EUnetHTA JA3 WP4 - Other technologies, OTCA28
External review by external experts of the 2nd draft assessment on lung cancer screening in risk groups

Comment from *Insert your name, title and affiliation*	Page number *Insert 'general' if your comment relates to the whole document*	Line/ section number	Comment and suggestion for rewording *Please insert each new comment in a new row.*	Character of comment • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	Author's reply
Vicenta Labrador Ministry Of Health (Spain)	General		In some tables in several tables (4.11, 0-5..) the variable "gender" is used instead of "sex" and I think the latter is the correct one. (We tend to refer to sex as being biologically defined, and gender as a social construct that is an internal sense of self, whether an individual sees themselves as a man or a woman, or another gender identity).	3	Thank you very much for this comment. We have made a document wide change.
Vicenta Labrador Ministry Of Health (Spain)	General		More information could be included about the ethical issues of lung cancer screening.		We agree that ethical issues are an important aspect in terms of screening programs. But, this report is a rapid assessment and a consideration of the ethics domain is not affordable in this context. Nevertheless, we have now added a few ethical considerations in the context of information strategies for lung cancer screening (shared decision making) in the discussion section of the report.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	General		Regarding the conclusion on the benefit in mortality, I don´t agree with sentences saying that there is little or no difference in overall mortality based on risk of bias	1	The wording used results from the application of the GRADE standard formulations to describe results. Since the quality of the evidence was rated as high and the meta-analysis showed no difference in effects, one ends up in the table in the top right-hand corner.

Please add extra rows as needed.

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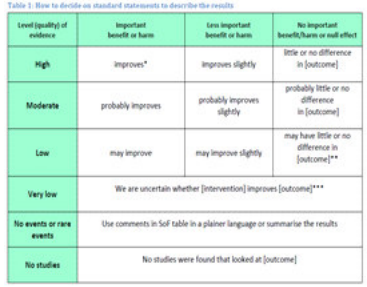
					https://colorectal.cochrane.org/sites/colorectal.cochrane.org/files/public/uploads/describing_results.pdf 
Summary					
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	19	534-536	Definition of high risk of bias based on "it was unclear whether the randomization sequence was adequately generated" seems too vague and subjective, particularly when the final conclusion is that the impact in mortality is low (see prior comment)	1	The high risk of bias is mainly based on the fact of an unclear allocation concealment. We there-fore deleted details on randomisation sequence generation.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	20	587-588	Same comment than previous		See answers above

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Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	23	686-695	Complications in operated patients were reported only 2 studies. The incidence of serious or minor complications were 0.04% and 0.3% respectively. However, the conclusion is that LDCT leads to harm (line 695). I strongly suggest adding a sentence "leads to harm in less than 0.04% of participants	1	In this part of the evaluation we are still at a pure description/documentation of the results. An evaluation/classification of the results, including weighing up the extent of benefit or harm, is carried out as part of the discussion. In this chapter no change is necessary.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	23	699	Overdiagnosis. Please clarify the concept of overdiagnosis. Lung cancer is a very aggressive disease so it is not expected at all that a lung cancer can be an asymptomatic finding for the rest of the life of the patient	1	First, an apology: the original footnote for the definition of overdiagnosis has been lost in table 0-1 and is now retained in the summary: „Defined as number of diagnoses (true positive find-ings), which would not have become clinically relevant during a person's lifetime." It is correct to assume that very aggressive cancer is less likely to lead to overdiagnosis. In prin-ciple, however, overdiagnosis is inevitable in any screening, including screening for lung cancer. As pointed out by Welch&Black, "even a rapidly growing cancer may still represent overdiagnosis if detected when it is very small or in a patient with limited life expectancy" (https://academic.oup.com/jnci/article/102/9/605/894608).

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					In heavy smokers, the remaining life span is reduced. This means that a non-negligible proportion of people die from non-lung cancer diseases (e.g. COPD, CHD, stroke, etc.) rather than develop-ing symptoms of lung cancer. How overdiagnosis can be measured was perfectly explained in this article: https://doi.org/10.1136/bmj.g7773. Please also see our very nicely animated video on overdiag-nosis (https://www.informedhealth.org/what-is-overdiagnosis.3058.en.html). Details for the determination of overdiagnosis are documented in Section 3.1.3.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	23	699	I cannot understand why the overdiagnosis rate is considered too heterogeneous for having an overall estimation while the sentence about harm was so categorical	1	There is probably a misunderstanding here. Neither in the previous case (keyword harm) nor for the endpoint overdiagnosis did the data structure allow a meta-analytical summary of the data. To describe it in your words: Similarly, a categorical statement is made for both endpoints at the end, taking into account the underlying data.
Pilar Garrido,	30	Table	Overdiagnosis comment: Please justify this sentence "participants which would not have caused any symptoms for the rest of the	1	First, an apology: the original footnote for the definition of overdiagnosis has been lost

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Hospital Universitario Ramón y Cajal, Spain			person´s life". I think this is not true in lung cancer. Please add the references to justify this sentence		in table 0-1 and is now retained in the summary: „Defined as number of diagnoses (true positive findings), which would not have become clinically relevant during a person's lifetime." It is correct to assume that very aggressive cancer is less likely to lead to overdiagnosis. In principle, however, overdiagnosis is inevitable in any screening, in-cluding screening for lung cancer. As pointed out by Welch&Black, "even a rapidly growing cancer may still represent overdiagnosis if detected when it is very small or in a patient with limited life expectancy" (https://academic.oup.com/jnci/article/102/9/605/894608). In heavy smokers, the remaining life span is reduced. This means that a non-negligible proportion of people die from non-lung cancer diseases (e.g. COPD, CHD, stroke, etc.) rather than developing symptoms of lung cancer. How overdiagnosis can be measured was perfectly explained in this article: https://doi.org/10.1136/bmj.g7773. Please also see our very nicely animated video on

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					overdiagnosis (https://www.informedhealth.org/what-is-overdiagnosis.3058.en.html). Details for the determination of overdiagnosis are documented in Section 3.1.3. An explanation with reference at this point is not necessary.
Giuseppe Gorini, ISPRO, Florence, IT	42	897-901	"It is conceivable that, due to competing causes of death, in particular other tobacco-related diseases such as other cancers or cardiovascular diseases, some of the screening participants saved from lung cancer death may die at a comparable time and thus the life span of these persons may not be significantly extended." I agree; however, I suggest to add one sentence at the end of these lines regarding the important contribution on this issue that smoking cessation could add: "If in the lung cancer screening pathway is embedded smoking cessation, the probability of dying from competing causes of death due to other tobacco-related diseases would gradually reduce since quitting smoking. This could significantly increase the life span of participants. Thus, incorporating smoking cessation into the lung cancer screening pathway could determine a significant contribution to reduce overall mortality and increase benefits of lung cancer screening"	2	Many thanks for these plausible considerations. However, as the available data do not reflect this statement, ultimately because this is not reflected in the underlying question, the proposal cannot be accepted as it stands.
Description and technical characteristics of the technology					
Health problem and current use					

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Clinical effectiveness					
Vicenta Labrador Ministry Of Health (Spain)	60	1461-1464	About the paragraph: "Recommendations regarding individuals eligible for screening adopted by major health organizations have mainly followed the NLST criteria regarding age, smoking history and quit time criteria as follow: current and former smokers age 55–80 years, smoking history of at least 30 pack years, and a minimum quit time of 15 years for former smokers, but some have also included individuals with lower or higher lung cancer risks". I think you should say: "a maximum quite time of 15 years…" according to the rest of the document.	2	Thank you for this advise. Corrected.
Giuseppe Gorini, ISPRO, Florence, IT	143	2560-63	"It is conceivable that, due to competing causes of death, in particular other tobacco-related diseases such as other cancers or cardiovascular diseases, some of the screening participants saved from lung cancer death may die at a comparable time and thus the life span of these persons may not be significantly extended." I agree; however, I suggest to add one sentence at the end of these lines regarding the important contribution on this issue that smoking cessation could add: "If in the lung cancer screening pathway is embedded smoking cessation, the probability of dying from competing causes of death due to other tobacco-related diseases would gradually reduce since quitting smoking. This could significantly increase the life span of participants. Thus, incorporating smoking cessation into the lung cancer screening pathway could determine a significant	2	Many thanks for these plausible considerations. However, as the available data do not reflect this statement, ultimately because this is not reflected in the underlying question, the proposal cannot be accepted as it stands.

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			contribution to reduce overall mortality and increase benefits of lung cancer screening"		
Giulia Picozzi, MD, ISPRO Firenze	144	2618	In the NLST the number of subjects with an asbestos work experience is reported as 4.6% in screening arm and 4,8% in x-ray arm. There are some screening studies conducted in asbesto workers, included in a metanalysis by Ollier et al. 2014 in which the lung cancer rate at baseline CT ranges between 0,4 to 4,3%. Remy-jardin (2004) in a study in asbesto workers stated that the low dose ct is an accurate technique for the detection of asbesto's related diseases.	2	Thank you for these hints. We now included the information about the percentage of subjects with an asbestos work experience in the discussion section on page 213. In the discussion section, results from a recent review by Maisonneuve et al 2019 on lung cancer screening in asbestos workers is already described. This review includes all studies, that are also included in the meta-analysis by Ollier et al 2014.Therefore, we would not additionally mention the meta-analysis by Ollier et al.2014.
Safety					
Appendix					

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