als effektivste Screening-Strategie, gefolgt von Cologuard®, FIT und ColoAlert®

in Bezug auf gewonnene Lebensjahre und verhinderte Darmkrebs-bedingte Todesfälle und Fälle per 1.000 gescreenten Individuen

Mortality. The EUnetHTA report 2019 [2] included three studies and found (based on a modelling analysis on diagnostic test accuracy data) the following when comparing different screening strategies to "no screening":

- One can expect a screening cohort of 1,000 individuals (from 50 to 74 year old) to experience 394, 385, 365, and 358 life years gained (LYG) with colonoscopy, Cologuard®, FIT, and ColoAlert® respectively.
- 31 CRC related deaths are averted with colonoscopy per 1,000 screened individuals as compared to 30, 28 and 27 with Cologuard®, FIT and Coloalert® respectively.

Additionally, the EUnetHTA report 2019 [2] transformed and interpreted these benefits on an individual level: In comparison to no screening, one expects a 50 year old person to gain averagely 144, 141, 133, and 131 life days with a colonoscopy, Cologuard®, FIT or ColoAlert® screening strategy respectively.

With respect to a potential effect of MT-sDNA test on morbidity, the decision analytic model of the EUnetHTA report 2019 [2] showed that 62, 52, 45 and 33 CRC cases are averted per 1,000 screened individuals when using a colonoscopy, Cologuard®, FIT or ColoAlert® screening strategy respectively.

Safety of MT-sDNA tests

Sicherheit: keine direkte Evidenz

The EUnetHTA report 2019 [2] included three case cohort studies [14-16] that did not report on either adverse events or user-dependent harms of MT-sDNA stool tests. Also, these studies did not directly report on the consequences of false positive or false negative test results.

Modellierung zeigt:

However, the EUnetHTA report 2019 [2] considered indirect measures of patient safety in their modelling analysis. Based on a cohort of 1,000 50-year-old patients (age of screening period: 50-74), the EUnetHTA report found

Anzahl der Koloskopien pro 1.000 Individuen mit FIT am geringsten:

FIT: 904
ColoAlert®: 1.053
Cologuard®: 1.292
Koloskopie: 2.777

- a strategy with FIT to have the lowest number of colonoscopies (n=904), followed by a strategy with ColoAlert® (n=1,053), Cologuard® (1,292) and colonoscopy (n=2,777) and
- A screening strategy with Cologuard® to have the highest number of false positive test results (n=389), followed by a screening strategy with ColoAlert® (n=317) and FIT (n=198) A strategy with colonoscopy did not yield any false positive test results[6].

falsch-positive Testresultate mit Cologuard® am höchsten

The two newly identified studies [10, 17] also sparsely reported on safety outcomes: None of the studies report on (consequences of) false negative/positive rate or numbers needed to harm. Only one study [17] stated that no adverse events occurred.

[6] *Further "harms" included complications and positive test results that can be found in Table 4-2*

A summary of benefits and harms based on the modelling analysis within the EUnetHTA report 2019 [2] can be found in Table 4-2.

Table 4-2: Summary of benefit and harms of different screening strategies

	Benefits			Harms			
Strategy	LYG	CRC-specific deaths averted	CRC cases averted	Complications	PT	FP	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

Retrieved from [13]

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); FP – false positive test results; LY=life years; PT – positive test results.

inkrementeller Vergleich (Base-Case-Analyse): 10-jährliche Koloskopie als effektivste Strategie

The EUnetHTA report [2] further conducted an incremental comparison (base-case analysis) of different screening strategies. This analysis indicates that the 10-yearly colonoscopy screening strategy is the most effective strategy, although with the greatest burden for tested individuals (due to the invasiveness of colonoscopies). While one MT-sDNA test was dominated in the benefit-harm analysis (ColoAlert®), the choice be-tween 10-yearly colonoscopy, 3-yearly MT-sDNA with Cologuard®, and bi-annual FIT is lastly dependent on the additional burden (from colonoscopies) one is willing to accept in order to gain one life year/ avert one additional CRC death. A detailed summary of the base case analysis can be found in Table 4-3.

Table 4-3: Benefit–harm analysis results of colorectal cancer screening strategies with incremental comparisons (base-case analysis)

	Benefits		Harms		Incremental Harm-Benefit Ratio			
Strategy	LY	CRC deaths **	PT	Colonoscopies	1: Δ colonoscopies/Δ LY	2: Δ colonoscopies/Δ CRC death	3: Δ positive test results/Δ LY	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

retrieved from [2]

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 DNAbased 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); LY=life years; Δ=difference.

Diagnostic test accuracy

diagnostische Genauigkeit: 3 Studien in EUnetHTA Bericht: Sensitivität hoch, aber Spezifizität vergleichsweise niedrig (v.a. im Vergleich zu FIT)

Based on three diagnostic test accuracy studies, the EUnetHTA report 2019 [2] found that MT-sDNA tests have a higher sensitivity and a lower specificity in comparison to FIT. That is, sensitivities for CRC were 84.8% for ColoAlert® [15] and 92.3% with a Cologuard® screening test [14]. The reported MT-sDNA test sensitivities for advanced precancerous lesions were 42.4% for Cologuard®[14] and not reported for ColoAlert®. The specificity for not having CRC was 89.8% for Cologuard® and 90.11% for ColoAlert® [15].

In comparison to a FIT test, Cologuard® has higher sensitivities for CRC and advanced precancerous lesions, but lower specificity with regard to CRC or advanced precancerous lesions based on one study [14] included in the EUnetHTA report [2]. Another study comparing a more advanced FIT test to Cologuard®, however, suggests that these (better) FIT tests could change the aforementioned comparative results [16]. The third study [15] included in the EUnetHTA report [2] also found higher sensitivities/ lower specificities for ColoAlert® with regard to CRC detection, although no results were reported on advanced precancerous lesions by the pre-clinical multicentre study.

New studies

2 Primärstudien aus Update zu Cologuard®:

The comparative diagnostic test accuracy data from the newly identified studies also suggests that Cologuard® has higher sensitivity, but lower specificity in comparison to FIT in one study [10], whilst another study did not report on comparative data [17].

Sensitivität (Darmkrebs) in 1 Studie: 85,7%

Sensitivity for CRC was reported by one of two included studies [10]: Cologuard® and FIT reached a sensitivity for detecting CRC of 85.7% (95%CI: 42.0-100.0) and 85.7% (95%CI: 42.0-100.0) respectively. The difference was not statistically significant, but the number of individuals with CRC was too small for relevant statistical analysis.

The sensitivity for precancerous lesions was reported in both included studies [10, 17]: One study [10] reported on a statistically significant difference favouring Cologuard® over FIT, with a sensitivity of advanced precancerous lesions of 46.2% (95%CI: 37.0-55.6) and 22.6% (95%CI: 15.1-31.6) respectively ($p<0.0001$). The other study [17] reported on a sensitivity for advanced precancerous adenoma of 32.7% (95%CI: 19.9-47.5) for Cologuard® to be used in a screening population aged 45 to 49 years.

Sensitivität (präkanzeröse Läsionen): 2 Studie 46.2% (vs. 22.6%für FIT) in 1 Studie, 32.7% in anderer Studie

Specificity (no lesions found at colonoscopy) was reported by both studies [10, 17]: One study [10] reported on specificity values of 94.1% (95%CI: 91.8-96.0) and 98% (95%CI: 96.1-98.8) for Cologuard® and FIT respectively (diff. s. s. with $p<0.001$). The other study [17] reported on a specificity of 96.3% (95%CI: 94.3-97.8) for Cologuard® to be used in a screening population aged 45 to 49 years.

Spezifizität niedriger (2 Studien): 94,1% vs. 98% (vs. FIT) in 1 Studie, 96.3% in 1 Studie (45-49 J.)

The specificity (precancerous lesions) was reported in one out of two studies [10]: Cologuard® reached a specificity of 89.1% (95%CI: 86.8-91.1) as opposed to a specificity of 97.2% (95%CI: 95.9-98.2) for FIT (diff. s. s. with $p<0.05$), with control individuals including nonneoplastic and nonadvanced polyps.

Spezifizität (präkanzeröse Läsionen) berichtet in 1 Studie: 89.1% vs. 97.2% (FIT)

Based on prevalence data retrieved from the original EUnetHTA report 2019 [2], moderate quality evidence was found that approximately 1-2 false negative and 36 to 101 false positive test results occur per 1,000 patients tested with Cologuard®. Very low quality evidence was found that 1-3 false negative and 64 to 141 false positives occur occur per 1,000 patients tested with ColoAlert®. A summary of the GRADE evidence profile for CRC detection only can be found in Table 4-5 (Cologuard®) and Table 4-6 (ColoAlert®).

A brief summary of selected diagnostic test accuracy results from the EUnetHTA report 2019 and new studies can be found in Table 4-4. For more detailed information, the reader is referred to the EUnetHTA report 2019 [2] and the data-extraction table (see Table A - 1)

Table 4-4: Summary table of diagnostic test accuracy results

Author, year	Imperiale, 2014 [14]	Dollinger, 2018 [15]	Brenner, 2017 [16]	Bosch, 2019 [10]	Imperiale, 2021 [17]
Source	EUnetHTA report 2019 [2]			New studies	
Study design; n of pts;	Preclinical case cohort study; 12,776	pre-clinical case cohort study; 734	Case cohort study with historical control	Prospective cohort study; 1,074	prospective cross-sectional study; 983
Risk of Bias	Low	High	Low	Low	Low
IND; REF	MT-sDNA Cologuard; COL	MT-sDNA ColoAlert; COL	Original FIT at 17 µg hb/g; COL	MT-sDNA Cologuard; COL	MT-sDNA Cologuard; COL
Comparator	FIT	gFOBT, M2-PK, gFOBT + M2-PK	vs. 8.4 FIT, adjusted cut off 8.4 µg hb/ historically by performance data of Cologuard®/Imperiale 2014 [14]	FIT (historical control)	None
diagnostic test accuracy results [7]					
SEN for CRC	92.3% (80.3-97.5) vs. 73.8% (61.5-84.0)	84.8% (71.9-93.1) vs. 68.0% (53.3- 80.5) vs. 82.9% (67.9- 92.8) vs. 90.2% (78.6- 96.7)	96.7% (82.8-99.9) vs. 96.7% (82.8-99.9)	85.7% (42.0–100.0) vs. 85.7% (42.0-100.0); diff. n. s.	NR
SEN for precancerous lesions	42.4 (38.9-46.0) vs. 23.8 (61.5-84.0)	NR[8]	33.7% (28.8-38.9) vs. 47.4% (42.1-52.7)	46.2% (37.0-55.6) vs. 22.6% (15.1-31.6); diff. s. s. (p<0.0001)	Nonadvanced adenoma: 7.1% (4.3–11.0) Advanced precancerous adenoma: 32.7% (19.9–47.5)
SPEC for CRC	89.8 (88.9-90.7) vs. 96.4 (95.9-96.9)	90.11% (85.7-93.5) vs. 96.4% (93.3-98.4) vs. 60.9% (54.3-67.1) vs. 61.9% (55.6-67.9)	NR	94.1% (91.8–96.0) vs. 98.0% (96.1–98.8), diff. s. s. (p<0.0003	96.3% (94.3–97.8)
PPV	NR	NR	NR	NR	NR
NPV	NR	NR	NR	NR	NR

Notes: p-values of studies included in the EUnetHTA report 2019 were not reported [2].
Abbreviations:
COL – colonoscopy; CRC – colorectal cancer; FIT - faecal immunochemical test; IND – index test; MT-sDNA – multi-target stool DNA; NPV – negative predictive value; NR – not reported; PPV – positive predictive value; REF – reference standard; SEN – sensitivity; SPEC – specificity.

[7] All values in % (95% Confidence interval).
[8] only reported for CRC or adenoma

Table 4-5: GRADE Evidence profile: Should mt-sDNA test (Cologuard®) be used to diagnose CRC in asymptomatic persons aged 45 years and older?

Sensitivity	0.85 to 0.92	Prevalences	0.655%	0.86%	
Specificity	0.90 to 0.96				

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsis-tency	Impreci-sion	Publication bias	pre-test probability of 0.655%	pre-test probability of 0.86%	
True positives (patients with CRC)	2 studies [10, 14] 13,850 patients	cross-sectional (cohort type accuracy study)	not serious	serious a	not serious	not seri-ous		6 to 6	7 to 8	Moderate
False negatives (patients incorrectly classified as not having CRC)								1 to 1	1 to 2	
True negatives (patients without CRC)	3 studies [10, 14, 17] 14,833 patients	cross-sectional (cohort type accuracy study)	not serious	serious a	not serious	not seri-ous		892 to 957	890 to 955	Moderate
False positives (patients incorrectly classified as having CRC)								36 to 101	36 to 101	

Explanations

[a.] *Indirect evidence due to the fact that patient-relevant endpoints were not directly measured*

Table 4-6: GRADE Evidence profile: Should mt-sDNA test (ColoAlert®) be used to diagnose CRC in asymptomatic persons aged 45 years and older?

Sensitivity	0.85 (95% CI: 0.72 to 0.93)	Prevalences	0.655%	0.86%
Specificity	0.91 (95% CI: 0.86 to 0.94)			

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.655%	pre-test probability of 0.86%	
True positives (patients with [target condition])	1 study [15] 734 patients	cohort & case-control type studies	very serious[a]	serious[b]	not serious	not serious		6 (5 to 6)	7 (6 to 8)	Very low
False negatives (patients incorrectly classified as not having [target condition])								1 (1 to 2)	2 (1 to 3)	
True negatives (patients without [target condition])	1 study [15] 734 patients	cohort & case-control type studies	very serious[a]	serious[b]	not serious	not serious		905 (851 to 929)	903 (850 to 927)	Very low
False positives (patients incorrectly classified as having [target condition])								88 (64 to 142)	88 (64 to 141)	

[a] *high risk of bias as to be seen in Table A 0 3*
[b] *concerns about indirectness can be found in Table A 0 4*

5 Discussion

DNA-Stuhltest: Update der Evidenz: 1 SR mit Modellierung und 5 Studien zur diagnostischen Genauigkeit

In this policy brief, the latest evidence for MT-sDNA tests was aimed to be identified and described. The EUnetHTA report 2019 [2] (with 3 included observational studies [14-16]) and two further primary studies [10, 17] were included. The current available evidence consists of 5 diagnostic test accuracy observational studies [10, 14-17]. Hence, there is currently no direct evidence evaluating the clinical effectiveness and safety of the screening device under investigation.

keine direkte Evidenz zu patient*innenrelevantem Nutzen, Modellierung: Koloskopie als effektivste Strategie

Indirect evidence from the EUnetHTA report 2019 (decision-analytic modelling based on three studies) indicates the 10-yearly colonoscopy screening strategy to be the most effective strategy, although with the greatest burden for tested individuals (due to the invasiveness of colonoscopies). While one MT-sDNA test was dominated in the benefit-harm analysis (ColoAlert®), the choice between 10-yearly colonoscopy, 3-yearly MT-sDNA with Cologuard®, and biannual FIT is lastly dependent on the additional burden (from colonoscopies) one is willing to accept in order to gain one life year/ avert one additional CRC death [2].

höhere Sensitivität, aber niedrigere Spezifizität im Vergleich zu FIT

The evidence found in the EUnetHTA report 2019 [2] suggests that MT-sDNA tests have a higher sensitivity, but lower specificity, than FIT. The newly identified studies [10, 17] confirm these results with regard to diagnostic test accuracy, although one non-comparative study reported on a considerably high specificity of MT-sDNA Cologuard® test to be used in patients aged 45 to 49 years [17].

andere Modellierung für Ö aus 2019 zeigt Koloskopie oder FIT in organisiertem Screening als effektivste Strategien

A recent decision analytic Markov state-transition cohort simulation model [18] tailored to the Austrian setting evaluated long-term effectiveness, harms and cost-effectiveness of different organised CRC screening strategies. Based on numerous choices (incl. no screening, annual FIT, 10-yearly COL and annual gFOBT), the model showed organised CRC Screening with 10-yearly COL or annual FIT to be most effective. Between these two strategies, one may consider individual preferences and benefit-harm trade-offs of screenees. It is to be noted that MT-sDNA tests were not included in the model due to limited evidence on diagnostic test accuracy for this screening test.

viel Forschung zu neuen Tests, aber Strategien zur Verbesserung der Teilnahmerate gleichzeitig erforderlich

It is further to be mentioned that the screening strategy also plays a role in reducing the population burden of CRC. Results of decision-analytic models are sensitive to screening utilization and adherence. Screening adherence remains low in Austria, with approximately 15,4 to 16,8% of the target population taking part in the CRC screening program [9]. Hence, the question of how to increase adherence to CRC screening programs is important. It appears that there is growing research in the field of pre-clinical biomarker analysis that aim to further detect CRC more accurately [19-23]. While non-invasive tests may have the potential to supplement CRC screening more broadly, focus should also be shifted toward reflecting whether the screening strategy in Austria could also be improved by implementing an organised screening program. In so doing, considering results from performance evaluations [24] may be essential in order to reach the most effective organised screening program.

9 rezente Leitlinien (LL): Empfehlung gegen eine Verwendung in 2 LL Empfehlung mit Restriktion in 2 LL 3 LL beschreiben DNA-Stuhltest als Option keine Empfehlung in 2 LL

Further, nine recent CRC screening guidelines have been identified (published between 2016 to 2021): While two guidelines [8, 25] recommend not to use MT-sDNA for CRC screening, another two guidelines [26, 27] recommended the test with restriction. That is, it is only recommended, if people refuse to use screening modalities such as colonoscopy or FIT. One of these guidelines [27] hereby specifically states that it is unlikely that MT-sDNA would replace FIT in an organised screening program. Further three guidelines solely listed it as screening options [28-30] and the remaining two guidelines [31, 32] did not make any recommendations on MT-sDNA tests, with one study specifically stating that no recommendation can be made due to the absence of RCT evidence on the MT-sDNA [31] A full description of the guideline recommendations can be found in the appendix (Table A - 5).

Further, a recent evidence report [33] by the US Preventive Services Task Force (USPSTF) included four observational studies (n=12,424) on the Cologuard® test performance and conducted a meta-analysis. Cologuard® reached a pooled sensitivity and specificity to detect colorectal cancer of 0.93 (95% CI, 0.87-1.0) and 0.85 (95% CI, 0.84-0.86) respectively. For the detection of advanced adenomas, Cologuard® had a pooled sensitivity and specificity of 0.43 (95% CI, 0.40-0.46) and 0.89 (95% CI, 0.86-0.92) respectively. It is, however, to be mentioned that one recent study was not included in the analysis that we found in this policy brief [17] and two studies [34, 35] included in the meta-analysis are arguably not applicable to the European setting and were, hence, excluded in this policy brief.

Limitations

Limitationen: Erstellung des Update-Reviews durch 1 Person

The results of this policy brief should be seen in light of its limitations: Due to the fact that this report was a rapid decision support document, only one person was involved in the screening process, data-extraction and synthesis of the evidence. This could have slightly increased the risk of error. However, it is unlikely that relevant studies were not identified.

EUnetHTA Modell mit österreichischen Annahmen, aber Stärke für Policy Brief

Also, the model-based analysis from the EUnetHTA report 2019 [2] is based on assumptions tailored to the Austrian population (e.g., mortality information, epidemiological calibration target values). While this is a limitation of the generalisability of the model as such, it is a strength for the policy brief since it aimed to inform Austrian decision makers. Nonetheless, a further weakness of the EUnetHTA report may be that cost-effectiveness of evaluated screening strategies with MT-sDNA tests was not analysed.

Conclusion

Evidenz unzureichend, um eindeutige populationsbezogenen Nutzen nachweisen zu können

The current evidence is insufficient to demonstrate superiority of MT-sDNA testing compared with other conventional screening methods. Based on diagnostic test accuracy data, modelling analysis shows that MT-sDNA with Cologuard® could be an option among other screening strategies such as FIT or colonoscopy, although 10-yearly colonoscopy is still the most effective strategy. There is still high uncertainty with regard to the use of MT-sDNA with ColoAlert®.

More high quality evidence derived from randomised controlled trials is needed to clearly show whether a screening strategy with MT-sDNA yields clinically relevant benefits in terms of reduced CRC mortality. It is suffice to say that adherence, patient preferences and costs and cost-effectiveness further need to be considered in decision making. The screening strategy as such (opportunistic vs. organized) plays a further pivotal role in reducing the burden of CRC that should lastly be prioritised. Next to clinical trials, further decision-analytic evaluations would be necessary to demonstrate an acceptable benefit-harm ratio and cost-effectiveness of screening strategies with varying test time intervals, combination of tests, start and end ages.

indirekte Evidenz: Cologuard® als Option Berücksichtigung der Kosten, Patient*innenpräferenz und Adhärenz notwendig

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A - 1: MT-sDNA for colorectal cancer screening: Results from (observational) diagnostic test accuracy studies

Author, year	Bosch, 2019 [10]	Imperiale, 2021 [17]
Country	NL	USA
Sponsor	Exact Sciences Corp. & public academic funding	Exact Sciences Corp.
Intervention/Product	Cologuard; Exact Sciences, Madison, WI	Cologuard; Exact Sciences, Madison, WI
Comparator	3 Historical control: FIT (thresholds of 50, 75, 100 hemoglobin/mL) –only results of FIT100 are extracted	None
Reference standard	Colonoscopy	Colonoscopy
Study design	Prospective diagnostic test accuracy cohort study	prospective cross-sectional study
Number of pts	1,047	983
Inclusion criteria	All screening participants who underwent a successful colonoscopy had a valid FIT result and who provided a stool sample appropriate for MT-sDNA testing were included in the analysis	NR[9]
Setting	NR	NR
Age of patients, in yrs	60 years (Ø; range 49–75)	47.8 (Ø, SD: 1.5)
Follow-up (months)	-	NR
Loss to follow-up, n (%)	-	167 (17%)
Outcomes		
Efficacy		
sensitivity for CRC, in % (95% CI)	85.7% (42.0–100.0) vs. 85.7% (42.0–100.0); diff. n. s.	NR
sensitivity for precancerous lesions, in % (95% CI)	46.2% (37.0–55.6) vs. 22.6% (15.1–31.6), diff. s. s. (p<0.0001)	Nonadvanced adenoma: 7.1% (4.3–11.0) Advanced precancerous adenoma: 32.7% (19.9–47.5)
Specificity (no lesion found at colonoscopy), in % (95% CI)	94.1% (91.8–96.0) vs. 98.0% (96.1–98.8), diff. s. s. (p<0.0003	96.3 (94.3–97.8) All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy: 95.2% (93.4–96.6)

[9] Identical to prior study included in this assessment: [14]

Author, year	Bosch, 2019 [10]	Imperiale, 2021 [17]
specificity (precancerous lesions), in % (95% CI)	89.1% (86.8–91.1) vs.; 97.2% (95.9–98.2) dif.. s. s. (p<0.05)[10]	NR
positive predictive value advanced adenoma	NR	NR
negative predictive value	NR	NR
CRC incidence	NR	NR
CRC mortality	NR	NR
overall mortality	NR	NR
number needed to screen (NNS) to detect CRC	NR	NR
NNS to detect advanced adenoma	NR	NR
Safety		
false negative rate for CRC and/or precancerous lesions	NR	NR
false positive rate for CRC and/or precancerous lesions	NR	NR
psychological harms from false negative and false positive test results	NR	No AEs ocurred
number needed to harm (NNH)	NR	NR
test performance: test failure rate	NR	NR
test performance: uncertain results rate	NR	NR
handling problems carrying out the test and/or taking the specimen	NR	NR

Abbreviations:

AE – adverse event; CI – confidence interval; NL – Netherlands; NR – not reported; USA – United States of America.

[10] Control individuals, including nonneoplastic and nonadvanced polyps

Risk of bias tables and GRADE evidence profile

Table A - 2: Risk of bias – study level (systematic reviews and meta-analyses) [12]

Author, year	Stürzlinger, 2019 [10]
1) Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from theprotocol?	Yes
3) Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4) Did the review authors use a comprehensive literature search strategy?	Yes
5) Did the review authors perform study selection in duplicate?	Yes
6) Did the review authors perform data extraction in duplicate?	Yes
7) Did the review authors provide a list of excluded studies and justify the exclusions?	Partial yes
8) Did the review authors describe the included studies in adequate detail?	Yes
9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10) Did the review authors report on the sources of funding for the studiesincluded in the review?	Yes
11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results	NA
12) If meta-analysis was performed, did the review authors assess the potential impact of RoBin individual studies on the results of the meta-analysis or other evidence synthesis?	NA
13) Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15) If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA
16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall confidence	High

Table A - 3: Risk of bias – study level (diagnostic test accuracy studies), see [13]

	Risk of Bias				Applicability concerns			
Study	1) Patient selection	2) Index test	3) Reference standard	4) Flow and timing	5) Patient selection	6) Index test	7) Reference standard	Comments
Imperiale, 2014 (Cologuard®) [14]	H	L	L	L	L	L	L	
Brenner, 2017 (Cologuard®) [16]	H	L	L	L	L	L	L	
Dollinger, 2018 (ColoAlert®) [15]	H	L	L	H	H	H	L	
Bosch, 2019 (Cologuard®) [10]	H	L	L	L	L	L	L	1) No consecutive enrolment (invitation based), observational study based on a bigger controlled study comparing Colonoscopy to Colonography.
Eckmann, 2020 (Cologuard®) [36]	H	H	H	U	L	L	L	1) retrospective enrolment; 2 and 3) index and reference test were interpreted with knowledge of the results.
Pickhardt, 2020 (Cologuard®) [37]	H	H	H	U	L	L	L	1) retrospective enrolment; 2 and 3) index and reference test were interpreted with knowledge of the results.
Vakil, 2020 (Cologuard®) [38]	H	H	H	U	L	L	L	1) retrospective enrolment; 2 and 3) index and reference test were interpreted with knowledge of the results.
Imperiale, 2021 (Cologuard®) [17]	H	L	L	L	L	L	L	1) no consecutive enrolment of pts (advertisement), 4) ITS performed

Notes: RoB from Imperiale 2014, Brenner 2017 and Dollinger 2018 are retrieved from the original assessment and can be found in more detail in the EUnetHTA report 2019 [2]
Abbreviations: H – High; L –Low; U – Unclear.

Applicability table

Table A - 4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	For Cologuard®, no substantial applicability concerns were identified with regard to the screening population. Of note is that studies that enrolled patients that were not in the target group for CRC screening (age 45 to 84) were excluded. Nonetheless, one (out of four) studies was intentionally weighted towards individuals 65 years of age and another study enrolled patients aged 45 to 49 years. For ColoAlert®, there are substantial applicability concerns, as the only available study does not represent an average CRC screening population (e.g., 40 year-old-individuals were also included in this study).
Diagnostic (index) test	With regard to the diagnostic (index) tests, no applicability concerns are identified. 4/5 studies investigated the use of Cologuard®, whilst another study investigated the use of ColoAlert ®. Both of these tests are CE-marked tests in Europe. Additionally, Cologuard® is also approved by the FDA and in routine use for non-invasive CRC screening. A slight applicability concern was identified with regard to the study investigating the use of ColoAlert ®: While ColoAlert® is CE marked for the combined use with a FIT, the clinical study incorporated a gFOBT test.
Reference standard	No applicability concerns were found with regard to the reference standard: colonoscopy was selected as reference standard by all included studies, which represents the appropriate reference standard for CRC from clinical practice.
Comparators	With regard to the comparators, no applicability concerns were found: FIT, gFOBT and M2-PK assay were selected as comparators in the included studies. Except for the latter, these are the tests that are also in routine use for CRC screening in most European countries.
Outcomes	The identified evidence is indirect: evidence on patient-relevant outcomes is based on a model-analyses conducted by the EUnetHTA report that used diagnostic test accuracy data from primary studies. The included primary studies focused solely on diagnostic test accuracy instead of patient-relevant outcomes such as CRC mortality and harms of the screening tests.
Setting	No applicability concerns were found with regard to the setting: in the clinical studies (and in clinical practice), screening tests were/ are carried out in medical practices and academic centers.

Informed by [2]

Overview of guidelines

Table A - 5: Overview of recent guidelines (2016-2021)

Name	Year of issue	Country/ies to which applicable	Recommendation with regard to MT-sDNA	Grade of recommendation/LoE	Full recommendation/ notes	Reference
American Society of Clinical Oncology (ASCO)	2019	North America	(✓)	Weak/ low	Reasons: lower specificity, lack of studies investigating follow-up of abnormal results with negative colonoscopy	[26]
German Guideline Program in Oncology (GGPO)	2019	Germany	✗	B/3b	Strong consensus	[8]
Cancer Council Australia	2018	Australia	✗	Grade C/ NA	The emerging faecal, blood or serum tests for cancer-specific biomarkers such as DNA are not recommended as population screening modalities for colorectal cancer.	[25]
American Cancer Society (ACS)	2018	North America	Optional	NA	ACS listed MT-sDNA as an option (every 3 years)	[30]
American Society for Gastrointestinal Endoscopy (ASGE)	2017	North America	(✓)	Grade B(strong recommendation)/ low-quality evidence	"We recommend CT colonography every 5 years or **FIT–fecal DNA** every 3 years or flexible sigmoidoscopy every 5 to 10 years" Guideline notes that it is unlikely that MT-sDNA would replace FIT in an organised screening program.	[27]
National Comprehensive Cancer Network: (NCCN)	2017	North America	Optional	2A	"The NCCN panel recommends inclusion of **mt-sDNA**–based testing as **a potential screening modality** in average-risk individuals, but data to help determine an appropriate interval between screening, adherence to/participation rates of screening, and how mt-sDNA testing may fit into an overall screening program are limited."	[29]
US Preventive Services Task Force (USPSTF)	2016	North America	Optional	NA	MT-sDNA (every 1 to 3 years) as an option among screening modalities "The harms of stool-based testing primarily result from adverse events associated with follow-up colonoscopy of positive findings. The specificity of FIT-DNA is lower than that of FIT alone,13 which means it has a higher number of false-positive results and higher likelihood of follow-up colonoscopy and experiencing an associated adverse event per screening test. There are no empirical data on the appropriate longitudinal follow-up for an abnormal FIT-DNA test result followed by a negative colonoscopy; there is potential for overly intensive surveillance due to clinician and patient concerns about the implications of the genetic component of the test."	[28]

Canadian Task Force on Preventive Health Care: (CTFPHC)	2016	North America	None	NA	The CTFPHC did not made any recommendations on MT-sDNA tests in the absence of RCT evidence on the mortality benefit	[31]
Scottish Intercollegiate Guidelines Network (SIGN)	2016	Europe	None	NA	"Population screening for colorectal cancer should continue in the Scottish population using quantitative FIT set at a faecal haemoglobin concentration cut-off that is appropriate for investigative capacity, but no lower than the anal tytical sensitivity of the FOBT guaiac test."	[32]

MT-sDNA recommendation:

✓ *Recommendation for use – guideline specifically recommends test to be used in a certain situation*

(✓*) Recommendation for use – with restriction*

Optional – guideline mentions MT-sDNA test as an option within CRC screening, without specifically recommending the test over others as such

✗ *Recommendation against use*

Abbreviations: LoE – Level of Evidence; MT-sDNA – Multi-target stool DNA.

Literature search strategies

Search strategy for Cochrane

Search Name:	Stool DNA tests for detecting CRC (Update of EUnetHTA search)
Last Saved:	06/05/2021 16:46:01
Comment:	GG 060521
ID	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	((colorectal OR colo-rectal OR colon* OR rectal OR rectum) AND (neoplasm* OR tumor* OR tumour* OR carcinoma* OR cancer*)):ti,ab,kw (Word variations have been searched)
3	#1 OR #2 (Word variations have been searched)
4	MeSH descriptor: [Feces] explode all trees
5	(stool* OR feces OR faeces OR fecal OR faecal):ti,ab,kw (Word variations have been searched)
6	#4 OR #5 (Word variations have been searched)
7	MeSH descriptor: [DNA] explode all trees
8	(dna):ti,ab,kw (Word variations have been searched)
9	("deoxyribonucleic acid*"):ti,ab,kw (Word variations have been searched)
10	("desoxyribonucleic acid*"):ti,ab,kw (Word variations have been searched)
11	#7 OR #8 OR #9 OR #10 (Word variations have been searched)
12	#6 AND #11 (Word variations have been searched)
13	(cologuard) (Word variations have been searched)
14	(colo-alert) (Word variations have been searched)
15	#13 OR #14 (Word variations have been searched)
16	#12 OR #15 (Word variations have been searched)
17	#3 AND #16 with Cochrane Library publication date Between Mar 2018 and May 2021 (Word variations have been searched)
53 Hits	

Search strategy for Embase

Session Results			
No.	Query Results	Results	Date
#20.	#19 AND [27-3-2018]/sd NOT [7-5-2021]/sd	547	6 May 2021
#19.	#5 AND #18	1,597	6 May 2021
#18.	#16 OR #17	17,209	6 May 2021
#17	#8 AND #11	17,147	6 May 2021
#16.	#12 OR #13 OR #14 OR #15	119	6 May 2021
#15.	colo*alert	2	6 May 2021
#14.	'colo-alert'	1	6 May 2021
#13.	cologuard	94	6 May 2021
#12.	'colorectal cancer detection kit'/exp	67	6 May 2021
#11.	#9 OR #10	1,680,390	6 May 2021
#10.	dna*:ti,ab OR 'de*oxyribonucleic acid*':ti,ab	1,294,703	6 May 2021
#9.	'dna'/exp	987,064	6 May 2021
#8.	#6 OR #7	228,872	6 May 2021
#7.	stool*:ti,ab OR feces:ti,ab OR faeces:ti,ab OR fecal:ti,ab OR faecal:ti,ab	208,734	6 May 2021
#6.	'feces'/exp	73,039	6 May 2021
#5.	#1 OR #4	492,354	6 May 2021
#4.	#2 AND #3	453,224	6 May 2021
#3.	neoplasm*:ti,ab OR tumo*r*:ti,ab OR carcinoma*:ti,ab OR cancer*:ti,ab	4,412,291	6 May 2021
#2.	colo*rectal:ti,ab OR 'colo-rectal':ti,ab OR colon*:ti,ab OR rectal:ti,ab OR rectum:ti,ab	931,402	6 May 2021
#1.	'colorectal cancer'/exp	192,956	6 May 2021

Search strategy for Ovid Medline

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to May 05, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to May 05, 2021>	
Search Strategy:	
ID	
1	*Colorectal Neoplasms/ (101156)
2	((colo?rectal or colo-rectal or colon* or rectal or rectum) and (neoplasm* or tumo?r* or carcinoma* or cancer*)).ti,ab. (395989)
3	1 or 2 (406036)
4	*Feces/ (30418)
5	(stool* or f*eces or f*ecal).ti,ab. (199929)
6	4 or 5 (204866)
7	*DNA/ (147820)
8	DNA.ti,ab. (1274090)
9	de?oxyribonucleic acid*.ti,ab. (17583)
10	7 or 8 or 9 (1305039)
11	6 and 10 (12280)
12	cologuard.mp. (48)
13	colo-alert.mp. (1)
14	12 or 13 (49)
15	11 or 14 (12295)
16	1 3 and 15 (1132)
17	limit 16 to dt=20180323-20210506 (369)
18	limit 16 to ed=20180323-20210506 (261)
19	17 or 18 (430)
20	remove duplicates from 19 (222)
06.05.2021	

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