

EXTERNAL EXPERTS

Comments were received from

External experts	Dr Fidencio Bao
	Dr Gerfried Lexer

Comment from <i>Insert your name, title and affiliation</i>	Page number <i>Insert 'general' if your comment relates to the whole document</i>	Line/section number	Comment and suggestion for rewording <i>Please insert each new comment in a new row.</i>	Character of comment • 'major' ^a =1 • 'minor' ^b = 2 • 'linguistic' ^c =3 <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	Author's reply
Fidencio Bao Hospital Urduliz Osakidetza	12	283-285	Individuals for screening not only without prior history of cancer or precancerous lesions but also without familial history of colorectal cancer.	"1"	Was added. A detailed description of the included population is given in the Scope (PICO).
Fidencio Bao Hospital Urduliz Osakidetza	14	355-359	One more screening strategy, i.e: an annual FIT based screening for people aged 50 - 75 years	"1"	We agree that the evaluation of additional strategies including annual FIT based screening is important. For this report, however, we needed to restrict the number of evaluated strategies and did, for example, also not evaluate shorter screening intervals for colonoscopy. This limitation was added to the discussion part.

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Summary					
Dr. Gerfried Lexer	11	226	According to the annual report of Exact Science, ColoGard is not available in Europe.	2	Wording adapted.
Dr. Gerfried Lexer	11	228	... for screening, prevention as well as diagnostic purposes in public health and workplace health promotion.	2	Wording not changed, as it directly refers to the citation (manufacturer submission file).
Dr. Gerfried Lexer	11	234	Due to the enclosed stool sample collector there are no special requirements for the toilet.	2	Wording adapted.
Dr. Gerfried Lexer	11	249 general	... is ≥ 1 ng of hDNA per μ L of total DNA extracted.	2	The fact that the current threshold is set at 1 ng/ μ L is already mentioned on page 84 (D1005). It was added within the technical description.
Dr. Gerfried Lexer	14	386 general	These results came at a specificity of 91.7% for no findings ...	1	Complete data are given in table 5.4 (with 91.7 % specificity for no findings).
	16	441 general	Currently two laboratories (in Germany) are qualified for analyzing ColoAlert®	2	Wording adapted / information added.
Dr. Gerfried Lexer	19	Footnote 1 general	Specificity of ColoAlert is 91.7% for no findings	1	Complete data are given in table 5.4 (with 91.7 % specificity for no findings).
Dr. Gerfried Lexer	20	490	In case a second specimen has to be collected, there are no additional costs for the patients.	3	Wording adapted.
Description and technical characteristics of the technology					
Dr. Gerfried Lexer	41	Table 3.1	The main features of ColoAlert and ColoGuard are swapped.	2	Corrected.

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Dr. Gerfried Lexer	41	906	Currently,there is one CE-marked stool DNA test in Europe, ColoAlert® (PharmGenomics).	2	Not quite clear. Both tests have a CE mark. See B0001, page 42, as well as your comment further below.
Dr. Gerfried Lexer	41	907	Only ColoAlert® (PharmGenomics) is actually sold on the European market.	2	Corrected.
Dr. Gerfried Lexer	42	922	..., which fits in every standard mailbox.	2	Information on the size of sample and packaging was added in B0008.
Dr. Gerfried Lexer	42	937	According to the annual report of Exact Science, ColoGard is not available in Europe.	2	Corrected.
Dr. Gerfried Lexer	44	993	... for screening, prevention as well as diagnostic purposes in public health and workplace health promotion.	2	Wording not changed, as it directly refers to the citation (manufacturer submission file).
Dr. Gerfried Lexer	44	995	Both ColoGuard and ColoAlert have a CE-mark for a non-invasive DNA colorectal cancer screening test.	2	ColoAlert consists of two individual CE-certified components. The complete product, including patient information and packaging, also has a CE mark, which, according to the document received from the manufacturer, does not include an explicit clinical indication for use. Information was taken from the manufacturer submission file.
Dr. Gerfried Lexer	45	1020	Due to the enclosed stool sample collector there are no special requirements for the toilet.	2	Wording adapted.

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Health problem and current use					
Dr. Gerfried Lexer	70	1758	ColoAlert ist not available in Romania	2	Corrected.
Clinical effectiveness					
Dr. Gerfried Lexer	72	Table 5.1	The content of column 2 belongs to the study of Dollinger et al. 2018 and the content of column 3 belongs to the study of Brenner et al. 2017.	2	Corrected.
Dr. Gerfried Lexer	76	Table 5.3	Due to the enclosed stool sample collector there are no special requirements for the toilet.	2	Transcription error: answer of the patient belongs to FIT and gFOBT only. Regarding the ColoAlert stool collecting no problems have been reported. Corrected
Dr. Gerfried Lexer	77	1930 general	Current threshold >1 ng/μL	2	The fact that the current threshold is set at 1 ng/μL is already mentioned on page 84 (D1005). It was added within the technical description.
Dr. Gerfried Lexer	86	2068	Due to the enclosed stool sample collector there are no special requirements for the toilet and therefor no difficulties with the sample collection with ColoAlert.	2	Transcription error, see above – was corrected.
Safety					
Benefit-Harm-Analysis					
Dr. Gerfried Lexer	91	Table 7.1 Table 7.2	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	We repeated all calculations with the updated specificity of 0.917 and updated all results in the report.
Dr. Gerfried Lexer	92	Figure 7	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	

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Dr. Gerfried Lexer	93	Figure 8 Figure 9	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	
Dr. Gerfried Lexer	94	Figure 10	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	
Dr. Gerfried Lexer	94	2227	Adherence rates for triannual stool test are likely to be higher.	2	We performed a sensitivity analysis over the adherence rate. of up to 70%.
Dr. Gerfried Lexer	95	Figure 11 Figure 12	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	We repeated all calculations with the updated specificity of 0.917 and updated all results in the report.
Dr. Gerfried Lexer	96	Figure 13	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	
Dr. Gerfried Lexer	97	Figure 14 Figure 15	Due to wrong specificity values of ColoAlert, the compared values for ColoGuard/ FIT are incorrect.	1	
Dr. Gerfried Lexer	97	Figure 15	Value of ColoGuard Incremental harm-benefit ratio should not change	2	IHBR may change due to changes in comparators. However, we repeated all calculations with the updated specificity of 0.917 for ColoAlert and updated all results in the report.
Discussion					
Dr. Gerfried Lexer	101	2384	The failure rate of ColoAlert is about 8%	2	Information was added after clarification through Email-correspondence.
Appendix					
Dr. Gerfried Lexer	143	Table A19	Specifity of ColoAlert is 91.7% for no findings	1	In the Dollinger paper, we were interpreting Table 5 "no CRC and

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					<p>adenomas" in the way that it is referred to subjects that did not have CRC and also did not have adenomas. Therefore, we applied the specificity of 88.4% in the model. However, besides the pure control subjects, subjects with hyperplastic polyps seem also to be included in "no CRC and adenomas".</p> <p>Note that in our decision model, we did not model hyperplastic polyps separately. Therefore, the data in the Imperiale and Dollinger paper are not exactly comparable, since the Imperiale study does not report hyperplastic polyps separately.</p> <p>However, we agree that the control group, as mentioned in Table 2, is comparable to the people in our health state "healthy".</p> <p>We therefore took an extra step and updated the analysis for the 91.7% specificity referring to the control group that is completely healthy.</p>

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MANUFACTURERS

Comments were received from

Manufacturer		PharmGenomics			
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PharmGenomics	11	235	The ColoAlert sample collection kit includes a paper stool collector which renders the kind of WC irrelevant.	2	Wording adapted.
PharmGenomics	11	236	CTA, M.Sc. Biology or comparable	2	Wording adapted: „... is only suitable for lab personnel with an appropriate academical/technical degree and at least 3 years of experience...”
PharmGenomics	11	249	Treshold value currently: >1 ng / µl	2	The fact that the current threshold is set at 1 ng/µ L is already mentioned on page 84 (D1005). It was added within the technical description.
PharmGenomics	14 19 143	387 Footnote 1 Table 19A	Specificity of ColoAlert for „No findings“ = 91.7 %	1	Complete data are given in table 5.4 (with 91.7 % specificity for no findings).

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PharmGenomics	e.g. 91 91 92 92 93 93 94 95 95 96 97 97	Table 7.1 Table 7.2 Figure 6 Figure 7 Figure 8 Figure 9 Figure 10 Figure 11 Figure 12 Figure 13 Figure 14 Figure 15	Wrong Specificity of ColoAlert leading to incoherent false results when compared to ColoGuard / FIT.	1	We repeated all calculations with the updated specificity of 0.917 and updated all results in the report.
PharmGenomics	16	441	2 laboratories are currently qualified for analyzing ColoAlert	2	Wording adapted.
PharmGenomics	20	490	For ColoAlert, further samples are asked for at no additional cost in case of wrong sample taking or other problems.	3	Wording adapted.
PharmGenomics	41	Table 3.1	Main features swapped for ColoAlert & ColoGuard	2	Corrected.
PharmGenomics	41	907	ColoAlert is produced by PharmGenomics.	3	Corrected.
PharmGenomics	41	914	The stool DNA-test sample collection kit....	3	Corrected.
PharmGenomics	42	934	169.95 €	3	Corrected.
PharmGenomics	42	937	On other pages is written, that ColoGuard is not available in the EU?!	2	Corrected.
PharmGenomics	44	994	...public or corporate health.	2	Wording not changed as it was taken directly from the manufacturer submission file.

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PharmGenomics	44	996	ColoAlert has a CE IVD marking as well.	2	Yes, that is mentioned in B0001.
PharmGenomics	45	1015	...mandatorily by a doctor.	2	Wording was adapted after clarification through Email-correspondence.
PharmGenomics	45	1020	The ColoAlert sample collection kit includes a paper stool collector which renders the kind of WC irrelevant.	2	Wording adapted.
PharmGenomics	45	1046	Recently, a first laboratory of the Limbach group has successfully completed the tech transfer and now offering ColoAlert as well.	2	Wording adapted.
PharmGenomics	70	7058	ColoAlert is not available in Romania.	2	Wording adapted.
PharmGenomics	72	Table 5.1	Column 3 and 4 swapped	2	Corrected.
PharmGenomics	72	1025	CTA, M.Sc. Biology or comparable	3	Wording adapted: „... is only suitable for lab personnel with an appropriate academical/technical degree and at least 3 years of experience...”
PharmGenomics	76	Table 5.3	The ColoAlert sample collection kit includes a paper stool collector which renders the kind of WC irrelevant.	2	Transcription error: answer of the patient belongs to FIT and gFOBT only. Regarding the ColoAlert stool collecting no problems have been reported. Corrected.

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PharmGenomics	86	2068	The ColoAlert sample collection kit includes a paper stool collector which renders the kind of WC irrelevant.	2	Transcription error, see above. Corrected.
PharmGenomics	94	2222	Adherence rate for stool tests with 3 year interval likely to be higher	2	We performed a sensitivity analysis over the adherence rate of up to 70%.
PharmGenomics	97	Figure 15	Value of ColoGuard should not change	2	IHBR may change due to changes in comparators. However, we repeated all calculations with the updated specificity of 0.917 for ColoAlert and updated all results in the report.
PharmGenomics	98	2319	Recently, a first laboratory of the Limbach group has successfully completed the tech transfer and now offering ColoAlert as well.	2	Wording adapted.
PharmGenomics	100	2369	...have not been reported separately in the study and were not available after request through the authors of this assessment.	2	Wording not changed, see also table A16. Request was made on January 30 th 2019 by Email.
PharmGenomics	101	2384	The current failure rate of ColoAlert is about 8 % (data from March 2019)	2	Information was added after clarification through Email-correspondence.

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