EarlyCDT Lung for assessing risk of lung cancer in solid lung nodules

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Oncimmune Limited	1	12	Plain English Summary	Oncimmune agrees with NICE that EarlyCDT Lung has the potential to improve the early detection of lung cancer by assisting in the determination of malignancy of nodules within the indeterminate range of 10-70% after PET CT and Herder assessment and this should be the focus moving forward. The evaluation report does, however, exclude well-powered and relevant studies but included studies that are underpowered or fall within the exclusion criteria. The sensitivity of the EarlyCDT Lung test is independent from the risk of malignancy in a population and is therefore, not a function of risk. The difference between a screening and a nodule population is purely one of risk of malignancy in that population, which means that data from both screening and nodule populations are valid for the assessment of the sensitivity of EarlyCDT Lung. There is strong evidence that shows a sensitivity of c35% across many trials which unfortunately have not been included in this evaluation. Of the five trials considered in the report, it is Oncimmune's request that four trials should be dismissed; two of the trials (US - Santa Clara Valley (Lin et al 2016) and Hong Kong- Pilot (Lau et al 2017)) were clearly too small so cannot provide a statistically relevant outcome. Additionally, according to the authors' exclusion criteria the EarlyCDT LCS -National Jewish Hospital (Jett et al 2017) study should also be omitted as it was mainly a screening study and the German RCT: Heidelberg (Maldonado et al 2021) study should not be included as it was based on retrospective samples rather than prospective. Either these studies need to be excluded or other studies excluded under these criteria need to be included. That leaves the HIPAA – Commercial Nodule Audit (Massion et al 2017) study as the only relevant study in the evaluation, which shows a sensitivity of 37.8% which is clearly in line with our evidence showing sensitivity of 35%.	See later responses to comment 2 The claim that sensitivity of the EarlyCDT Lung test is independent from the risk of malignancy requires clear evidence to support it. Test sensitivity, in general, is independent of disease prevalence, but that is not the same as being independent of risk, still less independence from nodule status. Such a claim requires compelling evidence to support it. The EAG report already states that the evidence is not compelling (see report section 3.1.7.3) See response to comment 2. The EAG notes that its concern is as much with the applicability and extent of the evidence for EarlyCDT Lung as the exact diagnostic accuracy estimate. A single study (of 166 patients) is insufficient to robustly demonstrate the clinical value of a test,

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					particularly given the EAG's judgements on risk of bias and applicability concerns for the HIPAA study (see report section 3.1.4)
				Oncimmune welcomes the assistance of the NICE evaluation process in encouraging an NHS driven IPN trial programme.	No response needed
Oncimmune Limited	2	37-46 + 48-63	Study selection – inclusion/ exclusion and Diagnostic accuracy and clinical effective-ness results	The sensitivity of a test is not a function of risk of disease in the population and therefore, to ignore the screening publications and then conclude on a sensitivity of 20.2% from nodule publications, many of which are severely underpowered, is unreasonable. In calculating sensitivity of EarlyCDT Lung, performance in screening populations is acceptable and this data should be included in this part of the assessment.	This statement is incorrect. Sensitivity is independent of disease prevalence in the study population, not of disease risk. The screening publications were case control studies of people without confirmed nodules. These have high risk of bias (Section 3.1.7.3 of the EAG report). There is no a priori reason to believe that diagnostic accuracy will be independent of nodule status.
				1. Overall nodule evidence **Key point:** There is no reason to expect sensitivity to differ significantly between screening and nodule scenarios as the underlying biology is similar. Diagnostic performance can therefore be based on screening studies as well.	This claim is made without robust evidence. The evidence that exists suggests the opposite of what has been claimed, as there is evidence of inferior diagnostic accuracy in people with nodules (see report Table 9)
				Justification: The evaluation report discounts several studies because they are in a screening population and do not include nodule information. Whilst this is acceptable for assessing clinical outcomes of EarlyCDT Lung use in nodule patients, it is erroneous to exclude this information when assessing the sensitivity of the test. The two populations in which EarlyCDT Lung has utility are those with IPNs and those who are asymptomatic but at high risk of lung cancer. These two populations differ in their risk and prevalence of lung cancer, but not in their aetiology. No-one has yet proposed a mechanism whereby the circulating tumour antigens should be any different between these two groups.	The EAG notes that the scope of the project was diagnosis of lung cancer in people with pulmonary nodules. We consider that focusing analysis on studies of patients with nodules is both consistent and appropriate. There is no robust evidence that test accuracy is independent of nodule status or risk of malignancy and, therefore, no support

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				The sensitivity of a test is not a function of risk of disease in the population and therefore, the screening publications, which have much higher statistical power, should not be ignored in the assessment of sensitivity. Oncimmune agrees that we have limited published data on EarlyCDT Lung in a nodule context but emphasise that we currently know of no reason to expect sensitivity to differ significantly in nodules as test positivity depends solely on cancer presence whether pre- or post-radiography.	for evidence outside of this population to be considered generalisable. See response above
				2**. Exclusion of studies** **Key point:** Out of the five studies the authors have included, the "US" and "Hong Kong" studies are far too small to be included. Also, according to the exclusion criteria the "EarlyCDT LCS" study should also be omitted as it was mainly a screening study and the "German RCT" study should not be included as it was based on retrospective samples rather than prospective. Either these studies need to be excluded or other excluded studies need to be included. **Justification:** The five cohorts in the final analysis (NICE Report Table 5) were: 1) HIPAA – Commercial Nodule Audit (Massion et al 2017) 2) EarlyCDT LCS - National Jewish Hospital (Jett et al 2017) 3) US - Santa Clara Valley (Lin et al 2016) 4) Hong Kong - Pilot (Lau et al 2017) 5) German RCT: Heidelberg (Maldonado et al 2021) Oncimmune makes some comments on four of these studies: **EarlyCDT LCS: National Jewish (Jett et al 2017)** This is an interim report of a study carried out at the National Jewish Hospital in Denver, Colorado. A final publication is under preparation by the study's Principal Investigators and is likely to appear in print early in the New Year. The final recruitment was 1343 patients. Even so, there were only 13 cancers leading to a wide 95% confidence interval for sensitivity: 23% (5% to 54%).	Study size was not grounds for exclusion in this systematic review. The EAG notes its concerns with the retrospective nature of the German trial in the report (Section 3.1.4) The EAG report notes that this study was not fully published, but that is not grounds for exclusion. Small sample size was not grounds for exclusion. The uncertainty and wide confidence intervals are accounted for in meta-analyses.

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				US (Lin et al): Santa Clara Valley (Lin et al 2016) Only 31 subjects were recruited in three years. The baseline risk was estimated as 23% but so far only 4/31 (13%) have developed lung cancer. The analysis assumes that subjects without diagnosed lung cancer are definitively benign. The sensitivity estimate is only based on a proportion of 0/4 with a confidence interval of 0% (0% to 60%). This study is therefore far too small to be of value in a systematic review.	Small sample size was not grounds for exclusion
				Hong Kong (Lau et al 2017) The Hong Kong publication is only an IASLC poster of a pilot study so has little status. The pilot study involved 30 subjects of whom only five developed lung cancer. The estimate of sensitivity is only based on a proportion of 1/5 with a confidence interval 20% (1% to 72%). This study has very limited value in a systematic review.	Small sample size was not grounds for exclusion.
				German RCT: Heidelberg (Maldonado et al 2021) This was a retrospective study using samples from the LUSI (German Lung Cancer Screening Intervention) trial. The sample size for many parts of the analysis (particularly sub-groups) was very small. As this is only a pilot study, a larger cohort is required.There is evidence from the high specificity (97%) quoted in the paper that the overall signal from the EarlyCDT Lung assay was lower than normal in this study. This can happen with pilot studies in new populations, and it also leads to low estimates of sensitivity. Hence a diagnostic performance metric relatively insensitive to signal level incorporating both specificity and sensitivity, such as the odds ratio (OR), is desirable. For example, the paper reports an analysis of only High positive results and finds an OR of 4.4 for cases versus benigns, similar to that found in the Massion et al paper (2017). This suggests that whilst the study was still too small to be conclusive, there was evidence of the effectiveness of EarlyCDT Lung.	Small sample size was not grounds for exclusion. The 97% specificity was based on the thresholds created by Healey et al (2017) designed to have that high specificity. The EAG does not understand the claim about signal made here. The EAG analysed diagnostic odds ratio, which is such a metric. Complete results were not presented in the report. We note here that LUSI had a DOR of 3.23 and Massion a DOR of 3.13, with a pooled DOR over all studies of 3.32 (95% CI: 1.75 to 6.31) (report section 3.1.5)
				3. Additional relevant data: validation studies **Key point:** For a diagnostic medical device such as EarlyCDT Lung, performance evidence must be collected from all phases of the development process, not just published prospective studies.	There is a plethora of literature describing why case-control studies are at high risk of bias when assessing diagnostic accuracy.

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				Justification: The evaluation report states, "Many references were excluded because the study populations consisted of patients with already diagnosed lung cancer (i.e. they studied validation cohorts of patients who would not receive the EarlyCDT Lung test in practice)". Hence the evaluation report (Tables 32 and 33) lists many publications excluded as they failed one or more selection criteria. All our validation studies were excluded. For diagnostic marker devices such as EarlyCDT Lung, case-control studies, using bio-banked samples and based on screening of high-risk subjects, are an essential tool during development of the product. Note the development phases for a diagnostic device (Pepe et al 2001): 1) Preclinical exploratory, 2) Clinical assay and validation (case-control), 3) Retrospective longitudinal, 4) Prospective screening and 5) Cancer control. Collecting nodule datasets is a much harder proposition because of their relative scarcity. Hence until large "Phase 5" prospective studies have been carried out, these case-control studies form the backbone of the clinical evidence and should not be ignored. A final crucial point is that diagnostic cut-off values and respective performance claim must be established before conducting prospective studies, even small ones. There is no choice but to use early phase data (see definitions above) to establish this. Adding in earlier phase data would lead to sensitivity estimates around 35% rather than the 20% or so currently in the evaluation report (see next section). Reference: Pepe MS, Etzioni R, Feng Z et al (2001) Phases of Biomarker Development for Early Detection of Cancer. Jnl Nat Cancer Inst 93(14). **4. Summary of EarlyCDT Lung performance** **Key point:** As emphasised above, to support a diagnostic device performance claim requires more data than just studies passing strict systematic review exclusion criteria.	This is summarised in Section 3.1.7.3 of the EAG report. The EAG does not dispute that early phase studies are important for establishing cut-offs, etc. However, these cut-offs, their diagnostic accuracy and clinical impact must be validated in the population of interest (people with nodules). The EAG disputes this claim. The purpose of a systematic review is to identify and synthesise the evidence that meet inclusion

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				Here we share with you a summary of the data we are submitting as part of our Performance Evaluation Report in accordance with the IVD Regulation (EU) 2017/746 in support of our clinical performance claim of approximately 90% specificity and 35% sensitivity. **Justification:** Oncimmune is about to make (September 2021) a submission for compliance assessment against the IVD Regulation (EU) 2017/746 (IVDR) where the Company will present evidence supporting our clinical performance claim. The studies to be included, based on a set of inclusion criteria, are in five groups (A to E) according to development stage and application. Groups A to C correspond approximately to Pepe's Phase 2 (see section 3 above), whilst groups D and E are a mixture of Phase 2 and 4. Some of the studies have been named to show correspondence to the evaluation report and the following text. **Summary of studies included in the IVDR submission.** **Please note, the table summarising the studies included with these comments is at the end of this document.**	criteria defined *a priori*; otherwise, the review would not be systematic. The EAG cannot comment at this stage on submissions or data that were not available at the time of the report.
				References (Validation studies): 1. Boyle, P. et al. (2011) Clinical validation of an autoantibody test for lung cancer, Annals of Oncology, 22(2), 383–389. 2. Lam, S. *et al.* **(2011)** EarlyCDT-Lung: An immunobiomarker test as an aid to early detection of lung cancer, *Cancer Prevention Research*, **4**(7), 1126–1134. 3. Chapman, C. J. *et al.* **(2012)** EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays., *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*, **33**(5), 1319–1326.	The EAG identified and reviewed all the studies listed here. See in particular report section 3.1.7
				Group A are early development demonstrating proof of concept. The claim will be made on the Group B and C studies giving an average specificity and sensitivity of about 90% and 35% respectively, and an average odds ratio of over 5.0, and the Group D and E studies are shown to be consistent with this claim, considering confidence intervals: **Screening:** Specificity: 90.7% and Sensitivity 31.6% (16.1% to 47.0%) **Nodules:** Specificity: 88.0% and Sensitivity 30.9% (15.7% to 46.1%).	The EAG notes that these estimates appear to relate to a single "commercial" EarlyCDT Lung test threshold, and not the double

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					threshold model proposed by the company at scoping stage.
				Oncimmune makes a few remarks about these studies: **Audit** This is Oncimmune's audit of the first series of commercial samples (evaluation report reference 33) and is thus based on the real-world setting (in the US) with a sensitivity of 37%. Reference: Jett, J. R. et al. (2014) 'Audit of the autoantibody test, EarlyCDT (R)-Lung, in 1600 patients: An evaluation of its performance in routine clinical practice', Lung Cancer, 83(1), 51–55.	Included as "HIPAA" in the EAG report
				The Early detection of Cancer of the Lung Scotland ("ECLS") two-year trial results The evaluation report stated: "However, many of the participants did not have pulmonary nodules - the trial was conducted in a high-risk screening population with the test result dictating whether CT imaging was performed. The results therefore have limited applicability to the population most likely to receive the EarlyCDT Lung test in NHS practice." Oncimmune notes that it is, to date, in fact the largest diagnostic biomarker study in lung cancer in the UK. The study design represented the common situation at the time where CT scanning was of only limited availability. The "limited applicability" statement above is thus unwarranted. The sensitivity for all lung cancers at two years was 33%. Reference: Sullivan FM, Mair FS, Anderson W, et al. (2021) Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. Eur Respir J 2021; 57.	Limited applicability here refers to applicability to people with identified nodules under assessment using BTS guidance (as per the project scope)
				Denmark and St Luke's Hospital (US) These are two more real-world nodule studies but not yet published, although for Denmark a manuscript has been accepted for publication (see reference). The studies had sensitivity estimates of 33% and 30% respectively.	The Borg et al (2021) paper was included in the EAG report (Section 3.1.7.2) We note this paper concluded that the accuracy of EarlyCDT Lung was insufficient to recommend its use in lung cancer screening.

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				Reference: Borg M, Wen SWC, Nederby L et al (2021) Performance of the EarlyCDT® Lung test in detection of lung cancer and pulmonary metastases in a high-risk cohort. Lung Cancer. Accepted 7 June 2021 **Panoptic** A further nodule sample set received from our US partners from the Panoptic study, a prospective, multicentre observational trial of 685 patients with 8mm-30mm lung nodules. Results have been presented at international conferences. The study had a 43% sensitivity. References: Interim study results have been presented in several publications: Phillips, M. et al. (2017) Analysis of the EarlyCDT-blood biomarker for lung cancer in higher vs. lower risk Cohorts, Journal of Thoracic Oncology, 12(1, S), S591. Jett J, Dyer D, Kern J et al. (2015) Screening for Lung Cancer with the Early CDT-Lung and Computed Tomography Session. Jett, J. et al. (2017) Screening for lung cancer with EarlyCDT-Lung blood biomarkers and computed Tomography', Journal of Thoracic Oncology, 12(1, S), S569–S570.	The EAG notes that this was included as the "EarlyCDT LCS" study in our review
Oncimmune Limited	3	67-73 + 84-88		**5. Additional comments** **Key point:** The evaluation report states that "No study reported data on area under the ROC curve (AUC)." In fact, Oncimmune has published a ROC curve (Healey et al 2017, evaluation report reference 10).	An ROC curve on its own is insufficient for AUC analysis, when it lacks a 95% confidence interval.
Oncimmune Limited	4	67-73 + 84-88	Risk model compar-ators	**6. Risk models** **Key point:** Biomarker tests such as EarlyCDT Lung can be additive to risk models at least in certain parts of the performance range. **Justification:** The evaluation report appears to be arguing that risk models are superior to EarlyCDT Lung. Our claim is that EarlyCDT Lung is in fact additive to risk models as it is providing completely independent information. It has been argued that it is difficult for biomarkers to add substantially to the performance of risk models, and that improvements of much over 5% are normally not possible. According to the published literature for this type of analysis researchers always use simple logistic regression covering the whole risk range. Not only is this analysis naïve, but Oncimmune also has evidence that including continuous assay variables in a logistic model can cause considerable instability under random assay variation.	The EAG made no such claim. We agree that EarlyCDT Lung would be used additively.

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				Oncimmune also notes that virtually all published risk models were developed in a single population context and usually from only one dataset and are therefore biased. The cohorts behind the datasets can vary considerably, giving different performance and predictability across the risk range. This is where biomarker test such as EarlyCDT Lung can be of use.	The EAG agrees that there are limitations in the evidence supporting the use of the different risk models within the scope of this evaluation (e.g. Report Section 3.2.3). The EAG notes that this same limitation applies to the risk model for EarlyCDT Lung (report Figure 2), as this too is based on limited data. The company claims that EarlyCDT Lung can be of use, but it is unclear how the clinical value of EarlyCDT Lung used in combination with the risk models can be established if the evidence surrounding both EarlyCDT and the risk models is not robust.
				The Massion et al paper (Supplementary data) demonstrates the additivity to three of the most well-known risk models (Gould/VA, Brock, Swensen/Mayo).	The EAG report covers this in section 3.1.5.2 We note an error in the report here: "It is not clear whether these results from using Mayo risk would be similar if Brock or Herder risk were used." Should read: "Results from the supplementary material of Massion et al suggest the results will be similar if combining EarlyCDT Lung with Brock risk."
Oncimmune Limited	5	146-8	Conclusion	Oncimmune agrees with NICE that EarlyCDT Lung has the potential to improve the early detection of lung cancer by assisting in the determination of malignancy of nodules within the indeterminate range of 10-70% after PET CT and Herder assessment and this should be the focus moving forward.	No response required
				The sensitivity of the EarlyCDT Lung test is independent from the risk of malignancy in a population and is therefore, not a function of risk. The difference between a screening and a nodule population is purely one of risk of malignancy in that population, which means that data from both screening and nodule populations are valid for the assessment of the sensitivity of EarlyCDT Lung.	See earlier response to comment 2

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				Of the five trials considered in the report, it is Oncimmune's request that four trials should be dismissed. That leaves the HIPAA – Commercial Nodule Audit (Massion et al 2017) study as the only relevant study in the evaluation, which shows a sensitivity of 37.8% which is clearly in line with our evidence showing sensitivity of 35%. Oncimmune welcomes the assistance of the NICE evaluation process in encouraging an NHS driven IPN trial programme.	See earlier response to comment 2 No response required
Roy Castle Lung Cancer Foundation	6	3	Abstract	Sensitivity data of 20.2% suggests evidence base that introduction of this test would enhance early detection of lung cancer is limited.	No response required
Roy Castle Lung Cancer Foundation	7	10	Scientific summary	Stage shift is unlikely for patients monitored with Early CDT, this may limit the benefit of introduction as a means of improving outcomes for patients.	No response required
Roy Castle Lung Cancer Foundation	8	12	Lay summary	Evidence to support Early CDT does not offer patients any additional expectation of earlier or more accurate nodule management.	No response required
Lay specialist	9	12	Plain English Summary	I don't understand the intended audience for the PE summary. The content is good; the style is adequate if it's targeted at people with subject-matter expertise in a different area and who are accustomed to reading research reports or publications. I would challenge that it's appropriate to a more general readership. One simple change would be to use the active voice and to maintain the use of "we" rather than "this project" or similar phrases. I note that a number of private clinics or generic testing services offer this test in England (and not in the context of CT scanning) so I anticipate that there might be some interest in this report. With this in mind, it might be helpful for the PE summary to include a summary of: the thresholds; its use with other case-finding techniques; the information that it can not distinguish LC for people who have a recent cancer etc.	The EAG can revise the summary if the committee requires this. The summary in this report is restricted in length, so could not include this level of detail. The EAG could produce an alternative summary, separate from the report, if requested.
Royal College of Pathologists	10			RCPath has reviewed this evidence and has no comments to add to the review.	

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Oncimmune: Summary of studies included in the IVDR submission taken from page 6, comment 2 above.

Phase	Study	Controls	Cases	Spec%	Sens%	OR
A) Pre-validation	Clinical Research Centre Cape Cod study[1]	143	137	90.9	36.5	5.7 (2.9-11.2)
A) Pre-validation	Professor Holdenreider, Institute of Clinical Chemistry, University Hospital Munich[1]	225	234	89.3	38.9	5.3 (3.2-8.7)
A) Pre-validation	Russian, US & UK cohort study[2]	483	249	89.9	25.7	3.1 (2.0-4.6)
A) Pre-validation	Department of Pulmonary Medicine, British Columbia Cancer Agency, Vancouver[2]	114	122	84.3	31.4	2.5 (1.3-4.6)
B) Main validation	EarlyCDT Lung LDT training study[3]	266	235	90.6	41.3	6.8 (4.2-11.0)
B) Main validation	EarlyCDT Lung LDT Clinical Validation study[3]	415	336	90.1	29.5	3.8 (2.6-5.7)
C) Kit confirmation	EarlyCDT kit training study	163	163	87.1	39.9	4.5 (2.6-7.8)
C) Kit confirmation	EarlyCDT Lung kit validation study	309	203	94.2	27.6	6.2 (3.5-10.9)
D) Screening	Audit	812	35	91.4	37.1	6.3 (3.0-13.0)
D) Screening	EarlyCDT LCS	1343	13	93.1	23.1	4.1 (1.1-15.0)
D) Screening	ECLS 2yr	6027	55	90.4	32.7	4.6 (2.6-8.1)
D) Screening	Denmark	171	75	87.7	33.3	3.6 (1.8-6.9)
E) Nodules	HIPAA	129	37	83.7	37.8	3.1 (1.4-7.0)
E) Nodules	St Luke's	121	10	91.7	30.0	4.7 (1.1-21.2)
E) Nodules	German RCT	90	46	96.7	13.0	4.4 (1.0-18.5)
E) Nodules	Panoptic	138	180	79.7	42.8	2.9 (1.8-4.9)

References (Validation studies): 1. Boyle, P. et al. (2011) Clinical validation of an autoantibody test for lung cancer, Annals of Oncology, 22(2), 383–389. 2. Lam, S. *et al.* **(2011)** EarlyCDT-Lung: An immunobiomarker test as an aid to early detection of lung cancer, *Cancer Prevention Research*, **4**(7), 1126–1134. 3. Chapman, C. J. *et al.* **(2012)** EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays., *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*, **33**(5), 1319–1326.