EUnetHTA Joint Action 3 2016-2020

Stool DNA testing for early detection of colorectal cancer

Project ID: ***OTJA10***

Project description and planning

Austrian Public Health Institute

National Institute of Public Health

Agency for Medicinal Products and Medical Devices of the Republic of Slovenia

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Version Log

Version number	Date	Modification	Reason for the modification
V1	16/05/18	Draft project plan for dedicated reviewers	
V2	05/06/18	Draft project plan for review by external experts and fact check by manufacturers	Comments from dedicated reviewers included
V3	24/07/18	Final project plan	Comments from external experts and manufacturer fact check included

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List of abbreviations

AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali
CRC	Colorectal cancer
CT	Computer tomography
CU	Confidentiality Undertaking
CUR	Domain “Health problem and current use of technology”
DEFACTUM	Social & Health Services and Labour Market
DNA	Deoxyribonucleic acid
DOICU	Declaration of Interest and Confidentiality Undertaking

EbM	Evidence based medicine
EFF	Domain “Clinical effectiveness”
ETH	Domain “Ethical analysis”
EU	Eruoepan Union
EUR	Euro
FIT	Fecal immunochemical test
gFOBT	Guaiac (based) faecal occult blood test
GOEG	Gesundheit Österreich GmbH
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
iFOBT	Immunochemical (based) faecal occult blood test
JAZMP	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke
LBI-HTA	Ludwig Boltzmann Institute for HTA
LEG	Domain “Legal aspects”
M	Mandatory
MeSH	Medical Subject Headings
NICE	National Institute for Health and Care Excellence
NIJZ	Nacionalni inštitut za javno zdravje
NNH	number needed to harm
NM	Non mandatory
NNS	number needed to screen
ORG	Domain “Organisational aspects”
PICO	Population-Intervention-Comparison-Outcomes
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
SAF	Domain “Safety”
SOC	Domain “Patient and social aspects”
TBD	To be defined
TEC	Domain “Description and technical characteristics”
UMIT	Private University of Health Sciences, Medical Informatics and Technology
US	United States
USPSTF	US Preventive Services Task Force
WHO	World Health Organization
WP	Work Package

1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Austrian Public Health Institute (GOEG)	Author	Austria	overall responsibility on production and quality of report; first author of TEC, EFF and SAF, check CUR
2.	National Institute of Public Health (NIJZ)	Co-Author	Slovenia	support production of report & check all steps; first author of CUR, check TEC, EFF and SAF
3.	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Co-Author	Slovenia	support production of report & check all steps; first author of CUR, check TEC, EFF and SAF
4.	National Institute for Health and Care Excellence (NICE)	Dedicated Reviewer	United Kingdom	thorough check of draft project plan and 1st draft report incl. studies + results
5.	National agency for regional health services (AGENAS)	Dedicated Reviewer	Italy	thorough check of draft project plan and 1st draft report incl. studies + results
6.	Social & Health Services and Labour Market (DEFACTUM)	Dedicated Reviewer	Denmark	thorough check of draft project plan and 1st draft report incl. studies + results
7.	Basque Office for HTA (Osteba)	Dedicated Reviewer	Spain	thorough check of draft project plan and 1st draft report incl. studies + results
8.	Slovenian Ministry of Health	Observer	Slovenia	-
9.	Private University of Health Sciences, Medical Informatics and Technology (UMIT)	Observer	Austria	-
Contributors				
10.	Gerfried Lexer	External expert	Austria	thorough check of draft project plan and 2nd draft report incl. studies + results
11.	Isabel Idigoras Rubio	External expert	Spain	thorough check of draft project plan and 2nd draft report incl. studies + results
12.	Eunate Arana-Arri	External expert	Spain	thorough check of draft project plan and 2nd draft report incl. studies + results
13.	Fidencio Bao	External expert	Spain	thorough check of draft project plan and 2nd draft report incl. studies + results
14.	TBD	Medical Editor		medical editing of 3rd draft report
15.	Ludwig Boltzmann Institute for HTA (LBI-HTA)	Project Manager	Austria	project management and external communication

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
PharmGenomics GmbH	Manufacturer
Exact Sciences Corp.	Manufacturer
Individual patients in Austria	Patient

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**30.1.2018**	**25.3.2019**
Scoping phase	**30.1.2018**	**24.7.2018**
Kick-off e-meeting with the assessment team	14.2.2018	14.2.2018
Identification of manufacturer(s), external experts and patients	30.1.2018	17.4.2018
Send the request for the completion of the Submission file template to manufacturer(s)	19.4.2018	See below
Scoping and development of draft Project Plan incl. preliminary PICO	13.2.2018	15.5.2018
Internal Scoping e-meeting with the assessment team	5.3.2018	5.3.2018
Share the preliminary PICO with external experts for comments	17.4.2018	25.4.2018
Patient involvement according chosen method	1.3.2018	7.5.2018
Scoping e-meeting with manufacturer(s)	9.5.2018	9.5.2018
Consultation of draft Project Plan with dedicated reviewers	16.5.2018	25.5.2018
Amendment of draft project plan	25.5.2018	5.6.2018
Consultation of draft Project Plan with external experts and fact check by manufacturers	5.6.2018	21.6.2018
Amendment of draft Project Plan & final Project Plan available	21.6.2018	24.7.2018
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file)	19.4.2018	1.6.2018
Assessment phase	**17.7.2018**	**25.3.2019**
Writing first draft rapid assessment	17.7.2018	1.12.2018*
Review by dedicated reviewer(s)	3.12.2018*	21.12.2018*
Writing second draft rapid assessment	21.12.2018*	18.1.2019*
Review by ≥ 2 external clinical experts and fact check by manufacturers	18.1.2019*	8.2.2019*
Writing third draft rapid assessment	8.2.2019*	1.3.2019*
Medical editing	1.3.2019*	11.3.2019*
Writing of fourth version of rapid assessment	11.3.2019*	18.3.2019*
Formatting	18.3.2019*	25.3.2019*
Final version of rapid assessment	25.3.2019*	25.3.2019*

* Timelines exclude decision-analytic-modelling (see Table 2-2). If decision-analytic-modelling is deemed to be feasible and integrated into the assessment, the finalisation phase of the first draft rapid assessment will have to be prolonged by around four months and subsequent timelines moved accordingly.

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research question whether Stool DNA testing (alone or in addition to occult blood testing) in adult patients from a colorectal cancer screening population is more effective and/or safer than other available colorectal cancer screening tests. The relevance of the topic lies in the fact that one of the objectives within the Austrian Cancer Framework Programme is the potential implementation of organised cancer screening programmes. With regard to the potential introduction of an organised colorectal cancer screening in the future, the Austrian Ministry of Health expressed an interest in the exploration of the evidence of new tests with a potential for high diagnostic performance as well as potentially good acceptance in the population in the end of 2017.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The selection of **assessment elements** will be based on The HTA Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 (1). Additional elements will be added, if applicable, from the HTA Core Model® Version 3.0 (2), Application for Screening Technologies. A systematic **search of the** scientific **literature** (mainly for the EFF and SAF domain) as well as a hand search (for all domains) will be performed (for more information see Table 2-3). If there is an existing systematic review of high quality that covers the research question in sufficient detail, only an update search will be done for primary studies. All relevant manufacturers of the technology under assessment will be asked for their consent to fill out the Medical Devices Evidence **Submission template.** This will be sent to all manufacturers who give their consent. Manufacturers will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology. The evidence provided will be used in addition to the literature identified by the literature search.

A systematic **review of the evidence** will be done for the **EFF** and **SAF** domain. If there is an existing systematic review of sufficiently high quality that covers the research question in sufficient detail, study data will be extracted only for primary studies not already included within the systematic review.

Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines. The Cochrane Risk of bias tool will be used on study and outcome level. Test accuracy studies will be assessed using QUADAS-2 (3). The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Relevant subgroup analyses (e.g. age, gender) will be performed if feasible especially for the most important outcomes.

For the **TEC** und **CUR** domains information from different sources will be compared and cross-checked for validity. Information will be synthesized in a **descriptive manner**.

A **descriptive analysis** of data and information identified will be provided in the **ETH, ORG, SOC and LEG** domains **(only) for relevant aspects** according to the checklist (see Appendix A, 5.2).

Patients/consumers will be involved during the scoping phase, either via telephone, e-meeting or face to face (interviews or moderated group discussion, depending on the number of patients identified). Patients from a typical colorectal cancer screening population (that is asymptomatic persons aged according to national screening recommendations) that have experience with DNA stool testing will be tried to identify via a request with European Patient Organizations. Patients should be sufficiently capable of German or English language. Additionally, Austrian patients from the same screening population and either experienced with DNA stool testing, occult blood testing or colonoscopy will be sought via contacting a number of selected doctors' offices and/or hospital outpatient departments. Information from patient involvement will be used as additional information 1) for assessing the relevance of ethical and social aspects, 2) for answering research questions related to patient aspects (mainly assessment elements D0011-13, D0030, D0017).

Depending on data availability **decision-analytic modelling** might be applied to systematically synthesize evidence and assess short- and long-term benefits and unintended harms taking into account uncertainty. Comprehensive sensitivity analysis allows for the evaluation of uncertainties including parameter uncertainty of test sensitivity and specificity, probability of adverse events and utility weights.

Table 2-3: Planned literature search strategy

Literature search strategy
• A systematic literature search will be performed in the Cochrane Library as well as in Medline and EMBASE based on a thorough search strategy including relevant Mesh-terms (e.g. Colorectal Neoplasms, Early Detection of Cancer) and key words (e.g. Stool DNA testing, colo-alert). The search strategy will be checked by co-authors and dedicated reviewers. • Clinical trial registries will be assessed for registered ongoing clinical trials or observational studies: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). • In addition, a hand search (in reference lists of relevant studies) as well as an internet-search will be performed.

• Two authors from GOEG will select the studies independently from each other based on pre-defined inclusion and exclusion criteria according to the PICOS (see Table 2-5). Inclusion and exclusion of literature will be checked by co-authors and any cases of dissent will be discussed with them.

Table 2-4: Plan for data extraction

Planned data extraction
Two primary studies (4, 5) have already been identified on the two DNA stool tests assessed (see table 2-5), one of them so far only published as conference abstract (the full publication is expected for the second quarter of 2018). The risk of bias of test accuracy studies will be assessed mainly according to QUADAS-2 (3). Data will be extracted for each of the primary studies according to the following data set. • Author(s), Year of publication • Study Objective • Country/ies of recruitment, Setting, Data collection period • Intervention test and cut off (if applicable) • Comparator test(s) and cut off (if applicable) • Reference standard and type of quality assurance • Study design • Sponsoring, conflict of interest • Number of patients recruited, number of patients enrolled, age, gender, eligibility criteria • Number of patients with symptoms which may be indicative of CRC • Outcomes assessed and method of analysis • Number of evaluable tests, number of uncertain test results, number of test failures or missing tests, number of patients with missing reference standard • Number of true positive / false positive / false negative / true negative with respect to 1) CRC and 2) precancerous lesions, sensitivity (95% confidence interval), specificity (95% confidence interval) • Safety outcomes

2.2.2 Project Scope

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, **need to be consulted** throughout the assessment process.

Table 2-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	**Screening population:** Asymptomatic, predominantly healthy persons aged 45 years or older, that do not belong to a high risk group for the development of CRC. According to European Guidelines (p. 285 ff.) and German Guidelines (p. 45 ff.) high risk groups for the development of CRC include: people with a family history of CRC (one first degree relative under 60 years of age or two first degree relatives aged 60 years or more), people who are (proven or potential) carrier for hereditary CRC (e.g. Lynch syndrome, familial adenomatous polyposis or hereditary nonpolyposis CRC), people found to have 5 colorectal adenomas, patients with inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis). **Screening for colorectal cancer (CRC) and precancerous lesions** According to ICD-10 (WHO, Version 2016): C18.- Malignant neoplasm of colon D01.- Carcinoma in situ of other and unspecified digestive organs D01.0 Colon D01.2 Rectum D12.- Benign neoplasm of colon and rectum D12.0 Caecum D12.2 Ascending colon D12.3 Transverse colon Incl.: Hepatic flexure, Splenic flexure D12.4 Descending colon D12.5 Sigmoid colon D12.6 Colon, unspecified Incl.: Adenomatosis of colon, large intestine not otherwise specified, polyposis (hereditary) of colon K63.5 Polyp of colon Incl.: serrated polyps (sessile serrated adenoma and traditional serrated adenoma) Excl.: adenomatous polyp of colon (D12.6), polyposis of colon (D12.6, see above) **Rationale:** Screening for CRC is recommend for asymptomatic persons aged: - 50 to 74 years by European Guidelines (6) - 50 or older by the German S3-Leitlinie (7) - 45 to 85 (maximum range, given as “qualified recommendations”) by the American Cancer Society Guideline for CRC Screening (8)
Intervention	Stool tests for the detection of altered DNA from cancerous and precancerous lesions of the colonic mucosa (also in addition to occult blood testing). The following tests were identified (both of which use a combination of DNA analysis and FIT for occult blood testing): • **ColoAlert®** (PharmGenomics GmbH) is a technology that supplements the established occult blood test (FIT) - through stool samples - for colon cancer with the analysis of tumor-DNA. With the help of ColoAlert® human DNA gets extracted and is analyzed for KRAS- and BRAF-Gene mutations in order to detect tumor tissues, CRC and early lesions.

	• The **Cologuard®** DNA test (Exact Sciences Corp.) includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay. As the hemoglobin immunoassay is essentially a FIT test, Cologuard® is a combination of gene mutation, methylation and occult blood tests. The multitarget stool DNA test provides various detecting technology to detect CRC and early colorectal lesions.
Comparison	• Colonoscopy (which also is the reference standard for test accuracy studies) • (Flexible) Sigmoidoscopy • Guaiac-based fecal occult blood test (gFOBT) • Fecal immunochemical test (FIT) • M2 PK test • Septin 9 test • CT colonography **Rationale:** - European Guidelines (6) as well as German S3-Leitlinie (7) recommend colonoscopy, flexible sigmoidoscopy, FIT (iFOBT), and gFOBT as tests for CRC screening. European Guidelines and German S3-Leitlinie mention, but do not (explicitly) recommend CT colonography, stool DNA stool test, capsule endoscopy, and M2 pyruvate kinase stool test (M2-PK) as tests for CRC screening. Also Septin 9 test is CE-marked and available in (at least one) EU member state(s).
Outcomes	**Effectiveness** - sensitivity for CRC - sensitivity for precancerous lesions - specificity for CRC - specificity for precancerous lesions - positive predictive value - negative predictive value - colorectal cancer incidence - colorectal cancer mortality - overall mortality - number needed to screen (NNS) to detect CRC - number needed to screen (NNS) to detect advanced adenoma **Safety** - false negative rate for CRC / precancerous lesions - false positive rate for CRC / precancerous lesions - psychological harms from false-negative and false-positive test results - number needed to harm (NNH) **Other outcomes** - test performance: test failure rate - test performance: uncertain results rate - health related quality of life - handling problems carrying out the test / taking the specimen - patient adherence (patient preferences) - cost of the test (intervention) **Rationale:** The intervention assessed is DNA stool testing for colorectal cancer (CRC) screening (i.e. adenocarcinoma) and/or for (advanced and non-advanced) precancerous lesions. Grading/classification of precancerous lesions e.g. according to European Guidelines (2010), or WHO (Classification of Tumours Pathology and Genetics of Tumours of the Digestive System, 2010, 4th edition), or WHO ICD-10 Version 2016. ***Glossary:***

	- sensitivity *(true positive rate): proportion of persons with disease who have a positive test result* ***- specificity*** *(true negative rate): proportion of persons without disease who have a negative test result* ***- false negative rate*** *(1 minus sensitivity): proportion of persons with disease who have a negative test result* ***- false positive rate*** *(1 minus specifity): proportion of persons without disease who have a positive test result* ***- positive predictive value****: proportion of persons with disease among those with a positive test* ***- negative predictive value****: proportion of persons without disease among those with a negative test* ***- NNS****: number of persons who would need to be screened to identify one person with the disease* ***- NNH****: number of persons who would need to be screened to cause harm in one person who would not otherwise have been harmed*
Study design	EFF: diagnostic accuracy studies, randomised controlled trials, prospective controlled studies, systematic reviews and meta analyses SAF: randomised controlled trials, prospective studies with or without a control group, qualitative studies for the psychological harms outcome, (medical device adverse event registers and post-marketing surveillance data on device-related adverse events), systematic reviews and meta analyses

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	5.3.2018	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager
	To discuss the preliminary PICO and draft project plan with manufacturer(s)	9.5.2018	E-meeting	Author(s), co-author(s), manufacturer(s), project manager
Feedback on draft submission file (optional)	*To point out the requirements for the final submission file by manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Author(s), project manager, manufacturers*
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.3 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: https://www.eunethta.eu/rapid-reas/.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.4 Collaboration with stakeholders

Collaboration with manufacturer(s)

There will be a fact check of the 2nd draft project plan and the 2nd draft assessment by the manufacturer(s). One of the two manufacturers participates in providing the submission file and attending a scoping e-meeting.

Collaboration with other stakeholders

Patients/consumers will be involved during the scoping phase (see table 2-2), individually and/or via a request with European Patient Organizations.

3.5 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.6 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.
Authors, co-authors and dedicated reviewers who declare a specific conflict of interest will be excluded from the whole work under this specific topic. However, they still may be included in other assessments.
For external experts, patients or other stakeholders involved, conflict of interest declarations are collected. External experts or patients who declare a specific conflict of interest will be excluded from parts of or the whole work under this specific topic. However, they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form regarding the specific project.

4 References

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5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes-critical	M	What is the test and the comparator(s)? What are the relevant features?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes-critical	M	For which indications has the test received marketing authorisation or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	yes	M	What is the claimed benefit of the test in relation to the comparator(s)?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of development and implementation of the test (and, if applicable, comparator tests)?
B0018	Features of the technology	Are reference values or cut-off points clearly established?	yes		Are reference values or cut-off points clearly established for the test?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	M	Who administers the test and the comparator(s) and in what context and level of care are they provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Yes	NM	What kind of special premises are needed to use the test (and, if applicable, comparator tests)?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies are needed to use the test (and, if applicable, comparator tests)?
B0012	Training and information needed to use the technology	What kind of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the technology?	Yes		What kind of requirements in terms of qualification and quality assurance processes are needed for the use or maintenance of the test?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What is colorectal cancer (CRC)?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	NM	What are the risk factors for CRC?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of CRC?
A0005	Target Condition	What are the symptoms and the burden of disease or	Yes	M	What are the symptoms and burden of CRC for the patient?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		health condition for the patient?			
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	NM	What are the consequences of CRC for the society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes - critical	M	How is CRC currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	M	How is CRC currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes - critical	M	What is the target population for the test?
A0021	Regulatory Status	What is the reimbursement status of the technology?	Yes	NM	What is the reimbursement status of the test?
A0023	Target Population	How many people belong to the target population?	Yes - critical	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	Yes	NM	How much are currently available tests utilised?
D1003	Test accuracy	What is the reference standard and how likely is it to classify the target condition correctly?	Yes		What is the reference standard and how likely is it to classify the CRC correctly?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	yes	M	What is the expected beneficial effect of the test on mortality?
D0026	Morbidity	How does the technology modify the effectiveness of subsequent interventions?	yes		How does the test modify the effectiveness of subsequent interventions?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	no	NM	
D0032	Morbidity	How does the technology modify the magnitude and frequency of morbidity?	yes		How does the test modify the magnitude and frequency of morbidity?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	no	NM	
D0011	Function	What is the effect of the technology on patients' body functions?	yes	M	What is the effect of the test on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	no	NM	
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	yes	M	What is the effect of the test on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	yes	M	What is the effect of the test on disease-specific quality of life?
D0030	Quality of life	Does the knowledge of the test result affect the patient's non-health-related quality of life?	yes		Does the knowledge of the test result affect the patient's non-health-related quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	yes	NM	Were patients satisfied with the test?
D1001	Test accuracy	What is the accuracy of the test against reference standard?	Yes - critical		What is the accuracy of the test against reference standard?
D1005	Test accuracy	What is the optimal threshold value in this context?	Yes - critical		What is the optimal threshold value in this context?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
D1006	Test accuracy	Does the test reliably rule in or rule out the target condition?	Yes - critical		Does the test reliably rule in or rule out the target condition?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	yes	M	How safe is the test in relation to the comparator(s)?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	no	NM	
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	yes	M	How does the frequency or severity of harms change over time or in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	yes	M	What are the susceptible patient groups that are more likely to be harmed through the use of the test?
C0006	Patient safety	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?	yes		What are the consequences of false positive, false negative and incidental findings generated by using the test from the viewpoint of patient safety?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	yes	NM	Are the test and comparator(s) associated with user-dependent harms?
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	no	NM	

5.2 Checklist for potential ethical, organisational, patient and social and legal aspects

1. Ethical	**Relevance***
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No**
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No**
2. Organisational	**Relevance***
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
An increased usage of DNA stool testing might result in a higher demand for laboratories that have the relevant knowledge/experience (e.g. at the moment there is only one laboratory for ColoAlert). Moreover, the (diagnostic) colonoscopy rate might change.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
See above.	
3. Social	**Relevance***

3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	**Relevance***
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

* If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.
** All forms of genetic technologies can potentially raise ethical issues. However, the technologies in questions do not seem to present any new specific ethical challenges.