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

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Giulia Picozzi ISPRO Firenze	general		I would suggest to investigate, as a secondary objective, whether there are incidental findings that can be detected in LDCT and which (i.e. coronary artery calcifications) can play a role in the all-causes mortality reduction. It would lead to a structured advice to be systematically embedded in the LDCT report.	1	We agree this is an interesting aspect in the context of all-cause mortality. Nevertheless, this is out of the scope of this rapid assessment of lung cancer screening.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Lung cancer screening has demonstrated a clear benefit in survival, but the implementation is still a huge problem in many countries. In my opinion the challenges related to the implementation should be also added to this discussion.		The benefit-harm ratio of lung cancer screening is not clear in our view. In 2013, a Cochrane review has shown no advantage of screening for lung cancer compared to no screening [Manser et al 2013; CD001991], and also current systematic reviews report discrepant results Snowsill et al 2018 (PMID 30518460)/ Huang et al 2019 (PMID 31296196)]. Therefore, the primary aim of this rapid assessment report is to investigate the benefit/harm of lung cancer screening using the current evidence from RCTs. If this assessment results in a positive

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					benefit/harm balance for lung cancer screening, the issue of implementation can be discussed. In addition, RQ4 already focusses on the question of the best approach to optimize an informed choice for participation, which is, according to the ESR/ERS statement paper on lung cancer screening, an important challenge regarding the implementation of lung cancer screening.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Project Stakeholders: Is the list of stakeholders complete? The only stakeholder named is patients association TBD. Medical societies can be added too and maybe insurances companies to understand why the implementation is so complicated		The primary aim of this rapid report is the assessment of effectiveness and safety of lung cancer screening, not organizational aspects. Therefore, the involvement of medical societies and insurance companies is not planed.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Do the authors choose the appropriate target population? Smoking status is too vague for me. According to NELSON study criteria: who have smoked 15 cigarettes or more per day for more than 25 years, or ten cigarettes or more for more than 30 years and were still smoking, or had stopped smoking less than 10 years ago		A very detailed definition of the inclusion criteria in terms of population would possibly lead to the exclusion of some relevant RCTs. Therefore, a generic definition of the population was chosen.

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			NLST: had a history of cigarette smoking of at least 30 packyears, and, if former smokers, had quit within the previous 15 years		We want to work on this in the context of subgroup analyses, provided the data make this seem reasonable.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Is the rationale for the choice of outcomes comprehensible and consistent with clinical practice? Q1. I don´t see the point to review again the benefit/harm of screening for lung cancer using LDCT compared to no screening or screening with chest x-ray in individuals at elevated risk of lung cancer. Two robust clinical trials, well designed, already asked this question. However, despite a magnitude of benefit like mammography, implementation is really challenging. I would suggest focusing on that Q2. What is the benefit/harm of screening for lung cancer using biomarkers in addition to LDCT?. This question cannot be answered based on the results of clinical trials. Adding it in this document, we take the risk to suggest waiting until the availability of results instead of dedicating effort to implement the lung cancer screening Q3. What is the benefit/harm of annual systematic screening for lung cancer as recommended in current guidelines compared to systematic screening with intervals other than one year? Once again, without scientific support we cannot discuss this question. In fact, by including this question, perhaps people could consider that different intervals have been prospectively validated and this is not true		Q1: The benefit-harm ratio of lung cancer screening is not clear in our view. In 2013, a Cochrane review has shown no advantage of screening for lung cancer compared to no screening [Manser et al 2013; CD001991], and also current systematic reviews report discrepant results [Snowsill et al 2018 (PMID 30518460)/ Huang et al 2019 (PMID 31296196)]. Therefore, the assessment of benefit/harm of lung cancer screening using the current evidence from RCTs is appropriate. Q2: Biomarkers are currently investigated as potentially useful adjuncts to LDCT for lung cancer screening. Therefore, the research question regarding the additional

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					benefit of biomarkers is important in the context of this rapid assessment. Nevertheless, only RCTs are appropriate to answer this question. If no such RCTs exist, this might be the answer to this question. However, the additional use of biomarkers is only one screening strategy and irrespective of the question of the implementation of lung cancer screening. Q3: The assessment of different screening strategies is an important aspect in this context and will have to be evaluated on the basis of the identified evidence.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Are there any important outcomes that are neglected in the literature? I would suggest adding the size threshold and volume-doubling time for lung nodules detected in low-dose CT screening. These aspects are quite relevant in terms of risk harm/benefit and can be a matter of debate.		These data will be presented as part of the characterization of the included studies.

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Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	general	general	Are there any important ethical, organisational, patient and social or legal aspects the authors do not consider? In my opinion, the role of medical societies should be considered. There are European position papers in which challenges and opportunities are analysed being, in my opinion, quite relevant for this particular document		We are aware of these position papers and will discuss them in the context of the TEC/CUR domains.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	8	71	Screening for lung cancer ~~might~~ help to detect lung cancer in earlier stages. I would suggest removing might because at least two clinical trials have already demonstrated that (NELSON, NLST)	1	We prefer to take into account all high-quality evidence that deals with this question.
Pilar Garrido, Hospital Universitario Ramón y Cajal, Spain	8	82-84	The research question number 2 is very interesting – the value of biomarkers for refining screening- but unfortunately there are not clinical trials supporting that yet. Due to that I am not sure about dedicating time and effort to review that when the problem we face is the lack of implementation in Europe based on 2 positive studies.	1	Biomarkers are currently investigated as potentially useful adjuncts to LDCT for lung cancer screening. Therefore the research question regarding the additional benefit of biomarkers is important in the context of this rapid assessment. Nevertheless, only RCTs are appropriate to answer this questions. If no such RCTs exist, this might be the answer to this question.
Pilar Garrido, Hospital Universitario	8	85-87	Research question number 3 is related to implementing different intervals for systematic screening than the ones including in the clinical trials. I strongly believe that the recommendations must be based on	1	The assessment of different screening strategies is an important aspect in this context. We will evaluate this on the basis

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Ramón y Cajal, Spain			strong evidence, so I don´t see the value of exploring literature for alternative intervals		of the studies to be included for research questions 1 and 2.
Giuseppe Gorini, ISPRO, Florence, IT	8	89	I think that one research question is lacking. I would put it as the number 4, before the research question on informing individuals: *"Which is the best strategy to embed smoking cessation into lung cancer screening pathways?"* Rationale: Inclusion for any lung screening program requires a history of smoking, and many undergoing screening (around 50%) are currently smoking. Screened patients are not only at risk for developing lung cancer, but also carry the risk of developing other smoking related diseases, and cessation at any point is beneficial. Counseling and pharmacotherapy are evidence-based strategies to help people quit smoking. Smoking cessation broadens the impact of lung cancer screening program beyond lung cancer diagnosis to reduce risk from many other diseases, and can positively impact many more patients than those with lung cancer. However, as lung cancer screening is an emerging field, the integration of smoking cessation in screening programs is not uniformly done, and there is no standardized approach. There is a gap in knowledge about how best to design systems to maximize smoking cessation in the context of lung cancer screening. In the U.S., 8 clinical trials address this gap and form the SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration. In Canada, the Cancer Care Ontario's Lung Cancer	1	I agree that smoking cessation intervention are important in the context of lung cancer and other diseases. Nevertheless, the assessment of smoking cessation strategies is a research question, which differs from this rapid assessment and cannot be investigated within the limited timeframe of this report.

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			Screening Pilot for People at High Risk, smoking cessation is embedded in the screening pathway. Objective of this research question: The goals of this research question could be to discuss the rationale for integrating smoking cessation into lung cancer screening, to review what types of resources may be effective, and to review different strategies of integration. I attached a brief and non-complete list of articles on this issue.		
Giulia Picozzi ISPRO Firenze	General, Pag 8	Pag.8 Line 85	*Given the wide heterogeneity of the screening trials and studies to date, and the actual lack of specific guidelines, some questions are still open and deserve to be analyzed.* *I will try to list the main topics so that could be integrated in the project, even adding research questions, as you feel it appropriate.* **Research question 3** **Issues that need to be investigated are:** **1. The screening regimen** - the duration of the screening interval, - the number of rounds, - the definition of an age limit (the problem of the screening in elderly people has been debated in many scientific community). **2. Technical aspects regarding radiological protocol such as**	1	These data will be presented as part of the characterization of the included studies.

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			- single or double readings of LDCT examinations, - the possible role of a computer-aided detection (This issue has a big impact on cost-effectiveness as reported in some meta-analysis I will mention below). **3. Definitions of positive test** - lung indeterminate nodules classification criteria (radiologic appearance –solid, pure ground glass opacity, part-solid nodules; dimensional cut-off). - Use of dimensional cut-off values, for baseline nodules and incident nodules. It has to be discussed since the dimensional threshold chosen affects the false positive rate and the recall rate (*Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecifi ed analysis of data from the NELSON trial of low-dose CT screening Nanda Horeweg*, Joost van Rosmalen*, Marjolein A Heuvelmans, Carlijn M van der Aalst, Rozemarijn Vliegenthart, Ernst Th Scholten, Kevin ten Haaf, Kristiaan Nackaerts, Jan-Willem J Lammers, Carla Weenink, Harry J Groen, Peter van Ooijen, Pim A de Jong, Geertruida H de Bock, Willem Mali, Harry J de Koning*, Matthijs Oudkerk*The Lancet Oncology 2014; R. Hip, et al. CT screening for lung cancer: alternative definitions of positive test, Radiology 2014).* 1. **The use of software for nodule volume measurements and for nodule growth assessment**.		

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			The European Position Statement recommends the use of lung nodules volume instead of manual diameter measurements for nodule classification and test definitions. (*European position statement on lung cancer screening* *Matthijs Oudkerk, Anand Devaraj, Rozemarijn Vliegenthart, Thomas Henzler, Helmut Prosch, Claus P Heussel, Gorka Bastarrika, Nicola Sverzellati, Mario Mascalchi, Stefan Delorme, David R Baldwin, Matthew E Callister, Nikolaus Becker, Marjolein A Heuvelmans, Witold Rzyman, Maurizio V Infante, Ugo Pastorino, Jesper H Pedersen, Eugenio Paci, Stephen W Duffy, Harry de Koning, John K Field Lancet Oncology 2017*). In some meta-analysis the use of volumetric software seems to reduce the false positive rates and consequently improves the cost-effectiveness of the screening practice (*Seigneurin et al. 2014; McMahon, 2011, Black, 2014, Kovalchik, 2013).* It has been recently shown that the appropriate nodule size thresholds for indeterminate nodules in screening depend on the type of volumetry software used since there is a wide difference in performances among different softwares. It consequently affects the recall rates and highlites the importance of benchmarking of volumetry packages (E. Soo, A.J Edey, et al EJR 2019). When software are used in that field there is the need to define and standardize the technical specific requirements needed to be used (correct segmentation rate, in vivo validation, ecc...).		

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			- 5. Lung nodule management. It is still a matter of debate to establish the correct time to follow-up in nodule management, namely in follow-up, and the dimensional threshold for definition of nodule growth. The aim is not to miss malignant lesions and at the same time to reduce the number of unnecessary invasive procedures. Volume doubling time values seem to play an important role and have been proposed in some studies to determinate the subsequent nodule management. (NELSON management protocol *Management of Lung Nodules Detected by Volume CT Scanning* Rob J. van Klaveren, NEJM 2009, *European position statement on lung cancer screening Matthijs Oudkerk, Anand Devaraj, Rozemarijn Vliegenthart, Thomas Henzler, Helmut Prosch, Claus P Heussel, Gorka Bastarrika, Nicola Sverzellati, Mario Mascalchi, Stefan Delorme, David R Baldwin, Matthew E Callister, Nikolaus Becker, Marjolein A Heuvelmans, Witold Rzyman, Maurizio V Infante, Ugo Pastorino, Jesper H Pedersen, Eugenio Paci, Stephen W Duffy, Harry de Koning, John K Field Lancet Oncology 2017*). The "correct" or appropriate nodule management is still to be determined and it is different for different types of nodule pattern (*CT screening for lung cancer: comparison of three baseline screening protocols European Radiology 2019 Claudia I. Henschke1,2,3 & Rowena Yip1 & Teng Ma1,4 & Samuel M. Aguayo2 & Javier Zulueta5 & David F. Yankelevitz1 & Writing Committee for the I-ELCAP Investigators).* A specific research should be focused on this topic. **6. use of risk calculators**		

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			Such as Brock malignancy risk calculator (*McWilliams NEMJ 2013)* They are mentioned and recommended by some association (Lung-RADS Version 1.1 released 2019, European Position Paper, British Thoracic Society M. Callister JTO Vol 12 no 11S2 nov 2017). **7.** I would suggest to investigate, whether there are **incidental findings** that can be detected in LDCT and which (i.e. coronary artery calcifications) can play a role in the all-causes mortality reduction. It would lead to a structured advice to be systematically embedded in the LDCT report.		
Giulia Picozzi ISPRO Firenze	Pag.8	82	**Research question 2** Biomarkers should be evaluated also as a support in decision making in an integrated screening approach combining Individual risk assessment, biomarkers and CT Scan (*Multimodal lung cancer screening using the Italung biomarker panel and low dose computer tomography. Results of the Italung biomarker study. Carozzi FM, et al. nt J Cancer 2017).* **Research question 5 (to be added)** The use of individual risk model assessment • Risk calculations use *all* lung cancer risk factors *efficiently* to more precisely delineate a person's benefit from screening		For RQ2 we will include all RCTs using any screening approach with biomarkers in addition to LDCT. The use of different risk models can be assessed within RQ3 if possible.

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			• Prediction model performs better than NLST-like criteria for selection *(Boiselle, JAMA 2013; Bach, Ann Int Med, 2013; Kovalchik, … Katki, N Engl J Med, 2013; Tammenagi, N Engl J Med, 2013)*		
Giulia Picozzi ISPRO Firenze			**Research question 6** **What is the add on effect of CT screening as compared to an anti-smoking policy** (to be discussed with epidemiologysts)		This is also an interesting question, but not feasible within the narrow timeframe of a rapid assessment.
Vicenta Labrador Ministry Of Health (Spain)	11	Lines 6, 7	As the search has been restricted to articles published in German and English, there may be bias in your selection. They should consider articles published in other languages such as Spanish, Italian or French. This choice of languages may be appropriate for a report in a national context it may not be so in the European context.	1	Publication language in German is due to the fortunate fact that the basis of this investigation is an ongoing evaluation of lung cancer screening in Germany. Since the questions are of multinational importance and since one recent systematic review on lung cancer screening, which used no language restriction [Huang et al 2019 (PMID 31296196)] identified no RCT published in languages other than English, we expect publications in English.
Vicenta Labrador	12	Line 13	Life expectancy could be added as an outcome	2	Life expectancy is usually not an endpoint in the studies. However, mortality is patient relevant and

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Ministry Of Health (Spain)					regularly taken into account in the studies
Vicenta Labrador Ministry Of Health (Spain)	13	Line 3	According to ICD-10 Version:2019 the code for "Malignant neoplasm of bronchus and lung" is C34 not C35.	1	Corrected.
Vicenta Labrador Ministry Of Health (Spain)	13	Last line	Biomarkers false negative rate, negative predictive value and positive predictive value could be added as outcomes.	2	Test-characteristics for biomarkers will be discussed in the TEC domain
Giulia Picozzi ISPRO Firenze	13	PICO Table	Suggestion which outcomes are critical, which are important and which are not important: All are critical and important		With regard to the GRADE assessment to be carried out, mortality will be categorized as "critical" and the remaining endpoints as "important".
Giuseppe Gorini, ISPRO, Florence, IT	13	PICO Table	Suggestion which outcomes are critical, which are important and which are not important: <u>Critical:</u> Mortality (overall mortality, lung cancer mortality); Harms resulting from screening itself or from subsequent diagnostic interventions, consequences resulting from false screening results, and harms from unclear findings. (Serious) adverse events <u>Important:</u>		With regard to the GRADE assessment to be carried out, mortality will be categorized as "critical" and the remaining endpoints as "important".

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			Smoking cessation rates among smokers within lung cancer screening pathways Morbidity (stage of lung cancer) Health-related quality of life Screening participation rate Participant satisfaction Participant empowerment Increased knowledge Informed decision-making		
Giuseppe Gorini, ISPRO, Florence, IT	21, 22		important ethical, organisational, patient and social or legal aspects: I think that offering smoking cessation supports within lung cancer screening pathways to current smokers is an important ethical aspect to be considered. The issue can be described with this question: "Why do not offer smoking cessation in the lung cancer screening pathway? Is it ethical not to advise to quit smokers who will undergo to LDCT? Is it enough to inform current smokers in the target group about a lung cancer screening program, without speaking about smoking cessation?		This will be discussed in the TEC/CUR domains and within PICO 4.

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Giuseppe Gorini, ISPRO, Florence, IT provided the following:
List of some articles on integrating smoking cessation into lung cancer screening (not complete; only to show the importance of the outcome “smoking cessation”):

- Joseph AM, Rothman AJ, Almirall D, et al. Lung Cancer Screening and Smoking Cessation Clinical Trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. Am J Respir Crit Care Med 2018;197(2):172-182. doi:10.1164/rccm.201705-0909CI. PMID: 28977754; PMCID: PMC5768904.
- Steliga MA, Yang P. Integration of smoking cessation and lung cancerscreening. Transl Lung Cancer Res 2019;8(Suppl 1):S88-S94. doi:10.21037/tlcr.2019.04.02. PMID: 31211109; PMCID: PMC6546623.
- Pistelli F, Aquilini F, Falaschi F, et al. Smoking cessation in the ITALUNG lung cancer screening: what does"teachable moment" mean? Nicotine Tob Res. 2019 Aug 23:ntz148. doi:10.1093/ntr/ntz148. Epub ahead of print. PMID: 31504798.
- Graham AL, Burke MV, Jacobs MA, et al. Anintegrated digital/clinical approach to smoking cessation in lung cancer screening: study protocol for a randomized controlled trial. Trials 2017;18(1):568. doi: 10.1186/s13063-017-2312-x. PMID: 29179734; PMCID: PMC5704639.
- Tremblay A, Taghizadeh N, Huang J, et al. A Randomized Controlled Study of Integrated Smoking Cessation in a Lung Cancer Screening Program. J Thorac Oncol 2019;14(9):1528-1537. doi:10.1016/j.jtho.2019.04.024. Epub 2019 May 8. PMID: 31077790.
- Goffin JR, Flanagan WM, Miller AB, et al. Biennial lung cancer screening in Canada with smoking cessation-outcomes and cost-effectiveness. Lung Cancer 2016 Nov;101:98-103. doi:10.1016/j.lungcan.2016.09.013. Epub 2016 Sep 28. PMID: 27794416.
- Fucito LM, Czabafy S, Hendricks PS, et al. Pairing smoking-cessation services with lung cancer screening: A clinical guideline from the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco. Cancer 2016;122(8):1150-9. doi: 10.1002/cncr.29926. Epub 2016 Feb 24. PMID: 26916412; PMCID: PMC4828323.
- Ostroff JS, Copeland A, Borderud SP, Li Y, Shelley DR, Henschke CI. Readiness of Lung Cancer Screening Sites to Deliver Smoking Cessation Treatment: Current Practices, Organizational Priority, and Perceived Barriers. Nicotine Tob Res 2016;18(5):1067-75. doi: 10.1093/ntr/ntv177. Epub 2015 Sep 7. PMID: 26346948; PMCID: PMC5903595.
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[b] “minor”: the comment does not necessarily have to be answered in a detailed manner
[c] “linguistic“: grammar, wording, spelling or comprehensibility of the document

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