Input from external experts and manufacturer on the **2nd draft project plan** "**Stool DNA testing for early detection of colorectal cancer**"

(Project ID:OTJA10)

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Content

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c]"linguistic": grammar, wording, spelling or comprehensibility

EXTERNAL EXPERTS

Comments were received from:

Name	Affiliation
Isabel Idigoras Rubio	Osakidetza, Spain
Eunate Arana-Arri	BIOEF research Institute, Basque Health Service, Spain
Gerfried Lexer	Registered physician in surgery, Austria
Fidencio Bao	Hospital Urduliz, Osakidetza, Spain

Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3	Author's reply
Eunate Arana- Arri Basque Health Service	8	87	I think it would be more interesting to measure the result variable efficiency instead of effectiveness. Besides detecting better malignant and premalignant lesions, DNA stool is more efficient? On the other hand, the term safer must be considered within the complications of a screening program (complications of colonoscopies, psychological damage, ...) but not false results.	1	We don't assess efficiency (that would relate to the ECO domain) within this REA. Second sentence not quite clear – we assess safety, primarily, of the test itself, not of the whole screening pathway including the test.
Idigoras Osakidetza	11	106	anus and anal canal should not being considered CRC	2	Thanks, corrected.
Eunate Arana- Arri Basque	11	106 (Table 2-5; Population)	I do not think it is appropriate to estimate a risk: greater or equal to 5 adenomas or adenomas greater than or equal to 20 mm.	1	Sentence has been modified.

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Health Service			These are premalignant lesions that must be detected in a screening program.		
Dr.med.univ. Gerfried Lexer	11	106	As far as I know in Germany colonoscopy in prevention colorectal cancer starts with the age of 55. In Austria we start with the age of 50. Women and men at the same age. As we know that CRC in men occur earlier the society of gastroenterology recommend starting age 45. As we know that the Adenoa Carcinoma growing time is between 10 and 15 years I urgently recommend screening start at least with the age of 40 in men - and - 45 in women. Within this time oncogenes get more in numbers so they can get catched during this time period as precancerous signs before the cancer is histologically diagnosed. I recommend starting with 40/45 years.	1	During the scoping phase we already discussed the starting age that should be defined within PICO and so far agreed on sticking to the recommendations published in Europe. Please give the exact sources for your comments and recommendations (citation or pdf) – so we can reconsider. Answer expert: American cancer society: CA:A Cancer Journal for Clinicians (2018;doi:10.3322/caac.21457) Comment authors: For the definition of the general target population of the assessment (i.e. a typical screening population) the age was modified to "45 years or older" according to the recently published recommendations of the American cancer society.
Dr.med.univ.	11	106	A major problem of colonoscopy as it is a subjective investigation	1	Many thanks for the relevant

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Gerfried Lexer			are the undetected pathologies - which are responsible for the so-called Intervall carcinomas. A DNA Test is like in criminology a objective testing.		comment.
Fidencio Bao Hospital Urduliz Osakidetza	11	2.2.2 Table 2-5 Screening poluplation	High risk for CRC: I recommend defining family history of high risk only one first degree relative (FGR) under 60 years or two FDR ages 60 or more.	1	Added
Fidencio Bao Hospital Urduliz Osakidedtza	11	2.2.2 Table 2-5 Polulation: Screening for colorectal camcer (CRC) and precancerous lesions	D01-. Is better to define as high grade dysplasia for the term carcinoma in situ	1	We do not want to change the wording here, as "D01 Carcinoma in situ" is the term used in WHO ICD-10.
Fidencio Bao Hospital Urduliz Osakidedtza	11	2.2.2 Table 2-5 Population: Screening for colorectal camcer (CRC) and precancerous lesions	K63.5 Polyp of colon Incl: serrated polyps I recommend dividing serrated polyps in sessile serrated adenoma and traditional serrated adenoma.	1	Has been added.
Fidencio Bao	11	2.2.2 Table 2-5	Number needed to screen must be divided in two targets: to detect colorectal cancer and advanced adenoma	1	Has been added.

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EUnetHTA JA3 WP4 - Other technologies
All comments and author´s replies on the 2nd draft project plan "Stool DNA testing for early detection of colorectal cancer"

July 2018

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Hospital Urduliz Osakidedtza		Outcomes: Effectiveness			
Idigoras Osakidetza	12	106	The cut off for Positivity of Fecal immunochemical test (FIT) should be clarified as it is different for being referred to colonoscopy around the different screening programmes around Europe.	1	Many thanks – of course a valid point. The cut off will be extracted (see also table 2-4) and results will be interpreted accordingly.
Idigoras Osakidetza	12	106	Rationale: according to European Guidelines (2012) should be editor 2010.	1	Thanks, corrected.
Eunate Arana- Arri Basque Health Service	12	106 (Table 2-5; Outcomes)	In the security section I do not think it is appropriate to include: - false negative rate for CRC / precancerous lesions - false positive rate for CRC / precancerous lesions - negative predictive value These are efficacy data. Safety is the complications derived from the program (psychological damage, complications of colonoscopies, complications of surgeries, ...) The errors of the test should be another section and neither are program safety	1	We assess safety, primarily, of the test itself, not of the whole screening pathway that includes the test. We agree with regard to false negative and false positive rates being (also) efficacy data, but for reasons of clearness want to have them mentioned in the safety section. The other mentioned outcomes (errors of the test) have been moved to "other outcomes".
Idigoras Osakidetza	16	161	REFERENCE: Frist edition ; typing error FIRST	3	Thanks, corrected.

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July 2018

MANUFACTURER

Comments were received from:

Name	Company
Philipp Freese, Moritz Eidens	PharmGenomics GmbH

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PharmGenomics	General		Everything is fine for us – no comments!		Thank you.

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