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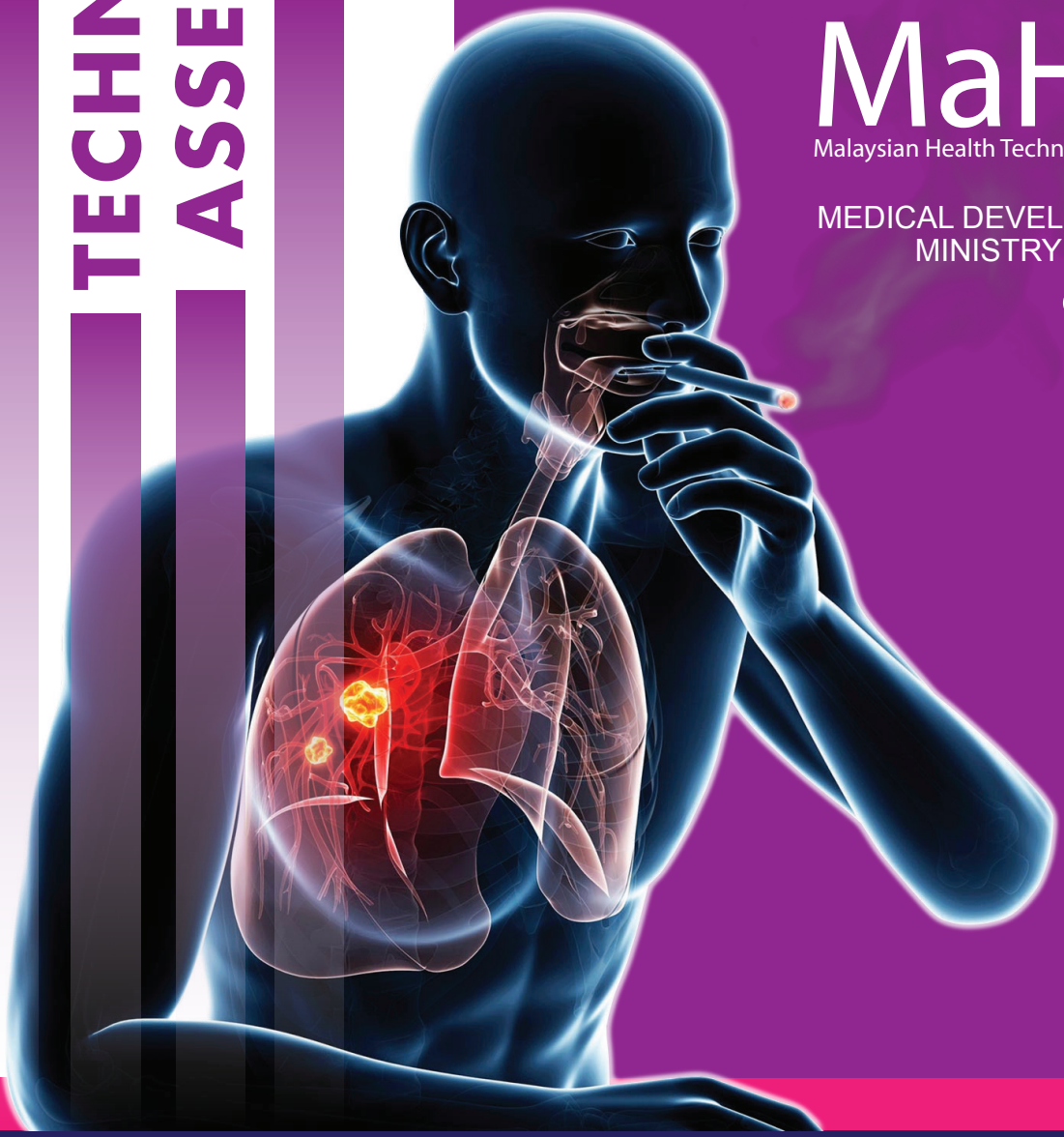
HEALTH TECHNOLOGY ASSESSMENT REPORT

MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH



EARLY CANCER DETECTION TEST FOR LUNG(EarlyCDT-Lung)

KEMENTERIAN KESIHATAN MALAYSIA

HEALTH TECHNOLOGY ASSESSMENT REPORT

EARLY CANCER DETECTION TEST FOR LUNG (EarlyCDT-Lung)

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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EXECUTIVE SUMMARY

Background

Most patients with lung cancer are diagnosed when they present with symptoms, at advanced stage disease, and curative treatment is no longer an option. An effective screening test has long been desired for early detection with the goal of reducing mortality from lung cancer. While low-dose computed tomography (LDCT) screening has shown promising result in the detection of early disease and has now been broadly documented to have the potential to reduce lung cancer mortality, it comes with risks of radiation-induced cancer, false-positive test results, unnecessary follow-up testing and increased financial costs, as well as over diagnosis. Currently, there has been a shift in the emphasis of biomarker using blood specimens as it is readily available through minimally invasive procedures and their measurements can be easily standardized. Following this, a commercially available assay, the EarlyCDT-Lung that measures autoantibodies to tumour associated antigens (TAAs) for the detection of lung cancer has been developed. Despite the magnitude of lung cancer cases been reported in Malaysia, there is no national lung cancer screening programme established yet. This review is timely to address the need for early detection of lung cancer in facilitating more effective non-invasive cancer control approaches in the country. Therefore, the purpose of this Health Technology Assessment (HTA) is to evaluate whether EarlyCDT-Lung would be effective, safe, and cost-effective as a screening tool for early lung cancer detection among high-risk group in the management of lung cancer in Malaysia. This assessment was requested by a Senior Consultant Pulmonologist from Serdang Hospital.

Technical features

EarlyCDT-Lung is a sophisticated blood test that detects autoantibodies against seven TAAs found in different types of lung cancer. An indirect enzyme linked immunosorbent assay (ELISA) is utilised to detect antibodies to a panel of antigens that includes p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2. A positive result is reported if antibodies to any one of the seven antigens are detected at a concentration above a defined cut-off. In combination with imaging techniques, EarlyCDT-Lung is now commercially available to assist clinicians in the early detection of lung cancer in a high-risk population. It can help reduce the number of patients in 'watchful waiting' and aid early lung cancer detection, leading to earlier intervention and better patient outcomes. A blood test like this could be repeated frequently and CTs only start when there is a positive blood test. EarlyCDT-Lung has been marketed in the United States since 2012 while received its CE mark as a general in vitro diagnostic in May 2017 and was updated in March 2019.

Policy question

i. Should EarlyCDT-Lung be used as a screening tool for early lung cancer detection among high-risk group in Malaysia?
ii. Does using the EarlyCDT-Lung reduce the incidence of patients with late stage (III/ IV) lung cancer or unclassified presentation at diagnosis?

Objective

i. To determine the diagnostic accuracy of EarlyCDT-Lung in increasing early-stage lung cancer detection.
ii. To determine the effectiveness and safety of EarlyCDT-Lung for lung cancer screening in the high-risk group, with regards to patient outcomes such as mortality, quality of life (QoL), and adverse events or complications.
iii. To determine the economic, organisational, social, ethical and legal implication of using EarlyCDT-Lung in screening setting.

Methods:

Part A: Systematic Review of Literature

Literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to EarlyCDT-Lung test for early lung cancer detection. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2022, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (January 2022), and EBM Reviews - NHS Economic Evaluation Database (4th Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. Detailed search strategy is as in Appendix 3. The last search was performed on 10th February 2022. Additional articles were identified from reviewing the references of retrieved articles.

Part B: Economic Evaluation

An economic evaluation was conducted to assess cost-effectiveness and to calculate ICER of EarlyCDT-Lung compared to no screening among high-risk lung cancer patients in Malaysia using decision analytic modelling. Sensitivity and specificity of EarlyCDT-Lung were obtained from the literature. One-year probability of lung cancer among high-risk group and probability of late-stage diagnosis was calculated based on Malaysia Cancer Registry.

Results:

Part A: Systematic Review of Literature

A total of 390 records were identified through the Ovid interface and PubMed while 26 were identified from other sources (references of retrieved articles). Following the removal of four duplicates, 412 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 29 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 29 full text articles, eight were included. The eight full text articles which were finally selected in this review comprised of two systematic review and meta-analysis, one randomised controlled trial (RCT), three observational studies (two prospective cohort and one nested case-control), and two economic evaluation studies. All studies included were published in English language between 2011 and 2021 and were mostly conducted in the United States, United Kingdom, Scotland, Denmark, Germany, and China.

Diagnostic accuracy and effectiveness

In the diagnosis of **all stages** lung cancer, the sensitivity of single or individual tumour-associated autoantibody (TAAb) ranged from 15.0% to 55.2% and the specificities ranged from 84.4% to 98.0%. However, combination or a panel of multiple TAAbs may improve sensitivity (70.3%) but at the cost of specificity (86.3%). For single TAAb in the diagnosis of **early-stage** lung cancer, the sensitivity and specificity were 55.6% and 89.3%, respectively. For the combination or a panel of multiple TAAbs, sensitivity of 71.1% with specificity 87.1% were reported. In addition, the diagnostic value of EarlyCDT-Lung for the same panel of 7-TAAbs appears to be higher than the panel of 6-TAAbs in the diagnosis of lung cancer, either at **all stage** (sensitivity 47.0% versus 38.0%; specificity 90.0% versus 89.0%) or **early-stage** disease (sensitivity 40.0% versus 29.7%; specificity 91.0% versus 87.0%). In

the context of large community-based trials, a positive EarlyCDT-Lung test followed by LDCT 6-monthly for up to two years significantly reduced the numbers of late-stage (III/IV) lung cancers (58.9% versus 73.2%) as compared with standard clinical care. Indirectly, more early-stage (I/II) disease were diagnosed (41.0% versus 27.0%). However, there were no significant differences in lung cancer mortality (0.28% versus 0.39%) and all-cause mortality (1.43% versus 1.76%) as well. The EarlyCDT-Lung has previously been tested in high-risk cohorts or lung cancer patients matched with control subjects on age, gender, and smoking status. As a result, this assay performed best (sensitivity) in heavy smokers with at least 50 tobacco pack years (44.0%), patients older than 75 years (55.0%), and advance stage disease (40.0%); gender does not seem to influence outcome. No studies of EarlyCDT-Lung in the target population reported health-related quality of life outcomes.

Summary of studies related to diagnostic accuracy and effectiveness for TAAbs are shown in **Table 1.**

Safety

Only one study reported the incidents of adverse events directly related to the EarlyCDT-Lung test (collection of blood sample), and all were considered minor. There was one injection site haematoma, one panic attack, and one pre-syncope.

Economic implication

Economic evaluation of an autoantibody test has been very limited and to date, two cost-effectiveness analyses have been undertaken. The first revealed that EarlyCDT-Lung is likely to be cost-effective compared to CT surveillance alone in patients with incidentally detected nodules who are estimated to have an intermediate-risk of lung cancer and a rescheduled for CT surveillance alone, with USD 24,330 to USD 24,833 per quality-adjusted life-year (QALY) gained, depending on the test accuracy parameters used (two alternative sets of estimates for sensitivity and specificity were considered based on published literature: 41%/93% and 28%/98%, respectively). Second study reported at £70 per test, the EarlyCDT-Lung will have a positive impact on patient outcomes and coupled with CT surveillance is a cost-effective approach to the management of patients with indeterminate pulmonary nodules (IPNs) compared to surveillance alone with an incremental cost-effectiveness ratio (ICER) of less than £2,500.

Organisational

No guideline presently recommends the use of blood-based biomarkers in clinical practice as an initial screening test in those at high risk although there are now commercially available. Recently, the National Institute for Health and Care Excellent (NICE) stated that there is not enough evidence to recommend routine use of EarlyCDT-Lung for assessing the risk of lung cancer in solid lung nodules.

Social, ethical and legal

No evidence retrieved on social, ethical and legal issues related to EarlyCDT-Lung in screening setting.

Table 1: Diagnostic accuracy and effectiveness of TAAbs reported by the included studies

Authors/ Year	Study design	TAAbs	Comparator	Diagnostic accuracy										Mortality rate (%)	
				All stages lung cancer					Early-stage lung cancer						
				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Cancer-related	All caused
J Qin 2018	SR & MA	Single	-	15.0	98.0	-	-	0.85	-	-	-	-	-	-	-
		EarlyCDT-Lung (6-TAAbs)	-	38.0	89.0	-	-	-	-	-	-	-	-	-	-
		EarlyCDT-Lung (7-TAAbs)	-	47.0	90.0	-	-	-	-	-	-	-	-	-	-
Tan ZM 2017	SR & MA	Single	-	55.2	84.4	-	-	-	55.6	89.3	-	-	-	-	-
		Combination	-	70.3	86.3	-	-	-	71.1	87.1	-	-	-	-	-
		EarlyCDT-Lung (6-TAAbs)	-	38.0	89.0	-	-	0.52	29.7	87.0	-	-	-	-	-
		EarlyCDT-Lung (7-TAAbs)	-	47.0	90.0	-	-	0.90	40.0	91.0	-	-	-	-	-
Sullivan FM 2021	RCT	EarlyCDT-Lung (7-TAAbs)	Standard clinical care	32.1	90.4	3.0	99.3	-	52.2	90.3	2.0	99.8	-	0.28 vs 0.39	1.43 vs 1.76
Shengxian Ren 2018	Cohort	7-TAAbs*	-	-	-	-	-	-	61.0	90.0	-	-	-	-	-
		7-TAAbs*	Tumour biomarkers	-	-	-	-	-	60.0	-	-	-	-	-	-
		7-TAAbs* + CT scan	7-TAAbs*	-	-	-	-	-	-	-	95.0 vs 85.2	-	-	-	-
		7-TAAbs* + CT scan	CT scan	-	-	-	-	-	-	-	95.0 vs 69.0	-	-	-	-
Borg M 2021	Cohort	EarlyCDT-Lung (7-TAAbs)	-	33.0	88.0	54.0	75.0	-	21.0	88.0	22.0	87.0	-	-	-
Maldonado SG 2021	Case control	EarlyCDT-Lung (7-TAAbs)	-	13.0	88.9-91.1	-	-	-	-	-	-	-	-	-	-

*Three of the 7-TAAbs panel (GAGE7, MAGE-A1 and PGP9.5) are not included in the EarlyCDT-Lung test
TAAbs, tumour-associated autoantibodies; PPV, positive predective value; NPV, negative predective value; AUC, area under the curve; SR & MA, systematic review & meta analysis; RCT, randomised controlled trial

Part B: Economic Evaluation

From the decision analytic modelling, the base-case analysis indicated that a positive EarlyCDT-Lung followed by LDCT and biopsy as compared with no screening yielded an ICER of MYR 37,169.04 per QALY gained. A sensitivity analysis suggested that the cost of EarlyCDT-Lung is the major factor that influenced the cost-effectiveness ratio.

Conclusion:

Part A: Systematic Review of Literature

The availability of evidence on the diagnostic value differs between autoantibodies for identifying patients at all stages or early-stage of lung cancer. There was fair to good level of retrievable evidence to suggest that EarlyCDT-Lung has low to moderate sensitivity but good specificity as serum diagnostic biomarkers of lung cancer in population screening among high-risk group. A positive EarlyCDT-Lung test followed by LDCT significantly reduced the numbers of late-stage lung cancers and indirectly more early-stage lung were diagnosed as compared with standard clinical care. However, there were no significant differences in lung cancer mortality and all-cause mortality. Given the existing evidence, economic evaluation conducted in countries that implemented LDCT as a screening tool with an addition of EarlyCDT-Lung was found to be cost effective. Future research focusing on novel TAAb panels that offer better diagnostic performance is encouraged.

Part B: Economic Evaluation

For the implementation of screening program using Early-CDT-Lung, the strategy needed to be in line with the LDCT and biopsy after the test screening. The population screened needed to be monitored closely and the treatment options needed to be considered after the patients tested and confirmation of cancer diagnosis.

Recommendation

Based on the above review, EarlyCDT-Lung has the potential to be used to complement LDCT in population screening for early lung cancer detection among high-risk group in Malaysia. However, its use should take into consideration the availability and acceptability of LDCT as a screening tool. Competitive price of EarlyCDT-Lung may improve the cost-effectiveness of this screening strategy.

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ABBREVIATION

AABT	Autoantibody test
AEs	Adverse events or adverse effects
AUC	Area under the curve
CASP	Critical Appraisal Skills Programme
CA	Carbohydrate antigen
CEA	Carcinoembryonic antigen
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CT	Computed tomography
CYFRA21-1	Cytokeratin 19 fragment 21-1
DNA	Deoxyribonucleic acid
DOR	Diagnostic odds ratio
ELISA	Enzyme linked immunosorbent assay
GGNs	Ground-glass nodules
GP	General practitioner
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPNs	Indeterminate pulmonary nodules
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
LDCT	Low-dose computed tomography
MaHTAS	Malaysian Health Technology Assessment Section
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
NHS	National Health Service
NICE	National Institute for Health and Care Excellent
NMB	Net-monetary benefit
NLST	National Lung Screening Trial
NSCLC	Non-small cell lung cancer
NPV	Negative predictive value
NSE	Neuron-specific enolase
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomised controlled trial
RNA	Ribonucleic acid
ROB	Cochrane Risk of Bias Tool
ROBIS	National Collaborating Centre for Methods and Tools
ROC	Receiver operator characteristic
SCLC	Small cell lung cancer
TAA	Tumour-associated antigen
TAAb	Tumour-associated autoantibody
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WTP	Willingness to pay

1.0 BACKGROUND

Epidemiology

With an estimated 2.2 million new cancer cases and 1.8 million deaths worldwide, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in five (18.0%) deaths.[1-2] According to the most recent data by Malaysia National Cancer Registry (MNCR) for the incidence year of 2012-2016, lung cancer was the third (9.8%) most common cancer in the country, the second (14.9%) most common cancer in males, and the fifth (5.6%) most common in females.[3] Despite advances in diagnostic approaches and treatment, the overall 5-year survival for lung cancer has not significantly changed and is estimated to be around 17.8%. Lack of early detection remains one of the biggest challenges in lung cancer management.[4]

Management of malignancy risk in pulmonary nodule

To improve the prognosis, methods that detect lung nodules at an earlier stage when it is more likely to be treated with curative intent are needed. Several clinical trials have addressed the application of a low-dose computed tomography (LDCT) screening program in a high-risk population to diagnose lung cancer at a resectable stage,[5-7] the largest being the National Lung Screening Trial (NLST)[8] in the United States and the Nelson trial[9] in the Netherlands and Belgium. Findings demonstrated that LDCT is more sensitive in discovering stage I lung cancers and all cancers than chest x-ray or no screening, and has resulted in 20% reduction in lung cancer mortality.[8] The conclusion drawn from these trials were in line with MaHTAS Health Technology Assessment (HTA) report in 2017[10] whereby in our recommendation, LDCT may be used for lung cancer screening among the high-risk group in a research environment or for research purpose since the specificity was low and poor patient uptake due to low awareness, refusal to be screened, and fear of cancer diagnosis. That LDCT screening can reduce lung cancer mortality has provided impetus to consider national screening programmes for the early detection of lung cancer. However, the widespread adoption of LDCT screening will likely remain limited by resource constraints and concerns about management of false positives test results, incidental findings, radiation exposure, and overdiagnosis.[11-12]

Currently, there is extensive ongoing research on the complementary use of blood-based biomarkers (a measurable DNA, RNA or protein component that indicates disease) in attempt to further improve early detection and outcomes for patients with lung cancer.[13] A valid biomarker could provide additional evidence as to whether a suspicious, screening-detected nodule is malignant, thereby reducing the number of false-positives at surgery or surgical biopsy.[14] Present diagnostic blood tests focus on detecting tumour-associated antigen (TAA) markers such as carcinoembryonic antigen (CEA), chromogranin, neuron-specific enolase, carbohydrate antigen (CA) 125 and CA19-9, which showed an increase positivity at advanced stages but are not advocated to be used as early biomarkers because of their low sensitivity and specificity.[15]

Initially, a promising blood test of serum tumour-associated autoantibodies (TAAbs) against over expressed, mutated, misfolded or aberrant autologous cellular antigens produced by cancer cells may identify individuals with early lung cancer and distinguish high risk smokers with benign nodules from those with lung cancer.[14, 16] Autoantibodies against TAAs may persist in the circulating blood longer than the antigens themselves, and may be more easily detected and have the potential to be highly useful diagnosis markers in a variety of cancers. In the blood of patients who develop lung cancer, the circulating autoantibodies have been found in some cases up to five years before CT was able to identify the tumour.[17] Following this, a commercially available assay, the EarlyCDT-Lung that measures autoantibodies to TAAs for the detection of lung cancer has been developed.

Reasons for request

Although serum TAAbs are considered a promising blood-based biomarkers for early lung cancer detection, their efficacy has been tested mostly in a clinical context but not in population screening settings. In Malaysia, despite the magnitude of lung cancer cases been reported, there is no national lung cancer screening programme established yet. This review is timely to address the need for early detection of lung cancer in facilitating more effective non-invasive cancer control approaches in the country. Therefore, the purpose of this HTA is to evaluate whether EarlyCDT-Lung would be effective, safe, and cost-effective as a screening tool for early lung cancer detection among high-risk* group in the management of lung cancer in Malaysia.

This assessment was prepared in corresponding to the request made by a Senior Consultant Pulmonologist from Serdang Hospital.

*The high-risk group was defined in Malaysia as current or ex-smoker between 50 to 70 years old, with a smoking history of 30 pack-years; or 20 pack-years with one additional risk factor (radon exposure, occupational exposure, cancer history, family history of lung cancer, or chronic lung disease such as chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis or post tuberculosis fibrosis).

2.0 TECHNICAL FEATURES

Figure 1: EarlyCDT-Lung

EarlyCDT-Lung (Oncimmune, Nottingham, UK) is a sophisticated blood test to assess the malignancy risk of solid lung nodules found by chest CT or x-ray. It measures the presence of autoantibodies to a panel of seven lung cancer associated antigens **(p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2).** Autoantibodies and TAAs are produced as the body's immune system's response to cancer antigens. Based on the immunoediting theory, TAAs are captured by the immune system and lead to the formation of autoantibodies via humoral immune responses. Interestingly, autoantibodies have been found to be present before the disease becomes symptomatic.[16-20] Therefore, they could be valuable for the early detection of lung cancer. Blood levels of autoantibodies are elevated in the earliest stage of lung cancer, can also be present at later stages, and exist in sufficient quantity and size to be measurable in blood even when the tumour may be small and/ or localized.[21-22]

After blood collection, the test is carried out in a laboratory in a secondary healthcare setting. This test is based on enzyme linked immunosorbent assay (ELISA) principles whereby microtiter plates coated with a set of serial dilutions of recombinant antigens were used. Test results are based on a comparison of relative autoantibody levels to fixed thresholds, reported as *"High level"*, *"Moderate level"* or *"No Significant level"* for every autoantibody. If any of the autoantibody results were *"High"* or *"Moderate"* they were regarded as a positive test, while *"No Significant level"* in all autoantibody tests was treated as a negative result.[21-22]

In combination with imaging techniques, EarlyCDT-Lung is now commercially available to assist clinicians in the early detection of lung cancer in a high-risk population. A blood test like this could be repeated frequently and CTs only start when there is a positive blood test. The test has been marketed in the United States since 2012 while received its CE mark as a general *in vitro* diagnostic in May 2017 and was updated in March 2019.[21-22]

3.0 POLICY QUESTION

3.1 Should EarlyCDT-Lung be used as a screening tool for early lung cancer detection among high-risk group in Malaysia?

3.2 Does using the EarlyCDT-Lung reduce the incidence of patients with late stage (III/ IV) lung cancer or unclassified presentation at diagnosis?

4.0 OBJECTIVE

4.1 To determine the diagnostic accuracy of EarlyCDT-Lung in increasing early-stage lung cancer detection.

4.2 To determine the effectiveness and safety of EarlyCDT-Lung for lung cancer screening in the high-risk group, with regards to patient outcomes such as mortality, quality of life (QoL), and adverse events or complications.

4.3 To determine the economic, organisational, social, ethical and legal implication of using EarlyCDT-Lung in screening setting.

The following **research questions** will be addressed:

i. What is the diagnostic accuracy of EarlyCDT-Lung for the detection of lung cancer in the high-risk group?

ii. Does screening with EarlyCDT-Lung improve lung cancer mortality?

iii. Is EarlyCDT-Lung cost-effective?

iv. What is the organisational, social, ethical and legal implication related to EarlyCDT-Lung?

5.0 PART A: SYSTEMATIC REVIEW OF LITERATURE

5.1 METHODS

5.1.1 Literature search strategy

Literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to EarlyCDT-Lung test for early lung cancer detection. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2022, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (January 2022), and EBM Reviews - NHS Economic Evaluation Database (4th Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. Detailed search strategy is as in **Appendix 3.** The last search was performed on 10th February 2022. Additional articles were identified from reviewing the references of retrieved articles.

5.1.2 Study selection

Two dedicated reviewers (SA and EZ) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection. Disagreement was resolved by discussion.

Inclusion criteria:

a.	Population	Adults who are at risk of having lung cancer
b.	Intervention	Early cancer detection test for lung (EarlyCDT-Lung), autoantibody test, biomarkers, tumour-associated autoantibody test
c.	Comparator	i. Standard clinical practice: chest radiography, computed tomography (CT), positron emission tomography-CT (PET-CT), low dose CT (LDCT) ii. No comparator
d.	Outcomes	i. Diagnostic accuracy: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), diagnostic odds ratio (DOR), receiver operator characteristic (ROC) curve, and area under the curve (AUC) ii. Effectiveness: lung cancer-related mortality, quality of life (QoL) iii. Safety: adverse events, complications iv. Economic implications: cost-effectiveness, cost-utility, cost-benefit analysis v. Potential psychological and behavioural harms and benefits of test results vi. Training requirements or learning curve

e.	Study design	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, diagnostic, cross-sectional, case-control, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	Study design	Animal study, laboratory study, case report, case series, narrative review
b.	Non-English full text articles	

5.1.3 Critical appraisal of literature/ assessment of risk of bias

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) [23] for Systematic Review and Meta-analysis, a revised Cochrane Risk of Bias Tool (RoB 2) for Randomised Controlled Trials [24], and Critical Appraisal Skill Programme (CASP) [25] for Observational and Economic Studies. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (Appendix 1).[26]

5.1.4 Analysis and synthesis of evidence

Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence Table* as shown in **Appendix 4**) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was also presented and discussed with the *Expert Committee*. The data extracted was as follows:

i. Details of methods and study population characteristics
ii. Detail of intervention and comparators
iii. Details of individual outcomes specified

Methods of data synthesis

Data on the accuracy, effectiveness, safety and cost-effectiveness associated with EarlyCDT-Lung were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

5.2 RESULTS

5.2.1 Selection of included articles

An overview of the systematic search and selection of the studies are illustrated in **Figure 2**. A total of **390** records were identified through the Ovid interface and PubMed while **26** were identified from other sources (references of retrieved articles). Following the removal of **four** duplicates, **412** titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, **29** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **29** full text articles, **eight** full text articles were included. **Twenty-one** articles were excluded as those primary studies were already included in systematic review and meta-analysis (n=15), irrelevant study design (n=4), and irrelevant intervention (n=2). The excluded articles were listed as in **Appendix 5.**

The **eight** full text articles which were finally selected in this review comprised of **two** systematic review and meta-analysis, **one** RCT, **three** observational studies (**two** prospective cohort and **one** nested case-control), and **two** economic evaluation studies.

All studies included were published in English language between 2011 and 2021 and were mostly conducted in the United States, United Kingdom, Scotland, Denmark, Germany, and China.

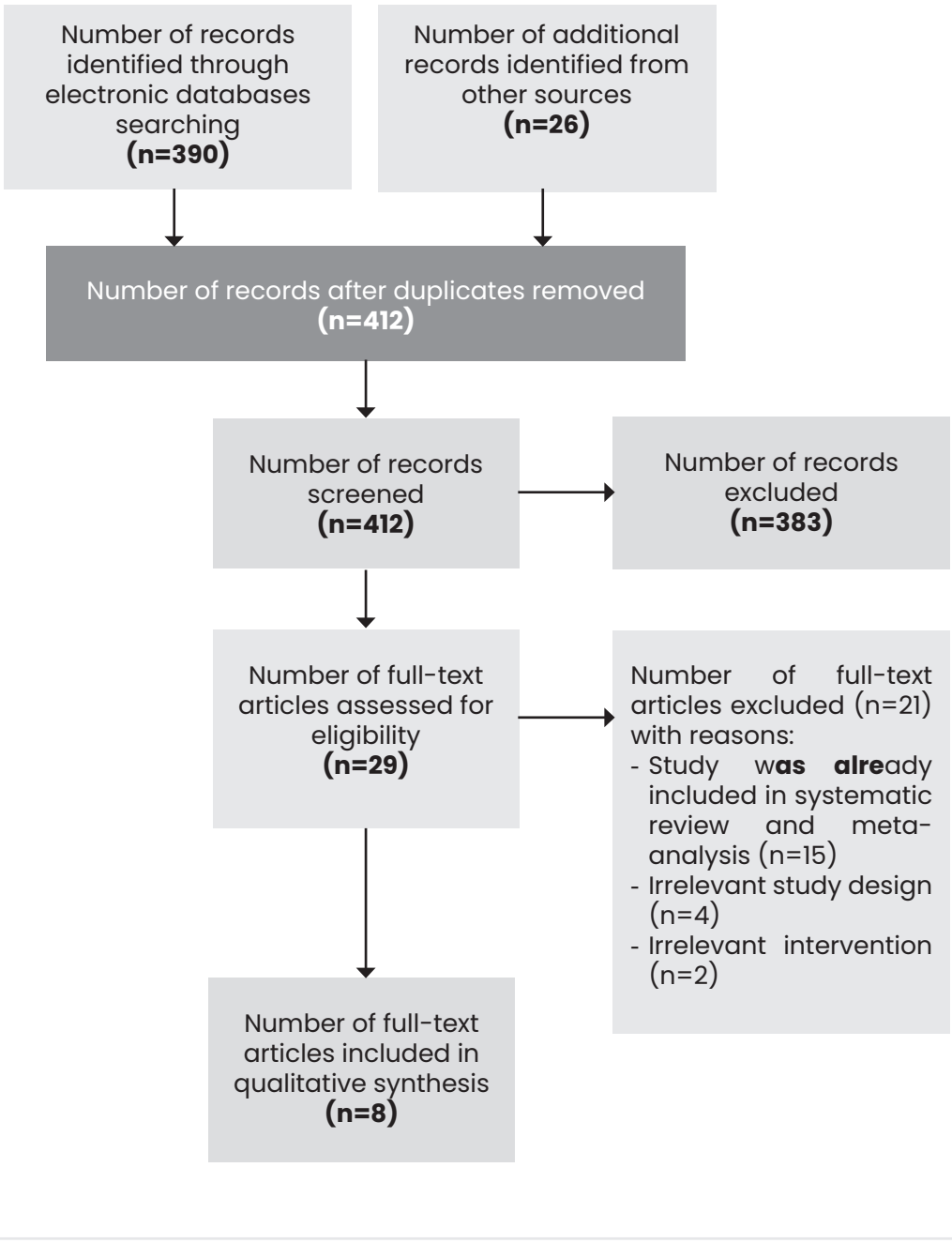

Figure 2: Flow chart of retrieval of articles used in the results

5.2.2 Quality assessment/ risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review and meta-analysis, Cochrane Risk of Bias (RoB) 2.0 for RCT, and Critical Appraisal Skill Programme (CASP) checklist for observational and economic studies. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.

Risk of bias assessment for included systematic review and meta-analysis

Two studies were included in this assessment. Both were judged to have overall low risk of bias (Figure 3.1).

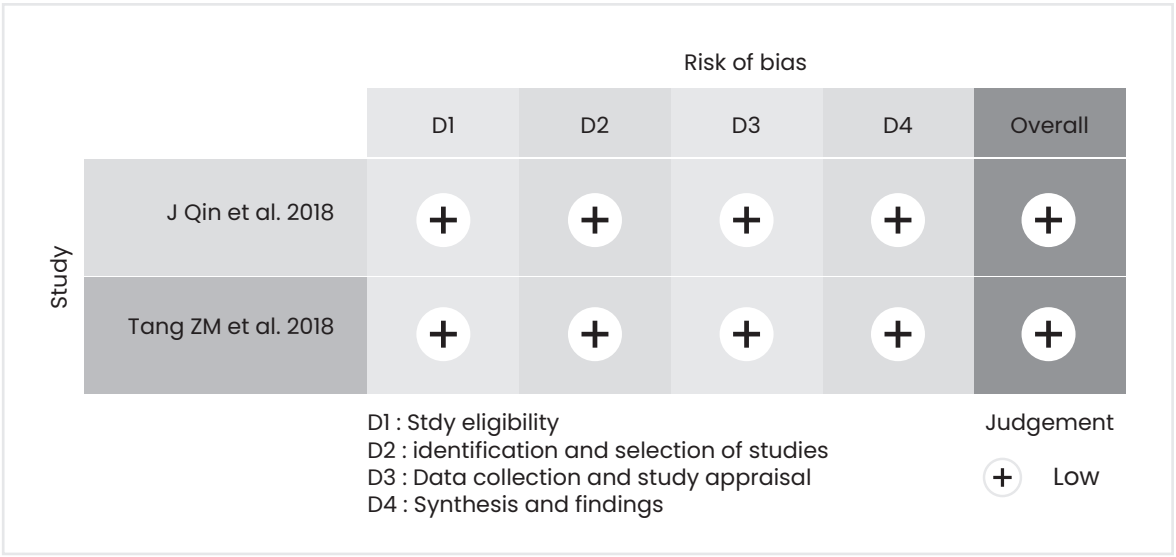

Figure 3.1: Summary of risk of bias assessment for systematic review and meta-analysis using ROBIS

Risk of bias assessment for included RCT

Article by Sullivan FM et al. 2021 was rated to have an overall low risk of bias as shown in **Figure 3.2**. The study included a large sample size and power calculations was done to detect the study endpoint. The method of randomisation was stated while random sequence generation and allocation concealment were performed adequately. Outcomes were analysed using intention to treat analysis while selective reporting was considered to have a low risk of bias as all pre-specified outcomes were reported and analysed.

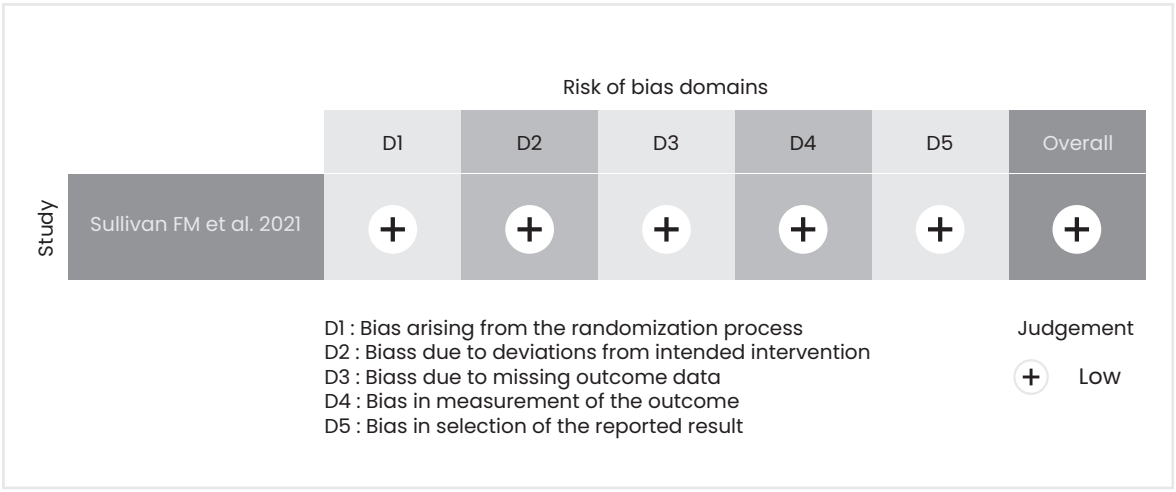

Figure 3.2: Summary of risk of bias assessment for RCT using RoB 2

Risk of bias assessment for included cohort study

Two articles were included in this assessment (Figure 3.3). First by Shengxiang Ren et al. 2018 was unclear whether the authors had considered the follow-up completeness since it was not declared systematically. Evidence lacking such information must be challenged as potentially flawed by selection bias and hence, was rated as being at moderate risk of bias. The other by Borg M et al. 2021 had high risk of bias for selecting participants into their study as it was based on clinical judgement of the general practitioner on suspicion of lung cancer. Thus, lung cancer patients and controls are not matched in risk of lung cancer.

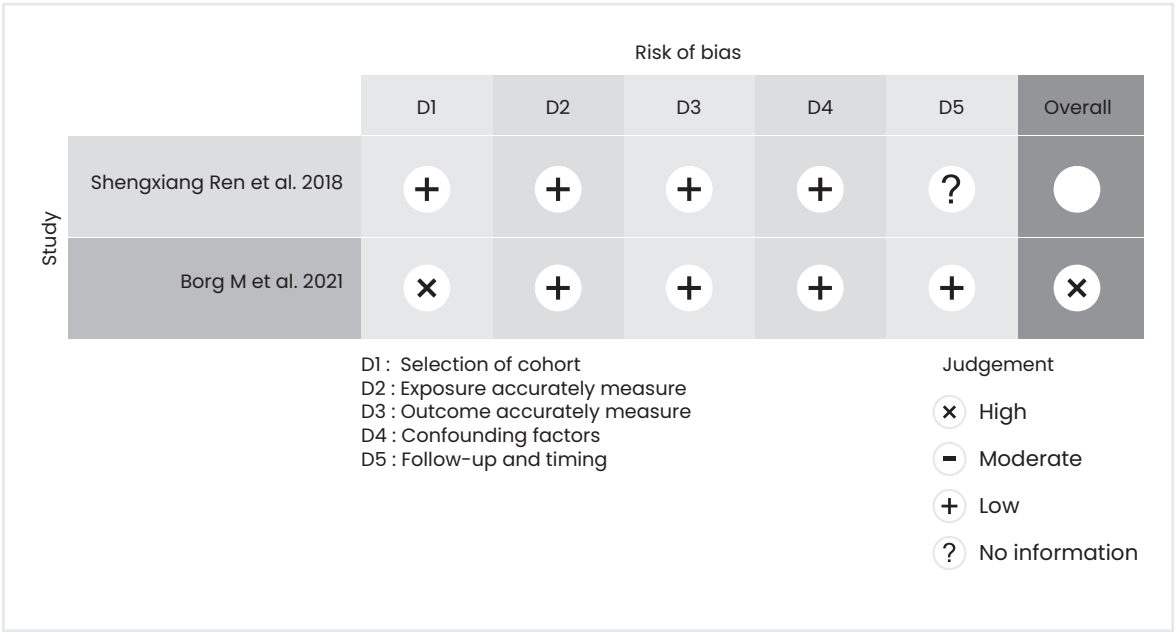

Figure 3.3: Summary of risk of bias assessment for cohort study using CASP checklist

Risk of bias assessment for included case-control

Article by Maldonado SG et al. 2021 was rated to have an overall low risk of bias as shown in Figure 3.4.

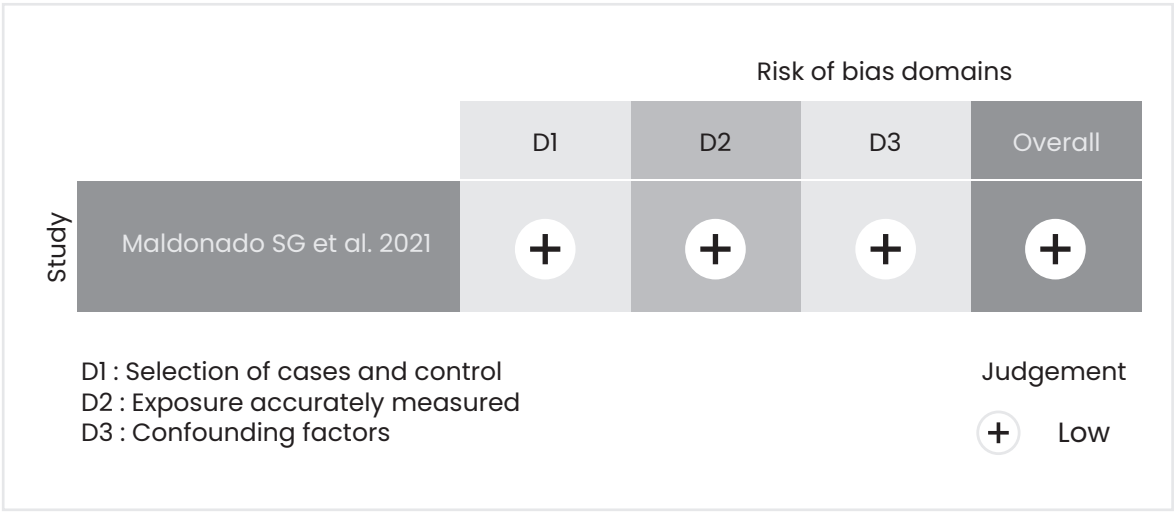

Figure 3.4: Summary of risk of bias assessment for case-control using CASP checklist

Risk bias assessment for included economic evaluation

Two cost-effectiveness analyses were included in this assessment and were summarised in Figure 3.5. Both were judged to have overall low risk of bias.

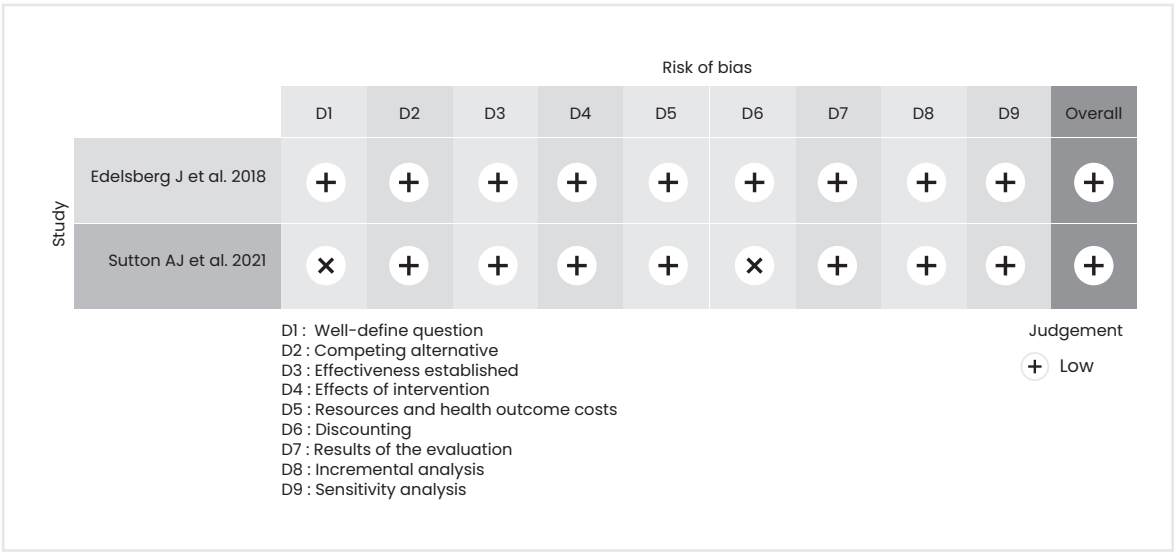

Figure 3.5: Summary of risk of bias assessment for economic evaluation using CASP checklist

5.2.3 Diagnostic accuracy/ effectiveness

To date, there have been two systematic reviews published on the diagnostic abilities of single (individual) or combination of multiple tumour-associated autoantibodies (TAAbs) panel for identifying patients at all stages of lung cancer. In 2018, J Qin et al. performed a meta-analysis which included 53 trials with 11,515 patients. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) while pooled values of sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR-), diagnostic odds ratios (DOR) and associated 95% confidence intervals (CIs) were calculated using the bivariate random-effect models. Summary receiver operating characteristic (SROC) curves were also used to summarise overall test performance. The meta-analysis demonstrated that each of TAAbs against tumour-associated antigens (TAAs) showed excellent specificity (ranged from 0.97 to 0.99; mean 0.98) for lung cancer but inadequate sensitivity (ranged from 0.07 to 0.19; mean 0.15) as shown in Table 2. However, combinations or panels of multiple autoantibodies may improve sensitivity but at the cost of specificity. One combination (TAAbs against six panels: p53, NY-ESO1, CAGE, GBU4-5, Annexin 1, and SOX2) showed estimated sensitivity of 0.38 (95% CI 0.35 to 0.40) and specificity of 0.89 (95% CI 0.86 to 0.91) while the other combination was TAAbs against seven panels (p53, CAGE, NY-ESO-1, GBU4-5, SOX2, MAGEA4 and HuD) that showed estimated sensitivity and specificity of 0.47 (95% CI 0.34 to 0.60) and 0.90 (95% CI 0.89 to 0.92), respectively. Since most cases (60-70%) of small-cell lung cancer (SCLC) were diagnosed at the extensive stage and mutations in the p53 and NY-ESO-1 gene were present in up to 80% of SCLC and 50% of non-small cell lung cancer (NSCLC) cases, subgroup analysis was performed to identify whether the presence of p53 and NY-ESO-1 TAAb could differentiate NSCLC (15 studies, 2,478 patients) and SCLC (9 studies, 1,630 patients). The results suggested that both p53 and NY-ESO-1 showed greater diagnostic performance for SCLC than for NSCLC, albeit with low diagnostic efficacy. This highlights the urgent need to develop serum biomarkers that might allow diagnosis of SCLC.[27, level II-2]

Table 2: Summary of diagnostic values of TAAbs

TAAbs	Cancer type	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)	DOR (95%CI)	AUC
p53	Lung cancer	0.19 (0.15-0.23)	0.98 (0.97-0.98)	8.6 (5.9-12.4)	0.83 (0.79-0.87)	10 (7-15)	0.82 (0.79-0.85)
	NSCLC	0.20 (0.13-0.29)	0.97 (0.94-0.98)	6.5 (3.6-11.8)	0.82 (0.76-0.90)	8 (4-15)	0.79 (0.75-0.82)
	SCLC	0.27 (0.18-0.39)	0.97 (0.94-0.99)	9.9 (5.6-17.6)	0.75 (0.65-0.86)	13 (7-24)	0.79 (0.76-0.83)
NY-ESO-1	Lung cancer	0.17 (0.10-0.26)	0.98 (0.96-0.99)	7.0 (4.6-10.8)	0.85 (0.78-0.93)	8 (5-13)	0.90 (0.87-0.92)
	NSCLC	0.25 (0.14-0.40)	0.95 (0.86-0.98)	4.9 (2.6-9.1)	0.79 (0.70-0.90)	6 (3-11)	0.67 (0.63-0.71)
	SCLC	0.10 (0.06-0.18)	0.98 (0.96-0.99)	5.2 (2.1-13.0)	0.91 (0.85-0.98)	6 (2-15)	0.96 (0.94-0.97)
Survivin	Lung cancer	0.19 (0.12-0.29)	0.99 (0.97-0.99)	14.5 (4.6-45.8)	0.82 (0.74-0.92)	18 (5-60)	0.96 (0.93-0.97)
c-myc	Lung cancer	0.14 (0.11-0.18)	0.98 (0.96-0.99)	8.4 (3.9-19.79)	0.87 (0.84-0.91)	10 (4-21)	0.45 (0.41-0.49)
Cyclin B1	Lung cancer	0.18 (0.14-0.24)	0.98 (0.96-0.99)	8.1 (4.3-15.4)	0.83 (0.79-0.89)	10 (5-19)	0.91 (0.88-0.93)
CAGE	Lung cancer	0.14 (0.09-0.21)	0.98 (0.96-0.99)	6.2 (3.5-11.0)	0.88 (0.82-0.94)	7 (4-13)	0.90 (0.87-0.92)
GBU4-5	Lung cancer	0.07 (0.02-0.22)	0.98 (0.94-0.99)	3.7 (0.5-26.7)	0.95 (0.85-1.05)	4 (0-31)	0.91 (0.88-0.93)
p16	Lung cancer	0.08 (0.03-0.22)	0.97 (0.94-0.99)	3.1 (1.1-8.8)	0.95 (0.87-1.03)	3 (1-10)	0.91 (0.88-0.93)
SOX2	SCLC	0.14 (0.06-0.30)	0.99 (0.97-0.99)	10.7 (5.7-20.0)	0.88 (0.77-0.99)	12 (6-24)	0.93 (0.90-0.95)
HuD	SCLC	0.17 (0.12-0.24)	0.99 (0.98-1.00)	21.3 (5.9-76.8)	0.84 (0.77-0.90)	25 (7-96)	0.82 (0.79-0.85)

TAAbs, tumour-associated autoantibodies; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratios; AUC, area under the curve

A systematic review by Tang ZM et al. (2017) was the first to evaluate the diagnostic values of serum single and multiple TAAbs in patients with lung cancer, especially for the early detection. A total of 31 articles with single autoantibody and 39 with multiple autoantibodies were included. Seven articles were used for the meta-analysis; out of 12 tests, eight were based on the same panel of 6-TAAbs for EarlyCDT-Lung (p53, NY-ESO-1, CAGE, GBU4-5, Annexin1, and SOX2; n=4,957) and four tests analysed the same panel of 7-TAAbs for EarlyCDT-Lung (p53, CAGE, NY-ESO-1, GBU4-5, SOX2, MAGEA4, and HuD; n=3,613). The pooled sensitivity and specificity forest plots were used to evaluate the diagnostic value of the same panel of autoantibodies, and the threshold effect was assessed using a SROC curves. For the diagnosis of patients with **all stages** lung cancer, individual TAAbs showed low sensitivity (ranged from 13.8% to 99.0%; mean 55.2%) and specificity (ranged from 19.7% to 100.0%; mean 84.4%) whereas combination of multiple autoantibodies offered relatively high values: sensitivity 70.3% (ranged from 30.0% to 100.0%) and specificity 86.3% (ranged from 43.0% to 97.3%). For single TAAb in the diagnosis of **early-stage** lung cancer, the sensitivities ranged from 24.1% to 100.0% (mean: 55.6%) and specificities ranged from 80.0% to 99.2% (mean: 89.3%). For the panel of mixed TAAbs, the sensitivities ranged from 27.5% to 100.0% (mean: 71.1%) while specificities ranged from 43.8% to 100.0% (mean: 87.1%) (**Table 3**). For the **meta-analysis** of a same panel of autoantibodies in patients at **all stages** of lung cancer, the pooled results of the panel of 6-TAAbs were: sensitivity 38.0% (95% CI 0.35 to 0.40), specificity 89.0% (95% CI 0.86 to 0.91), diagnostic accuracy 65.9% (range 62.5% to 81.8%), AUC 0.52 (0.48 to 0.57), while the summary estimates of 7-TAAbs were: sensitivity 47.0% (95% CI 0.34 to 0.60), specificity 90.0% (95% CI 0.89 to 0.92), diagnostic accuracy 78.4% (range 67.5% to 88.8%), AUC 0.90 (0.87 to 0.93). For the **meta-analysis** of the same panel of autoantibodies in patients at **early-stage** of lung cancer, the sensitivities of both panels of 7-TAAbs and 6-TAAbs were 40.0% and 29.7%, while their specificities were 91.0% and 87.0%, respectively (**Table 4**).[28, level II-2]

Table 3: Diagnostic values (single versus multiple TAAbs) for all- and early-stage lung cancer

TAAbs	All stages lung cancer		Early-stage lung cancer	
	Sensitivity	Specificity	Sensitivity	Specificity
Single	55.2%	84.4%	55.6%	89.3%
Combination	70.3%	86.3%	71.1%	87.1%

TAAbs, tumour-associated autoantibodies

Table 4: Diagnostic values (6-TAAbs versus 7-TAAbs) for all- and early-stage lung cancer

TAAbs	All stages lung cancer				Early-stage lung cancer	
	Sensitivity	Specificity	Accuracy	AUC	Sensitivity	Specificity
EarlyCDT-Lung (6-TAAbs)	38.0%	89.0%	65.9%	0.52	29.7%	87.0%
EarlyCDT-Lung (7-TAAbs)	47.0%	90.0%	78.4%	0.90	40.0%	91.0%

TAAbs, tumour-associated autoantibodies; AUC, area under the curve

Recently, the Early Diagnosis of Lung Cancer Scotland (ECLS) is the first trial conducted worldwide as a phase IV (prospective screening) evaluation of a blood-based biomarker antibody panel for early detection of lung cancer. The trial enrolled a total of 12,208 participants (adult age 50 to 75 years at increased risk of developing lung cancer), randomised to undergo either the test (6,087 individuals) or standard care (6,121 individual). Patients who had positive test then underwent LDCT scan at baseline and then every six months for two years. Participants allocated to the control arm and those who were test-negative received standard clinical care in the National Health Service (NHS) in Scotland following national guidelines for identification and management of symptoms suggestive of lung cancer with no further study investigations. Outcomes were assessed at two years post-randomisation using validated data on cancer occurrence, cancer staging, mortality and comorbidities. During the study, 127 lung cancers were diagnosed (56 in the intervention arm and 71 in the control). Of the intervention arm, 9.8% (598/6,087) had a positive result and 3.0% (18/598) of these had a confirmed case of lung cancer. In the test-negative EarlyCDT-Lung, 0.7% (38/5,489) had confirmed lung cancers. The trial met its primary endpoint, with fewer late-stage (III/IV) lung cancers diagnosed in the intervention arm (33 out of 56 [58.9%]) than the control (52 out of 71 [73.2%]), accounting for 14.3% absolute risk reduction. This yielded a hazard ratio at two years favouring the test of 0.64 (95% CI 0.41 to 0.99; p=0.043). Indirectly, more early-stage (I/II) lung cancers were diagnosed in the intervention arm (23 [41%] compared with 19 [27%]). At two years follow-up, the EarlyCDT-Lung test had an estimated sensitivity of 52.2% (95% CI 30.6 to 73.2%) for stage I/ II disease and 18.2% (95% CI 7.0 to 35.5%) for stage III/IV disease, with specificity of 90.3% (95% CI 89.6 to 91.1%) for stage I/ II disease and 90.2% (95% CI 89.4 to 91.0%) for stage III/IV disease. The positive predictive value (PPV) was 2.0% (95% CI 1.0–3.5%) for stage I/II disease and 1.0% (95% CI 0.4–2.2%) for stage III/ IV disease, while the negative predictive value (NPV) was 99.8% (95% CI 99.6 to 99.9%) for stage I/II disease and 99.5% (95% CI 99.3 to 99.7%) for stage III/IV disease in the population studied (Table 5). There were no significant differences in lung cancer mortality (intervention arm 17 out of 6,087 [0.28%] versus control arm 24 out of 6,121 [0.39%]) and all-cause mortality (intervention arm 87 out of 6,087 [1.43%] versus control arm 108 out of 6,121 [1.76%]) after two years.[29, level I]

Table 5: Estimated EarlyCDT-Lung test performance characteristics (6-month, 1-year and 2-year)

	Test-positive	Test-negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Subjects	598	5489				
Stage of lung cancer 6 months after randomisation (*post hoc*)						
I/II	7 (1.2)	2 (0.0)	77.8 (40.0–97.2)	90.3 (89.5–91.0)	1.2 (0.5–2.4)	100.0 (99.9–100.0)
III/IV	5 (0.8)	8 (0.2)	38.5 (13.9–68.4)	90.2 (89.5–91.0)	0.8 (0.3–1.9)	99.9 (99.7–99.9)
I–IV	12 (2.0)	10 (0.2)	54.6 (32.2–75.6)	90.3 (89.6–91.1)	2.0 (1.0–3.5)	99.8 (99.7–99.9)
Stage of lung cancer 1 year after randomisation (*post hoc*)						
I/II	9 (1.5)	4 (0.1)	69.2 (38.6–90.9)	90.3 (89.5–91.0)	1.5 (0.7–2.8)	99.9 (99.8–100.0)
III/IV	6 (1.0)	14 (0.2)	30.0 (11.9–54.3)	90.2 (89.5–91.0)	1.0 (0.4–2.2)	99.7 (99.6–99.9)
I–IV	15 (2.5)	18 (0.3)	45.5 (28.1–63.6)	90.4 (89.6–91.1)	2.5 (1.4–4.1)	99.7 (99.5–99.8)
Stage of lung cancer 2 years after randomisation						
I/II	12 (2.0)	11 (0.2)	52.2 (30.6–73.2)	90.3 (89.6–91.1)	2.0 (1.0–3.5)	99.8 (99.6–99.9)
III/IV	6 (1.0)	27 (0.5)	18.2 (7.0–35.5)	90.2 (89.4–91.0)	1.0 (0.4–2.2)	99.5 (99.3–99.7)
I–IV	18 (3.0)	38 (0.7)	32.1 (20.3–46.0)	90.4 (89.6–91.1)	3.0 (1.8–4.7)	99.3 (99.1–99.5)

Most studies in Europe were using 7-TAAbs panel of EarlyCDT-Lung (p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2) for early lung cancer detection. Since there are noticeable differences in the genetic makeup of Europeans and Asian lung cancer patients, this panel of TAAbs may not be ideal for the Asian populations, and a similar study needs to be performed to confirm these results. Shengxiang Ren et al. (2018) conducted a large-scale, multicentre study at six medical centres in China to validate the clinical value of 7-TAAbs with different panel of p53, GAGE7, PGP9.5, CAGE, MAGEA1, SOX2 and GBU4-5 for early detection of lung cancer among 2,308 Chinese population. Sensitivity and specificity of this TAAbs panel were then compared with traditional tumour biomarkers including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 fragment 21-1 (CYFRA21-1) in lung cancer patients with different disease stages. In addition, the utility of the 7-TAAbs panel in combination with a CT scan were analysed to achieve higher diagnostic accuracy for 540 patients presenting with ground-glass nodules (GGNs) and/ or solid nodules. The study indicated that immunoassays of the 7-TAAbs in combination enhanced cancer detection and achieved a panel sensitivity of 61% and panel specificity of 90% (**Figure 4A**). Subgroup analyses was performed to investigate the diagnostic value of the 7-TAAbs panel in patients with different disease stages and histological types and in control groups. The sensitivities ranged from 59% to 64% in NSCLC patients, with a sensitivity of 62% in stage I, 59% in stage II, 62% in stage III, and 64% in stage IV disease. The specificities ranged from 76% to 94% in control groups, with a specificity of 91% in benign lung diseases, 76% in other cancers, 94% in autoimmune diseases, and 89% in healthy controls (**Figure 4A and 4B**). When compared to sensitivity values of traditional tumour biomarkers, the 7-TAAbs panel showed a higher sensitivity in the early stages of lung cancer (stage I & II, 60%; limited-stage SCLC, 59%) than CEA, NSE, and CYFRA 21-1. In the same way, combination of 7-TAAbs panel and CT scan significantly improved the PPV when compared with TAAbs panel alone (95.0% versus 85.2%; $p<0.001$) or with CT scan alone (95.0% versus 69.0%; $p<0.001$) (**Figure 4D**). In comparison with CT alone, a combination of 7-TAAbs panel and CT significantly increased the diagnostic accuracy of malignant lesions from a PPV of 57.6% to 90.4% ($p<0.001$). For 110 patients with radiological GGNs and/ or nodules ≤8 mm in size, 64 were pathologically confirmed. In these patients, the PPV was improved from 63.4% to 89.7% ($p=0.013$). Similarly, for patients with GGNs and/ or nodules between 8 and 20 mm and >20 mm in size, the PPV was increased from 50.8% to 90.5% ($p<0.001$) and from 63.4% to 90.7% ($p<0.001$), respectively (**Figure 5A**). The combination of 7-TAAbs assay and CT also improved the PPV in patients with pure and mixed GGNs from 80.9% and 79.3% to 94.4% and 94.7%, respectively. In patients with just nodules, a similar trend was observed: the PPV was only 50.2% with CT alone but was increased to 89.2% with the combination ($p <0.001$) (**Figure 5B**). Moreover, 7-TAAbs assay plus CT significantly decreased the false positive rate in patients with distinct size and pathological types GGNs and/ or nodules (**Figure 5C and 5D**).[30, level II-2]

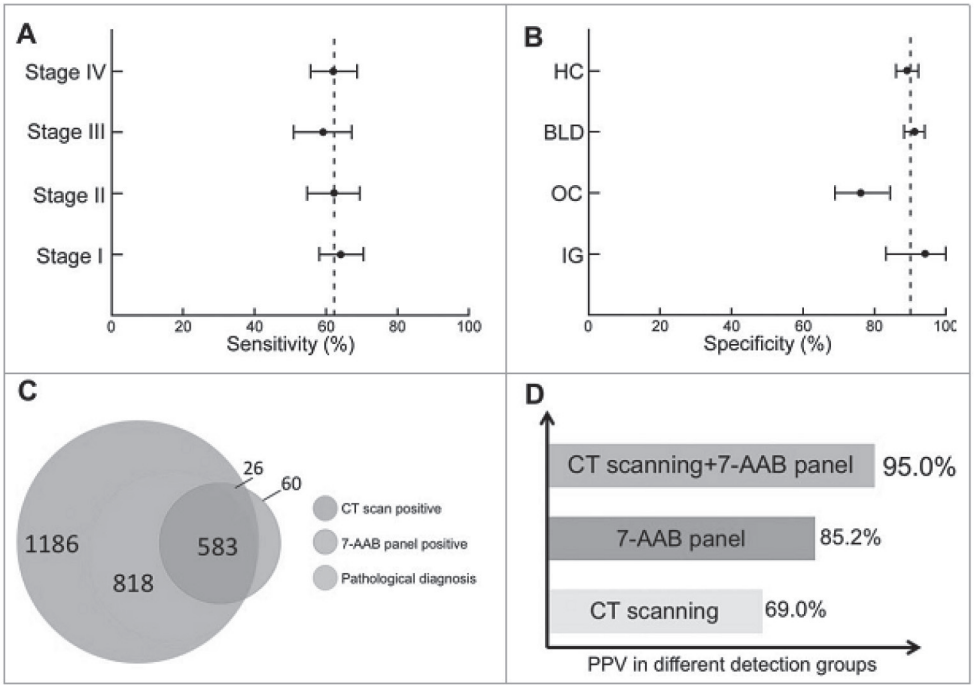

Figure 4: Diagnostic performance of the 7-TAAbs panel (A) sensitivity (patients with lung cancer); (B) specificity (control groups); (C) Venn diagram for patients who received the 7-TAAbs panel and/ or CT; (D) positive predictive value (PPV) of the 7-TAAbs panel combined with CT in lung cancer patients. IG, autoimmune disease; BLD, benign lung disease; HC, healthy controls; OC, other cancers.

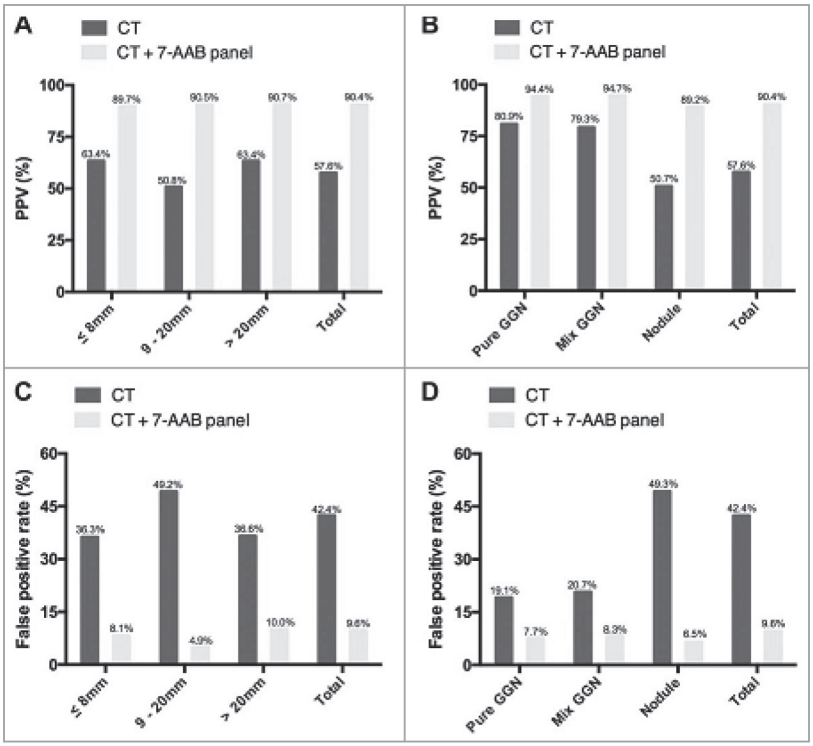

Figure 5: Effectiveness of the 7-TAAbs panel in patients with radiological ground-glass nodules (GGNs) and/ or nodules. (A) sub-analysis of PPV according to size; (B) sub-analysis of PPV according to pathological type; (C) sub-analysis of the false-positive rate according to size; (D) sub-analysis of the false-positive rate according to pathological type.

This prospective observational study by Borg M et al. (2021) evaluated the performance of the seven-panel TAAb assay (EarlyCDT-Lung) in a high-risk cohort of 246 patients referred from their general practitioner (GP) on suspicion of lung cancer at the Department of Medicine, University Hospital of Southern Denmark. Blood samples were taken at first visit and patients underwent diagnostic work-up on suspicion of lung cancer resulting in either a malignant diagnosis or ruled out cancer. Sensitivity and specificity of the EarlyCDT-Lung were calculated in the cohort and subgroups based on smoking history, age, and lung cancer stage, including patients currently eligible for LDCT screening in the United States. A total of 75 patients (30%) turned out to have lung cancer whereby 5% (12/246) with lung metastases originating from primary tumours in other organs and 65% (159/246) where cancer was ruled out. Overall sensitivity in the cohort was 33% (25/75) for lung cancer and 31% (27/87) for primary lung cancer and lung metastases combined. Assay specificity for the detection of both lung cancer and for any malignant diagnosis with lung metastases was 88%. Sensitivity of the assay in the subgroup of patients with at least 10 tobacco pack years was 33% while the sensitivity measured in patients with at least 50 tobacco pack years was 44%. In subgroups based on age, the assay yielded a sensitivity of 11% in patients 60 years or below. When tested in subgroups of patients aged 61 to 75 and >75 years, the sensitivities were 31% and 55%, respectively. The assay sensitivity in stage I-II lung cancer patients was 21%, while this was 40% in stage III-IV disease. In a subgroup of patients that met current LDCT screening criteria, the sensitivity and specificity were 37% and 81%, respectively (**Table 6**).[31, level II-2]

Table 6: Performance of the EarlyCDT-Lung test in different subgroups of patients

Total cohort	Sensitivity; n (95 % CI)	Specificity; n (95 % CI)	PPV	NPV
Lung cancer	0.33; 25/75 (0.23–0.45)	0.88; 150/171 (0.82–0.92)	0.54	0.75
Any malignant tumor	0.31; 27/87 (0.22–0.42)	0.88; 140/159 (0.82–0.93)	0.59	0.70
Smoking history subgroups				
Screening group#	0.37; 13/35 (0.21–0.55)	0.81; 39/48 (0.67–0.91)	0.59	0.64
10+ pack years	0.33; 21/63 (0.22–0.46)	0.86; 80/93 (0.77–0.92)	0.62	0.66
20+ pack years	0.33; 18/54 (0.21–0.47)	0.84; 58/69 (0.73–0.92)	0.62	0.62
30+ pack years	0.34; 15/44 (0.20–0.50)	0.81; 43/53 (0.68–0.91)	0.60	0.60
40+ pack years	0.35; 11/31 (0.19–0.55)	0.76; 31/41 (0.60–0.88)	0.52	0.61
50+ pack years	0.44; 8/18 (0.22–0.69)	0.79; 15/19 (0.54–0.94)	0.67	0.60
Age subgroups				
Age ≤ 60	0.11; 2/18 (0.01–0.35)	0.94; 59/63 (0.85–0.98)	0.33	0.79
Age 61–75	0.31; 11/35 (0.17–0.49)	0.87; 69/79 (0.78–0.94)	0.52	0.74
Age >75	0.55; 12/22 (0.32–0.76)	0.76; 22/29 (0.56–0.90)	0.63	0.69
Lung cancer stage subgroups				
Stage I-II lung cancer	0.21; 6/28 (0.08–0.41)	0.88; 150/171 (0.82–0.92)	0.22	0.87
Stage III-IV lung cancer	0.40; 19/47 (0.26–0.56)	0.88; 150/171 (0.82–0.92)	0.47	0.84
Sex				
Male	0.32; 13/40 (0.19–0.49)	0.86; 76/88 (0.77–0.93)	0.52	0.74
Female	0.34; 12/35 (0.19–0.52)	0.89; 74/83 (0.80–0.95)	0.57	0.76

95% CI, 95% confidence interval; # The screening group consisted of participants aged 55–80 years and with at least 30 tobacco pack years; PPV, positive predictive value; NPV, negative predictive value.

Recently, the EarlyCDT-Lung test was evaluated as part of the German Lung Cancer Screening Trial (LUSI) whereby participant selection within the trial were using a nested case-control design. The test was performed for all participants (n=2,022) with lung cancer detected via LDCT and with available blood samples taken at detection. Two set of control (n=180) were selected at the end of follow-up: the first was a random selection of 90 cancer-free participants (baseline controls, BC) and second among cancer-free participants with suspicious imaging findings (suspicious nodules controls, SNC). In the case group, the EarlyCDT-Lung produced *"High Level"* test results for six out of the 46 CT-detected lung cancer patients. This resulted in a detection sensitivity of 13.0% (95% CI 4.9 to 26.3%). Specificity was estimated at 88.9% (95% CI 80.5 to 94.5%) in the BC group, and 91.1% (95% CI 83.2 to 96.1%) among controls presenting CT-detected nodules (**Table 7**). Within the subset of participants with nodules <10 mm in diameter, the test produced *"High Level"* results for one out of 11 CT-detected lung cancer patients, yielding a sensitivity of 9.1% (95% CI 0.23 to 41.3%). For participants with nodules ≥10 mm, the estimated sensitivity was 14.7% (95% CI 4.9 to 31.1%).[32, level II-3]

Table 7: LDCT result by EarlyCDT-Lung results for lung cancer cases and cancer-free controls

	EarlyCDT®-Lung test result										
	Lung cancer			No lung cancer (BC)				No lung cancer (SNC)			
	H (n=6)	NS (n=40)	P	H (n=3)	M (n=7)	NS (n=80)	P	H (n=4)	M (n=4)	NS (n=82)	P
No nodules	0	0	1	3 (100.0)	1 (14.3)	48 (60.0)	0.15	0	0	0	0.11
LDCT result (%)											
Non-suspicious	0	0		0	4 (57.1)	22 (27.5)		0	0	0	
Immediate recall	6 (100)	36[§] (90.0)		0	0	2 (2.5)		0	1 (25.0)	4 (4.9)	
3-month recall	0	0		0	0	1 (1.2)		2 (50.0)	0	10 (12.2)	
6-month recall	0	4 (10.0)		0	2 (28.6)	7 (8.8)		2 (50.0)	3 (75.0)	68 (82.9)	

[§], for one subject, the CT scan evaluation at round 2 was deemed suspicious (with immediate recall) even in the absence of pulmonary nodules, due to the identification of atelectasis (collapsed lung) in the scan images. LDCT, low dose computed tomography; H, high test results; M, moderate level test result; NS, non-significant level test result.

5.2.4 Safety

Only one study revealed the incidents of adverse events or compilations. In the ECLS trial, five adverse events directly related to the EarlyCDT-Lung test were reported and all were considered minor (collection of blood sample). For those in the intervention arm, there was one injection site haematoma, one panic attack, and one pre-syncope. In the control arm, there were two episodes of syncope were observed.[29, level I]

5.2.5 Economic implication

Economic evaluation of an autoantibody test (AABT) or EarlyCDT-Lung has been very limited and to date, two cost-effectiveness analyses have been undertaken and were included in this review.

The first study was on at the financial analysis of the AABT performed by Edelsberg J et al. (2018). A decision-analytic model with two alternative strategies were created for nodule evaluation: one with AABT followed by biopsy if AABT-positive and CT surveillance if AABT-negative, and one with CT surveillance alone. Patients in the model population were assumed to have incidentally detected nodules of diameter 8-30 mm and an estimated 5-60% risk of lung cancer with 23.6% prevalence of malignancy. For each strategy, the model projects life-years (unadjusted and quality-adjusted) for 1,000 persons as well as expected

costs including AABT, CT, biopsy (i.e., diagnostic follow-up), and treatment, as appropriate. Cost-effectiveness was calculated using the ratio of the difference in expected costs to the corresponding differences in life-years and quality-adjusted life-years (QALYs) for the AABT strategy and CT surveillance alone strategy, respectively. The perspective of the analysis was the US healthcare system while future costs and life-years were discounted at 3% per year. In the base-case analyses, 95 out of 1,000 patients (9.5%) were assumed to have lung cancer. With use of the AABT set at a sensitivity/specificity of 41%/93%, expected costs would be higher by USD 949,442 (USD 949 per person) but life years would be higher by 53 (0.05 per person), resulting in a cost per life-year gained of USD 18,029 and a cost per QALY gained of USD 24,330. With use of the AABT set at a sensitivity/specificity of 28%/98%, corresponding cost-effectiveness ratios would be USD 18,454 and USD 24,833 (**Table 8**). Sensitivity analyses indicated that the cost-effectiveness of AABT was sensitive to the prevalence of malignancy, the sensitivity/specificity of the AABT, and the probability of stage progression among malignant nodules. Hence, they concluded that using AABT as an aid in the early diagnosis of lung cancer in patients with incidentally detected nodules who are estimated to have an intermediate-risk of lung cancer and a rescheduled for CT surveillance alone is likely to be a cost-effective use of health care resources (cost-effectiveness ratios less than USD 50,000 per QALY have long been considered to be a worthwhile investment of scarce healthcare resources in the US).[33]

Table 8: Outcomes (discounted) with use of AABT versus CT surveillance alone for early diagnosis of lung cancer in patients who have incidentally detected pulmonary nodules, are at intermediate risk, and were scheduled for CT surveillance alone*

	CT Surveillance	AABT	Difference
Sensitivity/Specificity AABT = 41% / 93%			
Life-Years	12,130	12,183	53
QALYs	9,793	9,832	39
Total Cost	$4,039,582	$4,989,024	$949,442
Cost per Life-Year Gained	—	—	$18,029
Cost per QALY Gained	—	—	$24,330
Sensitivity/Specificity AABT = 28% / 98%			
Life-Years	12,130	12,167	37
QALYs	9,793	9,821	27
Total Cost	$4,039,582	$4,722,069	$682,487
Cost per Life-Year Gained	—	—	$18,454
Cost per QALY Gained	—	—	$24,833

AABT, autoantibody test; CT: computed tomography; QALY, quality-adjusted life-year

*Model population assumed to comprise 1,000 patients

Another analysis by Sutton AJ et al. (2020) compared the cost-effectiveness between EarlyCDT-Lung in addition to CT surveillance and the current practice of surveillance alone for patients with indeterminate pulmonary nodules (IPNs), as recommended in the British Thoracic Society Guidelines. A model consisting of a combination of a decision tree and Markov model was developed using the outcome measure of the QALY (**Figure 6 and 7**). A life-time time horizon was adopted while data required to parameterise the economic model were obtained through the extensive use of secondary sources. All costs are in pounds sterling (£) for the 2016/17 price year. Discounting was applied at 3.5% for costs and outcomes, with the analysis conducted from the health-care provider perspective. The results were presented using the incremental cost-effectiveness ratio (ICER). Two alternative pairs of test accuracy parameters were also considered for the AABT. Scenario A (sensitivity 41% specificity 93%) with its higher sensitivity and lower specificity compared to Scenario B (sensitivity 28% Specificity 98%). This analysis took a baseline price of the AABT to be £70, but also investigated the maximum price the test could be set at.[34]

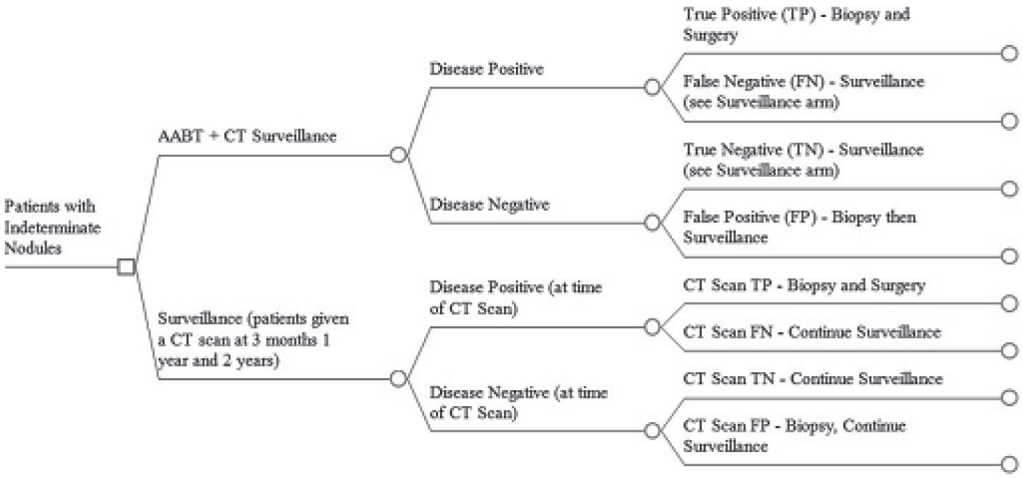

Figure 6: Testing pathways for the AABT and surveillance strategies

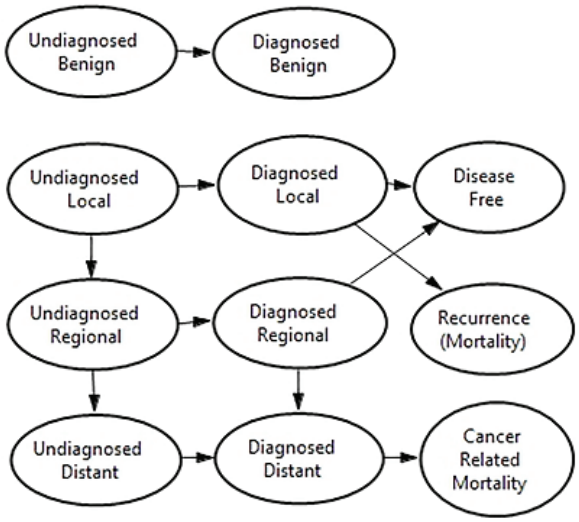

Figure 7: Markov model

Scenario A: sensitivity 41% specificity 93%

At a price of £70 per test, AABT plus CT surveillance is more costly and more effective in terms of QALYs gained than surveillance alone (**Table 9**). Given that the ICER is well under £20,000, AABT plus CT surveillance can certainly be regarded as cost-effective. Probabilistic sensitivity analysis (PSA) demonstrated that AABT plus CT surveillance is always more costly than surveillance alone and almost always (99.4%) more effective in terms of QALYs gained. The cost-effectiveness acceptability curve (CEAC) showed that AABT plus CT surveillance is more likely to be cost-effective at a willingness to pay (WTP) for the QALY of £2,000 and above. At a WTP of £20,000/QALY, AABT is approximately 99% likely to be cost-effective (**Figure 8**). It can be seen that the price of the AABT can be up to £1,150.37 and still have greater net-monetary benefit (NMB) than surveillance alone (**Figure 9**).[34]

Table 9: Cost-effectiveness of AABT plus CT surveillance versus surveillance alone (Scenario A)

Scenario A:					
	Total Cost	***Inc. Cost***	***QALYs Gained***	***Inc. QALYs***	***ICER (Cost/QALY)***
Surveillance	£2,261		10.6850		
AABT+Surveillance	£2,410	£149	10.7465	0.0614	£2,417

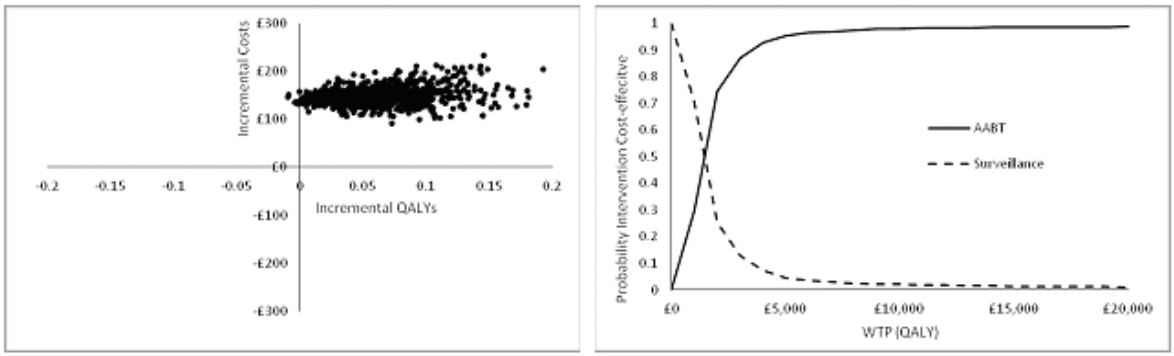

Figure 8: Probabilistic sensitivity analysis results for Scenario A for 1,000 model runs showing the cost effectiveness plane and the cost-effectiveness acceptability curve for Scenario A.

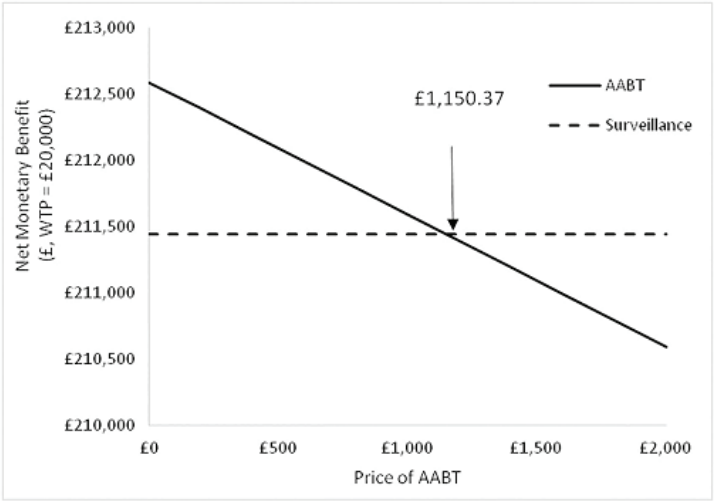

Figure 9: Net monetary benefit at a WTP=£20,000/QALY for the AABT plus CT surveillance and surveillance strategies with variation in the price of the AABT for Scenario A

Scenario B: sensitivity 28% specificity 98%

Similar to Scenario A, when the price for AABT=£70, and adopting the test accuracy parameters as described for Scenario B, AABT plus CT surveillance is more costly and more effective in terms of QALYs gained than surveillance alone (ICER £2,121). Again, given the low ICER value, AABT can certainly be regarded as cost-effective (**Table 10**). It can be seen from the results of the PSA for Scenario B (**Figure 10**) that AABT plus CT surveillance is always more costly than surveillance alone and always more effective in terms of QALYs gained. The CEAC showed that AABT plus CT surveillance is more likely to be cost-effective at a WTP for the QALY of £3,000 and above. At a WTP of £20,000/QALY, AABT is more than 98% likely to be cost-effective. The AABT can be priced up to £887.28, and be more cost-effective than surveillance alone (**Figure 11**).[34]

Table 10: Cost-effectiveness of AABT plus CT surveillance versus surveillance alone (Scenario B)

Scenario B:					
	Total Cost	***Inc. Cost***	***QALYs Gained***	***Inc. QALYs***	***ICER (Cost/QALY)***
Surveillance	£2,261		10.6850		
AABT+Surveillance	£2,358	£97	10.7308	0.0457	£2,121

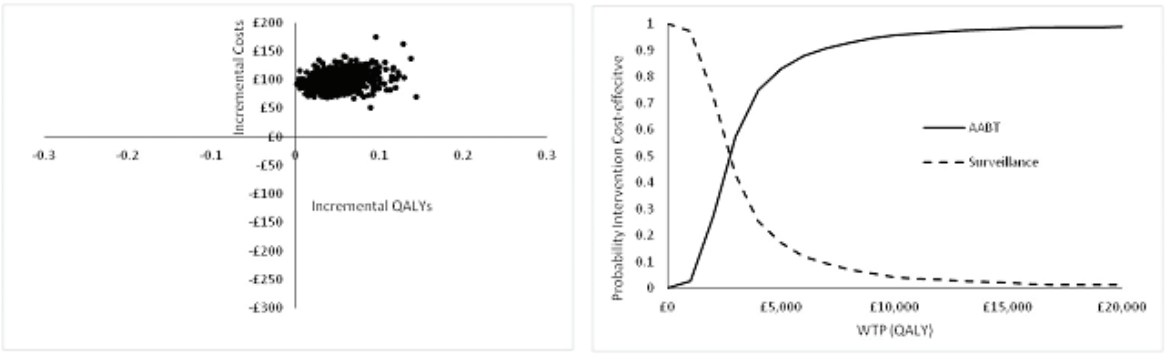

Figure 10: Probabilistic sensitivity analysis results for Scenario B for 1,000 model runs showing the cost effectiveness plane and the cost-effectiveness acceptability curve for Scenario B.

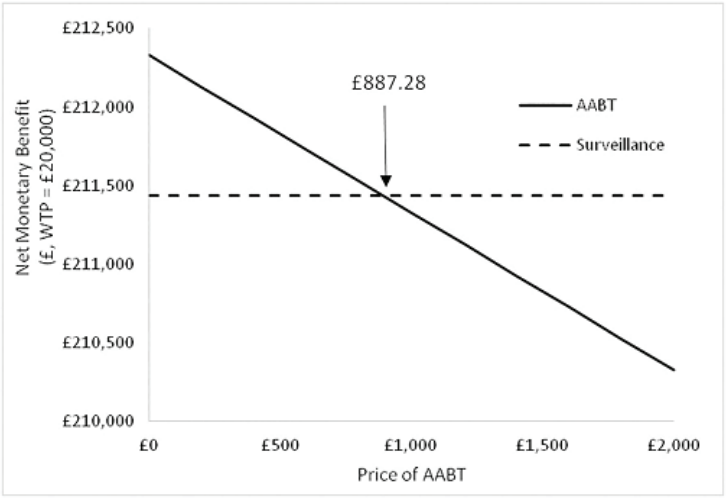

Figure 11: Net monetary benefit at a WTP=£20,000/QALY for the AABT plus CT surveillance and surveillance strategies with variation in the price of the AABT for Scenario B

Analysis of Scenario A versus Scenario B

Given that AABT plus CT surveillance is cost-effective compared to surveillance alone in both scenarios, it is important to establish whether the extra QALYs gained from Scenario A as compared to Scenario B are worth paying for. As shown in **Table 11,** the ICER for AABT plus CT surveillance in Scenario A (compared to Scenario B) is £3,277 which is well below the NICE acceptance threshold of £20,000. Thus, it can be concluded that Scenario A has the most cost-effective test accuracy parameters and as such these should be adopted. It can be seen from the CEAC shown in **Figure 12** that up to a WTP for a QALY of approximately £2,000, surveillance alone is most likely to be the most cost-effective scenario, and then from WTP of approximately £3,000 upwards AABT plus CT surveillance in Scenario A is most likely to be cost-effective. At a WTP for a QALY of £20,000 in Scenario A is approximately 90% likely to be the most cost-effective option, with this probability increasing with increased WTP values. In terms of which test accuracy parameters should be adopted, again the results here are clear, with Scenario A being the preferred option. The PSA supports the main conclusions and indeed provide reassurance that these results are robust to realistic variations in the input parameters. Thus, it can be concluded that the extra sensitivity of Scenario A compared to Scenario B (41% versus 28%) at the expense of some specificity (93% versus 98%) leads to improve patient outcomes that are worth paying for. The results here also demonstrated that at £70, the AABT is significantly under-priced

and could be priced at between approximately £900 and £1,170 (depending on the Scenario) and still be cost-effective based on the NICE acceptance threshold for the QALY.[34]

Table 11: Cost-effectiveness results between Surveillance and AABT for Scenarios A and B

	Total Cost	*Inc. Cost*	*QALYs Gained*	*Inc. QALYs*	*ICER (Cost/QALY)*
Surveillance	£2,261		10.6850		
AABT+Surveillance Scenario B	£2,358	£97	10.7308	0.0457	£2,121.43
AABT+Surveillance Scenario A	£2,410	£52	10.7465	0.0157	£3,277.41

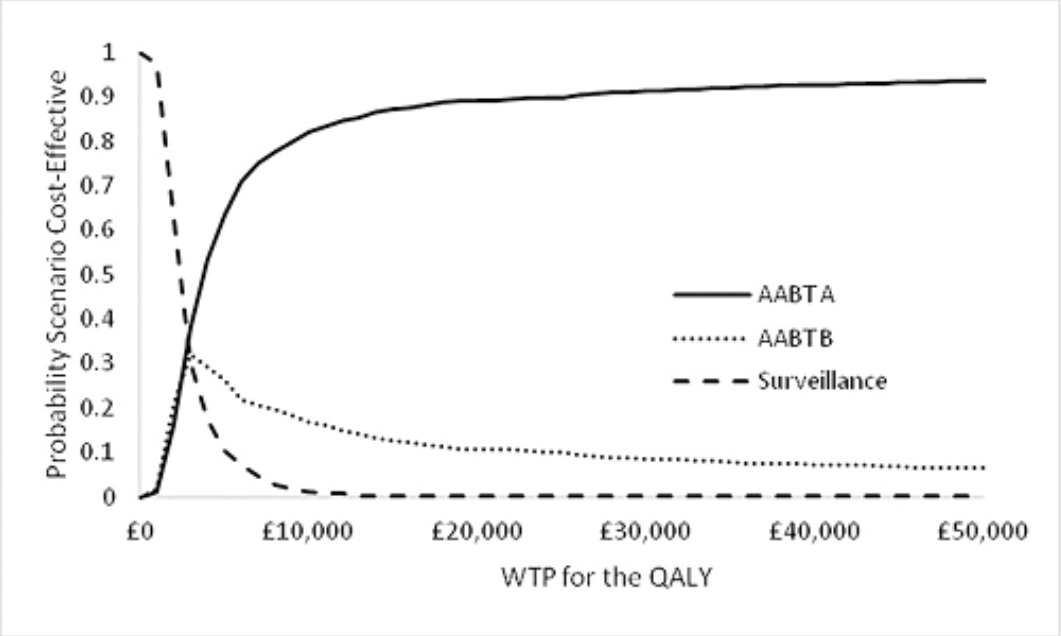

Figure 12: Cost-effectiveness acceptability curve comparing surveillance, AABT plus CT surveillance Scenario A, and AABT plus CT surveillance Scenario B

5.2.6 Organisational

No guideline presently recommends the use of blood-based biomarkers in clinical practice as an initial screening test in those at high-risk although there is now commercially available kit. In addition, the National Institute for Health and Care Excellent (NICE) in their diagnostic guidance published recently on 23rd February 2022 stated that there is not enough evidence to recommend routine use of EarlyCDT-Lung for assessing the risk of lung cancer in solid lung nodules. The committee noted that a better understanding of the population with lung nodules and of the current diagnostic pathway is critical for supporting a linked evidence model for EarlyCDT-Lung and for other new technologies that would be used in the same pathway. Hence, further research is recommended on: [35]

- ✓ The diagnostic accuracy of EarlyCDT-Lung, its performance when used with existing risk models, and its effect on clinical management decisions.
- ✓ Patient and nodule characteristics that may relate to the prevalence of malignant disease and disease progression.
- ✓ Current practice for managing intermediate-risk lung nodules.
- ✓ The clinical consequences of CT surveillance.
- ✓ The likelihood and impact of overtreatment of benign and indolent nodules.

5.2.7 Social, ethical and legal

No evidence retrieved on social, ethical and legal issues related to EarlyCDT-Lung in screening setting.

6.0 PART B: ECONOMIC EVALUATION

The general objective of this economic evaluation was to assess the cost-effectiveness of early cancer detection test compared to no screening. The specific objective was to calculate the incremental cost-effectiveness ratio (ICER) between early cancer detection test for lung (EarlyCDT-Lung) as compared to no screening among high-risk lung cancer patients.

6.1 METHODS

6.1.1 Decision analytic and economic modelling

Computed tomography is the most common imaging procedure for staging and core biopsy is the preferred sampling modality for primary diagnosis of lung cancer. A study indicated that the early screening using LDCT was having low uptake due to reasons like poor recruitment from the general public, low awareness, refusal to be screened, and fear of cancer diagnosis.[37] Therefore, a hypothetical pathway was developed to evaluate the use of early CDT-Lung as compared to no screening alone.

In the beginning, the high-risk population was identified and divided into pathway that either undergo EarlyCDT-Lung screening or no screening. For the patients who tested positive with EarlyCDT-Lung, LDCT plus biopsy were conducted to identify patients either in the early lung cancer stage (stage I and II) or in the late lung cancer stage (stage III and IV). Patients detected negative for EarlyCDT-Lung will not undergo LDCT and biopsy. All cancer patients will undergo treatment. No further action was taken for patients who have no cancer (**Figure 13**).

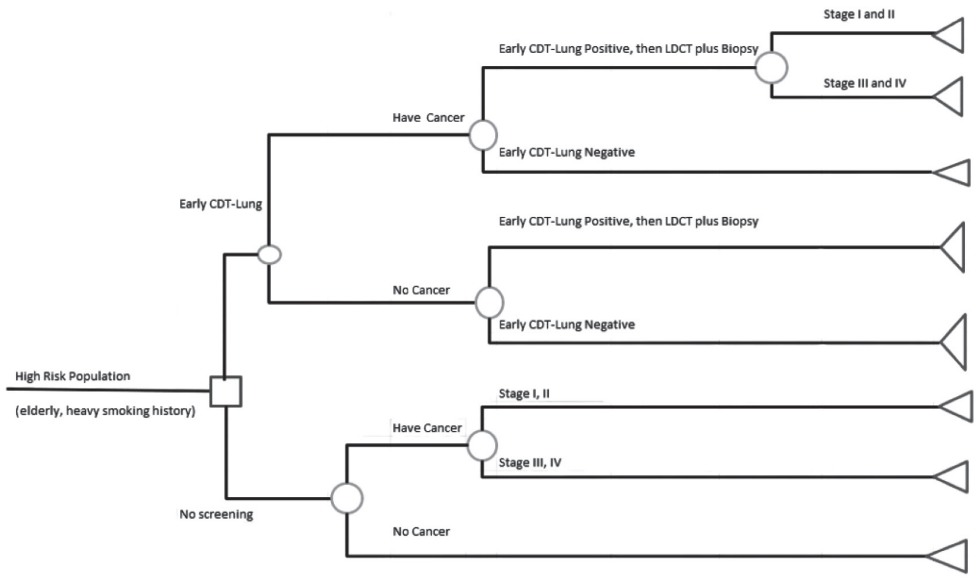

Figure 13: Decision tree model for EarlyCDT-Lung screening and no screening

6.1.2 Model input

Summary of input clinical parameters applied in the model are shown in **Table 12** while **Table 13** illustrated the costs input used.

Table 12: Input clinical parameters

Parameter	Probability	Reference
1-year probability of getting lung cancer among high-risk group	0.001233	Malaysia Cancer Registry (2012-2016)[3]
Sensitivity of EarlyCDT-Lung	0.522	Sullivan FM et al. (2021)[29]
Specificity of EarlyCDT-Lung	0.903	Sullivan FM et al. (2021)[29]
Probability of late-stage cancer (stage III and IV) at diagnosis without early screening	0.935	Malaysia Cancer Registry (2012-2016)[3]

Table 13: Cost input

Cost parameters	Unit cost	Sources of data
LDCT	MYR450.00	Fees Act 1951 - Fees (Medical) (Amendment) Order 2017
Surgical biopsy	MYR450.00	Fees Act 1951 - Fees (Medical) (Amendment) Order 2017
Early lung cancer treatment (stage I, II) (Respiratory Neoplasms SOI 1)	MYR4,523.80	MOH Casemix Data[38]
Late lung cancer treatment (stage III, IV) (Respiratory Neoplasms SOI 3)	MYR10,972.30	MOH Casemix Data[38]

*Cost of EarlyCDT-Lung was based on expert input

6.1.3 Model assumptions

The following key assumptions were used in this model due to limited available data:

1. Eligible high-risk population was calculated based on Malaysia population that is 50 years old and above (DOSM 2021) and number of smokers in this age group (NHMS 2015).
2. Assumption of 100% uptake for EarlyCDT-Lung screening for all the patients.
3. This model did not include the sensitivity and specificity of LDCT and biopsy.
4. For the no screening pathway, it was assumed that the lung cancers were diagnosed and treated at more advanced stages.
5. Early lung cancer treatment applied for stage I and stage II while late lung cancer treatment applied for stage III and stage IV.
6. The management cost for early lung cancer and late lung cancer treatment was obtained from MOH Casemix cost of handling respiratory neoplasm according to the severity of illness (SOI).

6.2 RESULTS

6.2.1 Base-case analysis

In the base case analysis, the model indicated that a positive EarlyCDT-Lung followed by LDCT and biopsy as compared with no screening yielded an ICER of MYR37,169.04 per QALY gained (**Table 14**). Based on the Department of Statistic Malaysia (DOSM) 2022 and National Health & Morbidity Survey (NHMS) 2015 [39-40], it was estimated that 1,353,920 of high-risk population eligible for the screening of EarlyCDT-Lung. The total budget needed for the screening is MYR4.7 billion. Assuming the uptake for the test is 50%, the total budget needed is roughly MYR2.3 billion. However, this estimated budget did not include the treatment cost needed due to late detection of cancer.

Table 14: Incremental cost-effectiveness ratio (ICER) for base case

Strategy	Cost per screening	ICER
EarlyCDT-Lung then LDCT plus biopsy	MYR3,593.17	MYR37,169.04
No screening	MYR14.12	

6.2.2 Sensitivity analysis

One way sensitivity analysis was performed to determine the parameters that may affect the ICER by varying the value of the clinical parameters and costs. The findings from the analysis are illustrated in **Table 15** and presented as tornado diagram (**Figure 14**) to demonstrate the ICER obtained from different scenarios in comparison to the deterministic ICER. Result suggested that the cost of EarlyCDT-Lung is the major factor that influenced the cost-effectiveness ratio.

Table 15: One way sensitivity analysis

Parameters	Range	ICER (MYR)	
		Minimum	Maximum
BASE CASE ICER			
Cost of EarlyCDT-Lung	MYR350.00 - MYR4,375.00	18,994.97	46,256.08
Cost of surgical biopsy	MYR225.00 - MYR675.00	36,944.04	37,282.04
Cost of LDCT	MYR225.00 - MYR675.00	36,944.04	37,282.04
Cost of early treatment for lung cancer	MYR3,994.06 - MYR4,971.31	37,168.06	37,169.87
Cost of late treatment for lung cancer	MYR5,958.29- MYR13,985.66	37,145.02	37,209.02
Sensitivity of EarlyCDT-Lung	0.306 - 0.732	37,094.26	37,246.39
Specificity of EarlyCDT-Lung	0.896 - 0.910	34,713.93	40,008.59

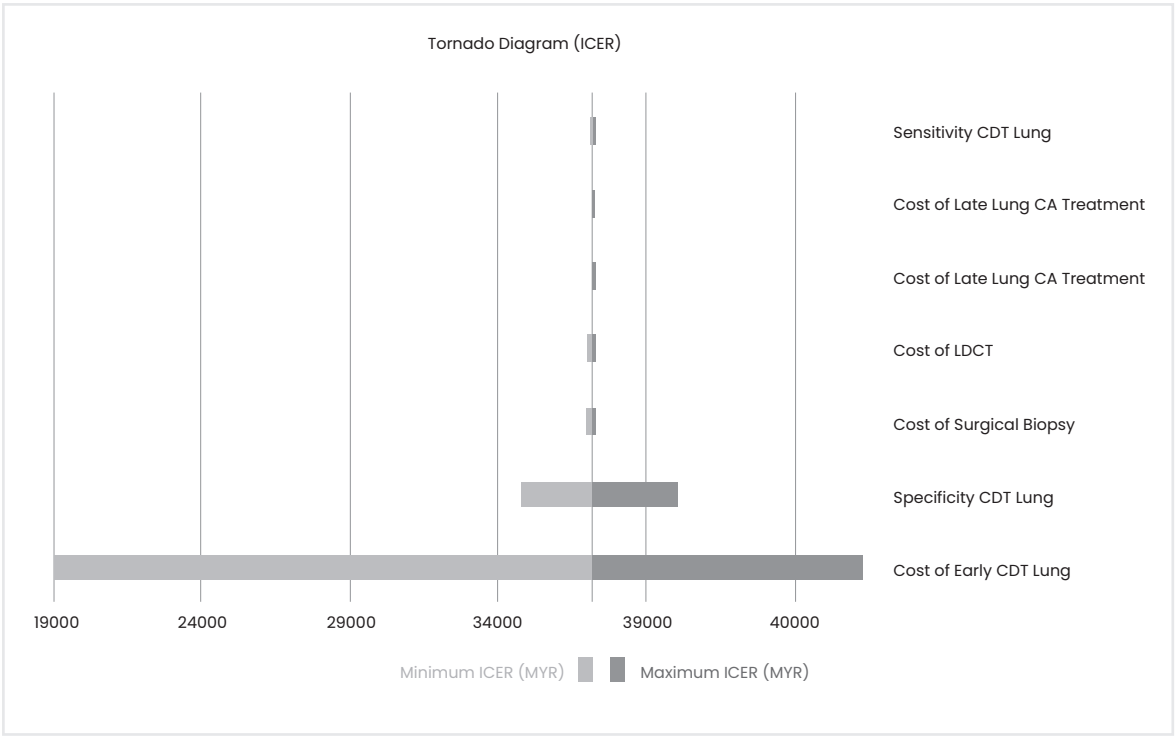

Figure 14: Tornado diagram for one-way sensitivity analysis

7.0 DISCUSSION

This review was designed to compare the overall diagnostic performance of seven autoantibodies (7-TAAbs) to the tumour-associated antigen panel of the EarlyCDT-Lung test. However, a wide variety of single or combinations of multiple autoantibodies have been reported and may have different diagnostic values for identifying patients at all stages or early-stage of lung cancer from healthy controls or benign diseases. Some of which may contribute to the diagnosis of early-stage lung cancer, while others are likely to have less diagnostic value.

Findings in general indicated that for single or individual TAAb in the diagnosis of **all stages** lung cancer, the sensitivities ranged from 15.0% to 55.2% and the specificities ranged from 84.4% to 98.0%. However, combination or a panel of multiple TAAbs may improve sensitivity (70.3%) but at the cost of specificity (86.3%). For single TAAb in the diagnosis of **early-stage** lung cancer, the sensitivity and specificity were 55.6% and 89.3%, respectively. For the combination or a panel of multiple TAAbs, sensitivity of 71.1% with specificity 87.1% were reported. Our review also demonstrated that the diagnostic value of EarlyCDT-Lung for the same panel of 7-TAAbs appears to be higher than the panel of 6-TAAbs in the diagnosis of lung cancer, either at all stage (sensitivity 47.0% versus 38.0%; specificity 90.0% versus 89.0%; AUC 0.90 versus 0.52) or early-stage disease (sensitivity 40.0% versus 29.7%; specificity 91.0% versus 87.0%). The moderate sensitivity of the test may be due to tumour-induced suppression of immune responses that lead to less autoantibody production and detection.

In comparison with the 7-TAAbs panel of the EarlyCDT-Lung test, a panel of 7-TAAbs used in China was found to achieve a sensitivity of 61.0% and a specificity of 90.0%. This 7-TAAbs panel proved to be better than traditional tumour biomarkers such as CEA, NSE, and CYFRA 21-1 to aid early diagnosis, and its value was consistent across different stages and pathological types of lung cancer, including early-stage lesions presenting as GGNs or solid nodules. This is probably due to a combination of various factors. First, they used different TAAbs - three of the 7-TAAbs panel (GAGE7, MAGE-A1 and PGP9.5) are not included in the EarlyCDT-Lung test. Secondly, the ethnic groups were different. It is theoretically possible that the concentrations of TAAbs and the predominance of certain TAAbs could be different in Chinese populations in comparison with European populations, reflecting the variation of the mutation spectrum between Asian and European populations. Indeed, this 7-TAAbs panel plus CT imaging significantly improved the PPV up to 95.0% when compared to TAAbs panel alone or with CT alone.

In the context of large community-based trials, a positive EarlyCDT-Lung test followed by LDCT 6-monthly for up to two years significantly reduced the numbers of late-stage (III/IV) lung cancers (58.9% versus 73.2%) as compared with standard clinical care and more early-stage (I/II) lung were diagnosed (41.0% versus 27.0%). There were no significant differences in lung cancer mortality (0.28% versus 0.39%) and all-cause mortality (1.43% versus 1.76%) as well. The biggest advantage of EarlyCDT-Lung is its superior safety profile. No severe adverse events directly related to the test were reported and all were considered minor.

The EarlyCDT-Lung has previously been tested in high-risk cohorts or lung cancer patients matched with control subjects on age, gender, and smoking status. As a result, this assay performed best (sensitivity) in heavy smokers with at least 50 tobacco pack years (44.0%), patients older than 75 years (55.0%), and late-stage disease (40.0%); gender does not seem to influence outcome.

In terms of cost-effectiveness, our review found that EarlyCDT-Lung with an addition to CT surveillance is likely to be a cost-effective approach to the management of patients with incidentally detected nodules or in patients with indeterminate pulmonary nodules (IPNs), with all results well under the threshold for acceptance. However, the settings of the studies were different from Malaysia since CT surveillance has been used as a

screening tool in those countries. By comparison, early screening using LDCT in this country was having low uptake due to reasons like poor recruitment from the general public, low awareness, refusal to be screened, and fear of cancer diagnosis. From the economic evaluation perspective and for an intervention to be considered cost-effective, the cost per QALY gained has to be at or below a given cost-effectiveness threshold. Based on a modelling approach and willingness to pay, positive EarlyCDT-Lung followed by LDCT and biopsy is a cost-effective strategy compared to no screening among high-risk group in Malaysia. However, the eligible high-risk population involved in this screening strategy is approximately one million and resulted about RM4 billion of the budget involved. Therefore, various factors needed to be considered before the implementation of the screening program. A sensitivity analysis in this study suggested that the cost of EarlyCDT-Lung is the major factor that influenced the cost-effectiveness ratio. The uptake of the screening also needs to be improved by creating more public awareness on the needs of early screening to prevent late cancer treatment.

No studies of EarlyCDT-Lung in the target population evaluated health-related quality of life outcomes. However, the ECLS trial reported that there were no statistically significant differences in lung cancer worry, health anxiety, illness perceptions, lung cancer risk perception or intrusive thoughts between patient with and without lung nodules at three and six months. A recent systematic review found that negative test results are unlikely to cause false reassurance, anxiety or a change in health-related behaviours; hence, it unlikely that false reassurance had a substantial impact on lung cancer presentation in those with negative test results. The ongoing Artificial Intelligence and Big Data for Early Lung Cancer Diagnosis (IDEAL) study is exploring the quality of life of people with lung nodules on CT surveillance. It might be thought that EarlyCDT-Lung test results could have an impact on anxiety, but that no evidence is available to support this. On the other hand, there was no evidence retrieved on social, ethical and legal issues related to EarlyCDT-Lung in screening setting.

Although no HTA report were retrieved in keeping with our purpose for this assessment, two recent reviews summarised some recent advances in blood-based lung cancer biomarkers that have the potential to be clinically useful in the near future. The authors found that only the miRNA signatures (the miR-Test for serum and the miRNA signature classifier test for plasma) and autoantibodies to TAAs are being assessed as non-invasive test to detect lung cancer at the early-stage. However, both of the reviews did not perform a meta-analysis of the same panel of autoantibodies.[14, 36] Above all, our findings are in line with the NICE diagnostic guidance, particularly regarding the evidence on the diagnostic performance and impact of EarlyCDT-Lung on clinical management.

Limitations

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. One of the important limitations was the methodological quality of the included studies, particularly in terms of heterogeneity and risk of bias. This could be because of the differences in the baseline characteristics of the study participants, differences in the inclusion and exclusion criteria, assessment of outcomes, and the geographic locations in which the studies were conducted. The compositions of single or multiple autoantibody combinations were very heterogeneous from study to study and various detection methods and cut-off points were used to distinguish lung cancer patients from controls, which may have a potential impact on our review. It should be mentioned that, although blood-based autoantibodies have a great potential for use in the near future, these tests cannot yet be used as stand-alone tests as they must be integrated with CT scan imaging in the screening procedure. Another reason, the EarlyCDT-Lung test was detected in a relatively small population of patients with lung cancer, thereby decreasing the power of the studies to detect a meaningful difference. Since most of the studies

were follow-up between 12 and 24 months, more trials with longer follow-up period are needed. Regarding economic evaluation, the cost of palliative care for patients that die of lung cancer have not been incorporated in to the analysis. However, given that patient outcomes are improved in the AABT plus CT surveillance scenario, their inclusion would cause the AABT to appear even more cost-effective than has been presented in the results. Rather than doing an extensive systematic review to identify the best available evidence to populate the model, both cost-effectiveness analyses has made extensive use of the parameters, data and model structured from secondary sources. While this should be regarded as a limitation, the uncertainty in the parameters valued used has have been subjected to extensive sensitivity analysis and this has shown that the conclusion drawn from this analysis are robust to realistic variation in the parameter values.

8.0 CONCLUSION

The availability of evidence on the diagnostic value differs between autoantibodies for identifying patients at all stages or early-stage of lung cancer. There was fair to good level of retrievable evidence to suggest that EarlyCDT-Lung has low to moderate sensitivity but good specificity as serum diagnostic biomarkers of lung cancer in population screening among high-risk group. A positive EarlyCDT-Lung test followed by LDCT significantly reduced the numbers of late-stage lung cancers and more early-stage lung cancers were diagnosed as compared with standard clinical care. However, there were no significant differences in lung cancer mortality and all-cause mortality. Given the existing evidence, economic evaluation conducted in countries that implemented LDCT as a screening tool with an addition of EarlyCDT-Lung was found to be cost effective whereas higher budget will be needed in Malaysia. Hence, further price negotiation needed to be done to negotiate the cost for EarlyCDT-Lung screening program for specific high-risk population. Future research focusing on novel TAAb panels that offer better diagnostic performance is encouraged.

9.0 RECOMMENDATION

Based on the above review, EarlyCDT-Lung has the potential to be used to complement LDCT in population screening for early lung cancer detection among high-risk group in Malaysia. However, its use should take into consideration the availability and acceptability of LDCT as a screening tool. Competitive price of EarlyCDT-Lung may improve the cost-effectiveness of this screening strategy.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomised controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomisation.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

Early cancer detection test for lung (EarlyCDT-Lung)

1.0 BACKGROUND INFORMATION

Epidemiology

With an estimated 2.2 million new cancer cases and 1.8 million deaths worldwide, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in five (18.0%) deaths.[1-2] According to the most recent data by Malaysia National Cancer Registry (MNCR) for the incidence year of 2012-2016, lung cancer was the third (9.8%) most common cancer in the country, the second (14.9%) most common cancer in males, and the fifth (5.6%) most common in females.[3] Despite advances in diagnostic approaches and treatment, the overall 5-year survival for lung cancer has not significantly changed and is estimated to be around 17.8%. Lack of early detection remain one of the biggest challenges in lung cancer management.[4]

Management of malignancy risk in pulmonary nodule

To improve the poor prognosis, methods that detect lung nodules at an earlier stage (when it is more likely to be treated with curative intent) are needed. Several clinical trials have addressed the application of a low-dose computed tomography (LDCT) screening program in a high-risk population to diagnose lung cancer at a resectable stage,[5-7] the largest being the National Lung Screening Trial (NLST)[8] in USA and the Nelson trial[9] in the Netherlands and Belgium. Initially, previous HTA report by MaHTAS indicated that screening for lung cancer using LDCT reduced lung cancer specific mortality and improved early detection (high sensitivity but low specificity) among the high risk group.[10] While LDCT screening has now been broadly documented to have the potential to reduce lung cancer mortality, it comes with risks of high radiation exposure, false-positive test results, over diagnosis, unnecessary follow-up testing, and increased patient anxiety as well as health-care associated costs.[11-12] Therefore, it is necessary to develop more effective, non-invasive methods for the screening and early diagnosis of lung cancer.

In view of improving the specificity of non-invasive lung cancer detection and diagnostic triage, there is extensive ongoing research on the complementary use of blood-based biomarkers.[13] A valid biomarker could provide additional evidence as to whether a suspicious, screening-detected nodule is malignant, thereby reducing the number of false-positives at surgery or surgical biopsy.[14] Present diagnostic blood tests which focus on detecting tumour-associated antigen (TAA) markers such as carcinoembryonic antigen (CEA), chromogranin, neuron-specific enolase, carbohydrate antigen (CA) 125 and CA19-9 had showed an increase positivity at advanced stages. However, these molecules are rarely used as early biomarkers because of their low sensitivity and specificity, whereby false-positives results can occurs as a results of infection, benign tumours, pregnancy, and other factors.[15]

Serum tumour-associated autoantibodies (TAAbs)

A promising blood test of serum TAAbs against over expressed, mutated, misfolded or aberrant autologous cellular antigens (produced by cancer cells) may identify individuals with early lung cancer and distinguish high risk smokers with benign nodules from those with lung cancer.[14, 16] Following this, a commercially available assay (EarlyCDT-Lung) that measures autoantibodies to TAAs for the detection of lung cancer has been developed. Compared with the traditional lung cancer serological markers, autoantibodies against TAAs may persist in the circulating blood longer than the antigens themselves and may be more easily detected, not only at initial diagnosis of lung cancer[17] but also in some cases up to five years before cancer is diagnosed.[18-19]

Technical Description

Figure 1: EarlyCDT-Lung

EarlyCDT-Lung is a sophisticated blood test that measures a group of seven autoantibodies (p53, NYESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2) to TAAs related to lung cancer. It is claimed to help early detection of lung cancer in people with high risk and allows differentiation of benign or malignant nodules. In the early stages of lung cancer, autoantibodies and TAAs are produced as the body's immune system's response to cancer antigens. Blood levels of autoantibodies are elevated in the earliest stage of lung cancer and are present at all stages of the disease. EarlyCDT-Lung test is based on enzyme linked immunosorbent assay (ELISA) principles. It uses microtiter plates coated with a set of serial dilutions of recombinant antigens. Test results are based on a comparison of relative autoantibody levels to fixed thresholds. Samples were judged to be positive if they fulfilled two criteria; when (i) they showed a dose response to the antigen titration series and (ii) the measured autoantibody signal to one or more of the antigens was above the accepted cut-off set for that antigen assay. EarlyCDT-Lung first received its CE mark as a general *in vitro* diagnostic in May 2017 and was updated in March 2019.[20] In combination with imaging techniques, the test is now commercially available to assist clinicians in the early detection of lung cancer in a high risk population. The test can potentially improve the current pathway for lung nodule by enhancing the precision of estimate from existing risk-based models and thus disease management. This would mean patients with results showing increased risk of malignancy can be managed early.

Reasons for request

Although TAAbs are considered promising markers for early lung cancer detection, their efficacy has been tested mostly in a clinical context but not in population screening settings. Moreover, it has not been studied whether serum TAAb concentrations are elevated in patients with small malignant nodules (<10 mm in diameter) as detected by LDCT screening, and whether antibody tests such as EarlyCDT-Lung can detect tumours in an equally early stage as with LDCT-based screening.[21] There is, therefore, a need to evaluate the diagnostic performance of EarlyCDT-Lung to support the introduction of this test in the management of lung cancer in Malaysia. This HTA protocol was prepared in connection to the request made by Senior Consultant Pulmonologist from Serdang Hospital.

2.0 POLICY QUESTION

2.1 Should EarlyCDT-Lung be used as a screening tool for early lung cancer detection in Malaysia?

2.2 Does using the EarlyCDT-Lung reduce the incidence of patients with late-stage lung cancer or unclassified (III/ IV/ U) presentation at diagnosis?

3.0 OBJECTIVES

3.1 To assess the diagnostic accuracy of EarlyCDT-Lung in increasing early-stage lung cancer detection.

3.2 To assess the effectiveness and safety of EarlyCDT-Lung in patients at high risk of lung cancer, with regards to patient outcomes such as mortality, quality of life (QoL), and adverse events or complications.

3.3 To assess the economic implication, social, ethical, and organisational aspects related to EarlyCDT-Lung as compared to standard clinical practice.

The following research questions will be addressed:

3.1.1 What is the diagnostic accuracy/ performance of EarlyCDT-Lung for the detection of lung cancer?

3.1.2 Does screening with EarlyCDT-Lung improve lung cancer mortality?

3.1.3 Is EarlyCDT-Lung cost-effective?

3.1.4 What is the social, ethical, and organisational implication/ impact related to EarlyCDT-Lung?

4.0 METHODS

4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to EarlyCDT-Lung for early lung cancer detection.

4.1.1 Databases as follows: MEDLINE, EMBASE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the references of the retrieved articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion criteria

a. Population : Adults who are at risk of having lung cancer

b. Intervention : Early cancer detection test for lung, EarlyCDT-Lung, autoantibody test, biomarkers, blood test, tumour-associated autoantibody

c. Comparators :
   i. Standard clinical practice: chest radiography, computed tomography (CT), positron emission tomography-CT (PET-CT), low dose CT (LDCT)
   ii. No comparator

d. Outcome :
   i. Diagnostic accuracy: sensitivity, specificity, predictive value (positive and negative), diagnostic odds ratio, receiver operator characteristic (ROC) curve, and area under the curve (AUC)
   ii. Effectiveness: lung cancer-related mortality, quality of life (QoL)

iii. Safety: adverse events, complications
iv. Economic implications: cost-effectiveness, cost-utility, cost-benefit analysis
v. Potential psychological and behavioural harms and benefits of test results
vi. Training requirements or learning curve

e. Study design : HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, diagnostic accuracy and economic evaluation

f. English full text articles

4.2.2 Exclusion criteria

a. Study design : Animal study, laboratory study, case-control, case report, case series, narrative review

b. Non-English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The risk of bias of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) and Cochrane risk of bias tool for randomised trials (RoB 2).

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

i. Details of methods and study population characteristics
ii. Detail of intervention and comparators
iii. Details of individual outcomes specified

4.4.2 Methods of data synthesis

Data on the accuracy, safety and cost-effectiveness associated with EarlyCDT-Lung will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this HTA.

5.0 REPORT WRITING

6.0 REFERENCES

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APPENDIX 3: SEARCH STRATEGY

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. ADULT/
2. Adult*.tw.
3. LUNG NEOPLASMS/
4. Cancer of lung.tw.
5. Cancer of the lung.tw.
6. (lung adj3 (cancer* or neoplasm* or carcinoma or tumo?r*)).tw.
7. (pulmonary adj1 (cancer* or neoplasm*)).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. EARLYCDT LUNG/
10. Earlycdt lung.tw.
11. EARLY DETECTION OF CANCER/
12. (cancer early adj1 (detect* or diagnos*)).tw.
13. Cancer screening.tw.
14. Cancer screening test*.tw.
15. Early detect* of cancer.tw.
16. Early diagnos* of cancer.tw.
17. AUTOANTIBODIES/
18. Autoantibod*.tw.
19. ANTIBODIES, NEOPLASM/
20. ((neoplasm* or tumo?r) adj1 antibod*).tw.
21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. RADIOGRAPHY, THORACIC/
23. Thoracic radiograph*.tw.
24. TOMOGRAPHY, X-RAY COMPUTED/
25. CT x ray*.tw.
26. X-ray ct scan*.tw.
27. Tomodensitometr*.tw.
28. X-ray computed tomograph*.tw.
29. Computed x ray tomograph*.tw.
30. ((computed x-ray or electron beam or transmission computed) adj2 tomograph*).tw.
31. ((x ray computer assisted or x ray computerized axial) adj1 tomograph*).tw.
32. POSITRON-EMISSION TOMOGRAPHY/
33. (pet adj1 (imaging* or scan*)).tw.
34. Positron emission tomograph*.tw.
35. Positron emission tomography imaging*.tw.
36. LOW DOSE CT/
37. Low dose CT.tw.
38. 22 or 23 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 8 and 21 and 38
40. Limit 39 to (humans and yr="2010 -Current" and "all adult (19 plus years)")

PubMed

Search	Query	Items found
#4	Search ((((((((((LUNG NEOPLASMS[MeSH Terms]) OR Pulmonary neoplasm*[Text Word]) OR Lung neoplasm*[Text Word]) OR Lung cancer*[Text Word]) OR Pulmonary cancer*[Text Word]) OR Cancer of the lung*[Text Word]) OR Cancer of lung*[Text Word]) OR Lung carcinoma*[Text Word]) OR Lung tumor*[Text Word])) AND ((((((((((((AUTOANTIBODIES[MeSH Terms]) OR autoantibod*[Text Word]) OR ANTIBODIES[MeSH Terms]) OR antibod*[Text Word]) OR Early cancer detection test[MeSH Terms]) OR Cancer Early Detection*[Text Word]) OR Cancer Screening*[Text Word]) OR Cancer Screening Test*[Text Word]) OR Early Diagnosis of Cancer*[Text Word]) OR Cancer Early Diagnosis*[Text Word]) OR Autoantibody test[MeSH Terms]) OR Autoantibody test*[Text Word]) OR serum tumour-associated antibodies[MeSH Terms]) OR serum tumour-associated antibod*[Text Word])) AND ((((((((((((((((((((((((((((chest radiography[MeSH Terms]) OR chest radiography*[Text Word]) OR computed tomography (CT)[MeSH Terms]) OR X-Ray Computed Tomography*[Text Word]) OR Computed X Ray Tomography*[Text Word]) OR X Ray Computer Assisted Tomography*[Text Word]) OR X-Ray Computerized Tomography*[Text Word]) OR CT X Ray*[Text Word]) OR Tomodensitometry*[Text Word]) OR Computed X-Ray Tomography*[Text Word]) OR Xray Computed Tomography*[Text Word]) OR X-Ray CAT Scan*[Text Word]) OR Transmission Computed Tomography*[Text Word]) OR X-Ray CT Scan*[Text Word]) OR X Ray Computerized Tomography*[Text Word]) OR Cine CT*[Text Word]) OR Electron Beam Computed Tomography*[Text Word]) OR Electron Beam Tomography*[Text Word]) OR X-Ray Computerized Axial Tomography*[Text Word]) OR X Ray Computerized Axial Tomography*[Text Word]) OR Positron Emission Tomography Computed Tomography[MeSH Terms]) OR PET-CT Scan*[Text Word]) OR PET CT Scan*[Text Word]) OR CT PET*[Text Word]) OR Positron Emission Tomography-Computed Tomography*[Text Word]) OR PET-CT*[Text Word]) OR CT PET Scan*[Text Word]) OR low dose CT (LDCT)[MeSH Terms]) OR low dose CT*[Text Word])	0
#3	Search ((((((((((((((((((((((((((((chest radiography[MeSH Terms]) OR chest radiography*[Text Word]) OR computed tomography (CT)[MeSH Terms]) OR X-Ray Computed Tomography*[Text Word]) OR Computed X Ray Tomography*[Text Word]) OR X Ray Computer Assisted Tomography*[Text Word]) OR X-Ray Computerized Tomography*[Text Word]) OR CT X Ray*[Text Word]) OR Tomodensitometry*[Text Word]) OR Computed X-Ray Tomography*[Text Word]) OR Xray Computed Tomography*[Text Word]) OR X-Ray CAT Scan*[Text Word]) OR Transmission Computed Tomography*[Text Word]) OR X-Ray CT Scan*[Text Word]) OR X Ray Computerized Tomography*[Text Word]) OR Cine CT*[Text Word]) OR Electron Beam Computed Tomography*[Text Word]) OR Electron Beam Tomography*[Text Word]) OR X-Ray Computerized Axial Tomography*[Text Word]) OR X Ray Computerized Axial Tomography*[Text Word]) OR Positron Emission Tomography Computed Tomography[MeSH Terms]) OR PET-CT Scan*[Text Word]) OR PET CT Scan*[Text Word]) OR CT PET*[Text Word]) OR Positron Emission Tomography-Computed Tomography*[Text Word]) OR PET-CT*[Text Word]) OR CT PET Scan*[Text Word]) OR low dose CT (LDCT)[MeSH Terms]) OR low dose CT*[Text Word]	0
#2	Search ((((((((((((AUTOANTIBODIES[MeSH Terms]) OR autoantibod*[Text Word]) OR ANTIBODIES[MeSH Terms]) OR antibod*[Text Word]) OR Early cancer detection test[MeSH Terms]) OR Cancer Early Detection*[Text Word]) OR Cancer Screening*[Text Word]) OR Cancer Screening Test*[Text Word]) OR Early Diagnosis of Cancer*[Text Word]) OR Cancer Early Diagnosis*[Text Word]) OR Autoantibody test[MeSH Terms]) OR Autoantibody test*[Text Word]) OR serum tumour-associated antibodies[MeSH Terms]) OR serum tumour-associated antibod*[Text Word]	519
#1	Search ((((((((LUNG NEOPLASMS[MeSH Terms]) OR Pulmonary neoplasm*[Text Word]) OR Lung neoplasm*[Text Word]) OR Lung cancer*[Text Word]) OR Pulmonary cancer*[Text Word]) OR Cancer of the lung*[Text Word]) OR Cancer of lung*[Text Word]) OR Lung carcinoma*[Text Word]) OR Lung tumor*[Text Word]	15

APPENDIX 4: EVIDENCE TABLE

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
1. J Qin, N Zeng, T Yang et al. Diagnostic value of autoantibodies in lung cancer: a systematic review and meta-analysis. Cell Physiol Biochem. 2018; 51(6): 2631-2646	**Systematic review and meta-analysis** A systematic searched of published literature (PubMed, Scopus, Web of Science and other databases) evaluating available evidence on the diagnostic value of autoantibodies against tumour-associated antigens (TAAs) in lung cancer was performed. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) while pooled values of sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, diagnostic odds ratios and associated 95% CIs were calculated using the bivariate random-effect models. Summary receiver operating characteristic (SROC) curves were also used to summarize overall test performance. Deek's funnel plot was used to detect publication bias.	II-2	Review of 468 candidate articles identified 53 articles with 11,515 patients for qualitative review and meta-analysis. A total of 50 articles were based on serum specimens, three on plasma; 50 articles measured TAAb levels using ELISA, three using immunoblotting; five of the included studies examined only small-cell lung cancer (SCLC), and eight included only non-small cell lung cancer (NSCLC).	Tumour-associated autoantibodies (TAAbs) against the following TAAs: 1. p53 2. NY-ESO-1 3. Survivin 4. c-myc 5. Cyclin B1 6. GBU4-5 7. CAGE 8. p16 9. SOX2 10. HuD	In 41 articles, diagnosis of lung cancer was based on histopathology while 12 articles did not report.	-	**Diagnostic performance of TAAbs** Each TAAb on its own showed excellent diagnostic specificity for lung cancer but inadequate sensitivity. Pooled sensitivity, specificity and area under the SROC curve were as follows for TAAbs against the following proteins: 1. p53, 0.19, 0.98, 0.82 2. NY-ESO-1, 0.17, 0.98, 0.90 3. Survivin, 0.19, 0.99, 0.96 4. c-myc, 0.14, 0.98, 0.45 5. Cyclin B1, 0.18, 0.98, 0.91 6. GBU4-5, 0.07, 0.98, 0.91 7. CAGE, 0.14, 0.98, 0.90 8. p16, 0.08, 0.97, 0.91 9. SOX2, 0.14, 0.99, 0.93 10. HuD, 0.17, 0.99, 0.82 However, combinations or panels of autoantibodies may improve sensitivity (0.38-0.47) but at the cost of specificity (0.89-0.90). **Subgroup analyses** Since most cases of SCLC (60-70%) are diagnosed at the extensive stage (reducing the possibilities for good prognosis), and mutations in the p53 and NY-ESO-1 gene are present in up to 80% of SCLC and 50% of NSCLC cases, subgroup analysis was performed to identify whether the presence of p53 and NY-ESO-1 TAAb could differentiate NSCLC (15 studies, 2,478 patients) and SCLC (9 studies, 1,630 patients). The results suggested that both p53 and NY-ESO-1 showed greater diagnostic performance for SCLC than for NSCLC, albeit with low diagnostic efficacy. This highlights the urgent need to develop serum biomarkers that might allow diagnosis of SCLC	Most studies had low risk of bias (QUADAS-2). No evidence of publication bias for the TAAbs (all p>0.05.

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
2. Tang ZM, Ling ZG, Wang CM, et al. Serum tumor-associated autoantibodies as diagnostic biomarkers for lung cancer: A systematic review and meta-analysis. PLoSONE. 2017; 12(7): e0182117	**Systematic review and meta-analysis** A systematic searched of MEDLINE and EMBASE databases for relevant studies investigating the diagnostic values of serum single and multiplex tumour-associated autoantibodies (TAAbs) in patients with lung cancer, especially for the early detection was performed. The quality of the included studies was assessed using the quality appraisal tool for studies of diagnostic reliability (QAREL). The pooled sensitivity and specificity forest plots were used to evaluate the diagnostic value of the same panel of autoantibodies, and the threshold effect was assessed using a summary receiver operating characteristic (SROC) curves. A funnel plot and Egger test were used to assess the publication bias.	II-2	A total of 31 articles with single autoantibody and 39 with multiplex autoantibodies were included (five articles were related to the combination of both single and multiplex autoantibodies). Seven articles were used for the meta-analysis; out of 12 test, eight tests were based on the same panel of 6 TAAbs (n=4,957) and four tests analysed the same panel of 7 TAAbs (n=3,613).	Single and multiplex TAAbs	-	-	**Diagnostic value of single and multiple autoantibodies** For the diagnosis of patients with all stages and early-stage lung cancer, different single or combinations of TAAbs demonstrated different diagnostic values. Individual TAAbs showed low sensitivity and specificity (55.2% and 84.4%, respectively) whereas combination of multiplex autoantibodies offered relatively high values (sensitivity 70.3% and specificity 86.3%). For single TAAb in the diagnosis of early-stage lung cancer, the sensitivities ranged from 24.1% to 100.0% (mean: 55.6%), and specificities ranged from 80.0% to 99.2% (mean: 89.3%). For the panel of mixed TAAbs, the sensitivities ranged from 27.5% to 100.0% (mean: 71.1%), and specificities ranged from 43.8% to 100.0% (mean: 87.1%). **Meta-analysis of the same panel of autoantibodies** For the meta-analysis of a same panel of autoantibodies in patients at all stages of lung cancer, the pooled results of the panel of 6 TAAbs (p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1 and SOX2) were: sensitivity 38% (95% CI 0.35 to 0.40), specificity 89% (95% CI 0.86 to 0.91), diagnostic accuracy 65.9% (range 62.5-81.8%), AUC 0.52 (0.48 to 0.57), while the summary estimates of 7 TAAbs (p53, CAGE, NY-ESO-1, GBU4-5, SOX2, MAGE A4 and Hu-D) were: sensitivity 47% (95% CI 0.34 to 0.60), specificity 90% (95% CI 0.89 to 0.92), diagnostic accuracy 78.4% (range 67.5 to 88.8%), AUC 0.90 (0.87 to 0.93). For the meta-analysis of the same panel of autoantibodies in patients at early-stage of lung cancer, the sensitivities of both panels of 7 TAAbs and 6 TAAbs were 40% and 29.7%, while their specificities were 91% and 87%, respectively.	The methodological quality of most studies included in the meta-analysis was generally good.

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
3. Sullivan FM, Mair FS, Anderson W et al. Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. Eur Respir J. 2021; 57: 2000670	**Randomised controlled trial** The Early Diagnosis of Lung Cancer Scotland (ECLS) is the first trial conducted as a phase IV (prospective screening) evaluation of a blood-based biomarker panel for lung cancer, involving 12,208 participants recruited through general practices and community-based recruitment strategies in Scotland in the UK. The primary analysis compared the rate of stage III/ IV lung cancer within two years of randomisation between the intervention and control arms. The analyses followed the intention-to-treat principle. Similar methodology was used to analyse the secondary outcomes of mortality rates.	I	Adult age 50 to 75 years at increased risk of developing lung cancer compared with the general population. High-risk were defined as current or former cigarette or tobacco smokers with at least 20 pack-years, or with a history of smoking of <20 pack-years plus immediate family history (mother, father, sibling or child) of lung cancer.	Participants received the EarlyCDT-Lung test (n=6,087), and those who were test-positive received low-dose CT scanning (LDCT) 6-monthly for up to two years.	Participants allocated to the control arm and those who were test-negative received standard clinical care (n=6,121)	24 months post-randomisation	**Results of testing** During the study, 127 lung cancers were diagnosed (56 in the intervention arm and 71 in the control). Of the intervention arm, 9.8% (598/6,087) had a positive EarlyCDT-Lung test and 3.0% (18/598) of these had a confirmed case of lung cancer within two years. In the test-negative EarlyCDT-Lung, 0.7% (38/5,489) had confirmed lung cancers. **Primary outcomes** The rate of late-stage (III/ IV) lung cancer diagnosis was lower in the intervention arm (33 out of 56 [58.9%]) than the control (52 out of 71 [73.2%]) (14.3% absolute risk reduction). The number of participants to be screened to prevent one stage III/ IV lung cancer diagnosis was 325 (95% CI 13 to 637) and the hazard ratio for stage III/ IV presentation was 0.64 (95% CI 0.41 to 0.99; p=0.0432). More early-stage (I/ II) lung cancers were diagnosed in the intervention arm (23 compared with 19). The EarlyCDT-Lung test had an estimated sensitivity of 52.2% (95% CI 30.6 to 73.2%) for stage I/ II disease and 18.2% (95% CI 7.0 to 35.5%) for stage III/ IV disease, and specificity of 90.3% (95% CI 89.6 to 91.1%) for stage I/ II disease and 90.2% (95% CI 89.4 to 91.0%) for stage III/ IV disease. **Secondary outcomes** There were no significant differences in lung cancer mortality (intervention arm 17 out of 6,087 [0.28%] versus control arm 24 out of 6,121 [0.39%]) and all-cause mortality (intervention arm 87 out of 6,087 [1.43%] versus control arm 108 out of 6,121 [1.76%]) after two years. **Safety** Five adverse events directly related to the test (collection of blood sample) were reported and all were considered minor. For those in the intervention arm, there was one injection site haematoma, one panic attack, and one pre-syncope. In the control arm there were two episodes of syncope.	The study included a large sample size. Power calculations were done to detect the study endpoint. The method of randomisation was also stated.

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
4. Shengxiang Ren, Shucai Zhang, Tao Jiang et al. Early detection of lung cancer by using an autoantibody panel in Chinese population. Oncolmmunology. 2018; 7(2): ei384108	**Prospective cohort** This large-scale, multicentre study was undertaken to validate the clinical value of seven autoantibodies (7-AABs) panel for early detection of lung cancer in a Chinese population. The concentrations of AABs were quantitated by enzyme-linked immunosorbent assay (ELISA), and the optimal cut off value for each AAB was determined in the training set and then applied in the validation set. Sensitivity and specificity of this AAB panel were compared with traditional tumour biomarkers, including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and cytokeratin 19 fragment 21-1 (CYFRA21-1) in lung cancer patients with different disease stages. In addition, the utility of the 7-AABs panel in combination with a CT scan were analysed to achieve higher diagnostic accuracy for patients (n=540) presenting with ground-glass nodules (GGNs) and/ or solid nodules.	II-2	Two independent sets of plasma samples from 2,308 participants were available for the assay of AABs: 1-Training set (n=300) 155 patients with NSCLC and SCLC, and 145 healthy controls 2-Validation set (n=2008) 818 patients with lung cancer (722 with NSCLC and 90 with SCLC), 386 with benign lung disease, 101 with other cancers, 93 post-thoracic surgery patients, 195 interfering group patients (with different disease), and 415 healthy controls.	7-AABs panel against tumour-related antigens: 1. p53 2. PGP9.5 3. SOX2 4. GAGE7 5. GBU4-5 6. MAGEAI 7. CAGE	Traditional tumour biomarkers (CEA, NSE, and CYFRA21-1)	-	**Diagnostic performance of the 7-AABs panel** Immunoassays of the 7-AABs in combination enhanced cancer detection and achieved a panel sensitivity of 61% and panel specificity of 90%. **Subgroup analyses** Subgroup analyses was conducted to investigate the diagnostic value of the 7-AABs panel in patients with different disease stages and histological types and in control groups. The sensitivities ranged from 59% to 64% in NSCLC patients, with a sensitivity of 62% in stage I, 59% in stage II, 62% in stage III, and 64% in stage IV disease. The specificities ranged from 76% to 94% in control groups, with a specificity of 91% in benign lung diseases, 76% in other cancers, 94% in autoimmune diseases, and 89% in healthy controls. When compared the sensitivity values for traditional tumour biomarkers, the 7-AABs panel showed a higher sensitivity in the early stages of lung cancer (stage I & II, 60%; limited-stage SCLC, 59%) than CEA, NSE, and CYFRA 21-1. The combination of the 7-AABs panel and CT significantly improved the diagnostic yield when compared with AABs panel alone (95.0% vs. 85.2%; p<0.001) or with CT alone (95.0% vs. 69.0%; p<0.001). In patients with GGNs and/or solid nodules, the combination of the 7-AABs panel and CT significantly: ▪ Increased PPV of malignant lesions from 57.6% to 90.4% (p<0.001). ▪ Improved PPV from 63.4% to 89.7% (p=0.013), 50.8% to 90.5% (p<0.001), and 63.4% to 90.7% (p<0.001) in patients with radiological GGNs and/or solid nodules ≤8 mm, 8 and 20 mm, and >20 mm in size, respectively. ▪ Improved PPV in patients with pure, mixed GGNs, and just nodule from 80.9%, 79.3%, and 50% to 94.4%, 94.7%, and 89.1%, respectively. ▪ Decreased the false positive rate in patients with distinct size and pathological types GGNs and/or solid nodules.	

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
5. Borg M, Wen S, Nederby L et al. Performance of the EarlyCDT® Lung test in detection of lung cancer and pulmonary metastases in a high-risk cohort. Lung Cancer. 2021; 158: 85-90	**Prospective cohort** The purpose of this prospective observational study was to evaluate the performance of the seven-panel TAAb assay (EarlyCDT-Lung) in a cohort of patients referred from their general practitioner (GP) on suspicion of lung cancer. Blood samples were taken at first visit and patients underwent diagnostic work-up on suspicion of lung cancer resulting in either a malignant diagnosis or ruled out cancer. The primary aim was to evaluate the ability of the assay to detect cancer in the total cohort. Secondary aims included detection of lung cancer in stage I-II versus stage III-IV, detection of specific histological types of lung cancer and detection of lung cancer in subgroups of age and smoking history, including patients currently eligible for LDCT screening in the United States.	II-2	High-risk cohort composed of 246 patients referred from their GP on suspicion of lung cancer at the Department of Medicine, University Hospital of Southern Denmark.	7-AABs (EarlyCDT-Lung test)	-	1-year	**Patients** Diagnostic work-up resulted in 30% (75/246) of patients with a diagnosis of lung cancer, 5% (12/246) with lung metastases originating from primary tumours in other organs and 65% (159/246) where cancer was ruled out. **Primary outcome** Overall sensitivity in the cohort was 33% (25/75) for lung cancer and 31% (27/87) for primary lung cancer and lung metastases combined. Assay specificity for the detection of both lung cancer and for any malignant diagnosis with lung metastases was 88%. **Secondary outcomes** The assay was tested in subgroups of patients with different tobacco smoking history. Sensitivity of the assay in the subgroup of patients with at least 10 tobacco pack years was 33% while the sensitivity measured in patients with at least 50 tobacco pack years was 44%. In subgroups based on age, the assay yielded a sensitivity of 11% in patients 60 years or below. When tested in subgroups of patients aged 61 to 75 and >75 years, the sensitivities were 31% and 55%, respectively. The assay sensitivity in stage I-II lung cancer patients was 21%, while this was 40% in stage III-IV lung cancer patients. In a subgroup of patients that met current LDCT screening criteria (age 55 to 80 years and minimum 30 tobacco pack years) the sensitivity and specificity were 37% and 81%, respectively.	The cohort of this study is solely formed on the basis of their GP's suspicion of lung cancer. Thus, lung cancer patients and controls are not matched in risk of lung cancer.

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/Effect Size	General Comments
6. Maldonado SG, Johnson T, Motsch E et al. Can autoantibody tests enhance lung cancer screening?-an evaluation of EarlyCDT ®-Lung in context of the German Lung Cancer Screening Intervention Trial (LUSI). Transl Lung Cancer Res. 2021; 10(1): 233 -242	**Nested case-control** This study evaluated the early detection accuracy of EarlyCDT-Lung as part of the German Lung Cancer Screening Intervention Trial (LUSI); participant selection within the trial was a nested case-control design. EarlyCDT-Lung test was performed for all participants (n=2,022) with lung cancer detected via LDCT and with available blood samples taken at detection, and for 180 retrospectively selected cancer-free participants at the end of follow-up: 90 randomly selected from among all cancer-free participants (baseline controls, BC) and 90 randomly selected from among cancer-free participants with suspicious imaging findings (suspicious nodules controls, SNC). Positive results were reported as: 1- "Moderate Level" (M)] if the levels of one or more autoantibodies in the EarlyCDT-Lung panel are above the low cut-off value but all are below the high cut-off value 2- "High Level" (H) if the levels of one or more autoantibodies are above the high cut-off value 3- "No Significant Level" [NS] if the levels of autoantibodies in the panel are below the low cut-off value.	II-3	LUSI trial involved 4,052 long-term smokers age 50-69 years recruited from the general population. Participants were randomised into an intervention arm of five annual LDCT screenings (n=2,029) and a control without screening (n =2,023). In the LDCT arm, 69 lung cancer cases were observed during the active screening period; 46 eventually diagnosed with lung cancer at time of blood collection.	EarlyCDT-Lung test	-	-	EarlyCDT-Lung produced "High Level" test results for six out of the 46 CT-detected lung cancer patients. This resulted in a detection sensitivity of 13.0% (95% CI 4.9 to 26.3%). Within the subset of participants with nodules <10 mm in diameter, the test produced "High Level" results for one out of 11 CT-detected lung cancer patients, yielding a sensitivity of 9.1% (95% CI 0.23 to 41.3%). For participants with nodules ≥10 mm, the estimated sensitivity was 14.7% (95% CI 4.9 to 31.1%). When considering both "High Level" and "Moderate Level" [H/M] results as positive, specificity was estimated at 88.9% (95% CI 80.5 to 94.5%) in the BC group, and 91.1% (95% CI 83.2 to 96.1%) among controls presenting CT-detected nodule.	Small sample size.

Evidence Table : Diagnostic accuracy/ effectiveness/ safety/ economic implication/ organisational
Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
7. Edelsberg J, Weycker D, Atwood M et al. Cost effectiveness of an autoantibody test (EarlyCDT- Lung) as an aid to early diagnosis of lung cancer in patients with incidentally detected pulmonary nodules. PLoSONE. 2018; 13(5): e0197826	**Cost-effectiveness analysis** A decision-analytic model was used with two alternative strategies for nodule evaluation: autoantibody test (AABT) followed by biopsy if AABT-positive and CT surveillance if AABT-negative, and one without use of the AABT (i.e., CT surveillance alone), but otherwise similar in all respects. Model parameter values were estimated using published data where available, and expert assumptions where needed. Life expectancy (unadjusted and quality-adjusted) and expected costs including AABT, CT, biopsy (i.e., diagnostic follow-up), and treatment, as appropriate were calculated for 1,000 persons in each of the two strategies. Cost-effectiveness was calculated using the ratio of the difference in expected costs to the corresponding differences in life-years and quality-adjusted life-years (QALYs) for the AABT strategy and no-AABT strategy, respectively. The perspective of the analysis was the US healthcare system; future costs and life-years were discounted at 3% per year. For the AABT, two alternative sets of estimates for sensitivity and specificity were considered in base-case analyses based on published literature: 41%/93% and 28%/98%, respectively.		Patients in the model population were assumed to have incidentally detected nodules of diameter 8-30 mm and an estimated 5-60% risk of lung cancer. Prevalence of malignancy was 23.6%.	AABT (EarlyCDT-Lung)	CT surveillance alone	-	**Base-case analyses** Among 1,000 patients (who have incidentally detected nodules, have an intermediate-risk of lung cancer, and were evaluated by CT surveillance alone), 95 (9.5%) are assumed to have lung cancer (local 73.6%; regional 22.0%; distant 4.4%). Healthcare costs among all patients in the model population would total USD 4.0 million (USD 4,040 per person), and life years (discounted), 12,130 (12.13 per person). With use of the AABT set at a sensitivity/ specificity of 41%/93%, expected costs would be higher by USD 949,442 (USD 949 per person) but life years would be higher by 53 (0.05 per person), resulting in a cost per life-year gained of USD 18,029 and a cost per QALY gained of USD 24,330. With use of the AABT set at a sensitivity/ specificity of 28%/98%, corresponding cost-effectiveness ratios would be USD 18,454 and USD 24,833. **Sensitivity/ scenario analyses** The cost-effectiveness of using AABT for incidentally detected pulmonary nodules in this intermediate-risk CT-surveillance population was sensitive to the prevalence of malignancy, the sensitivity/specificity of the AABT, and the probability of stage progression among malignant nodules.	Cost-effectiveness ratios less than $50,000 per QALY have long been considered to be a worthwhile investment of scarce healthcare resources in the US.

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Question : What is the diagnostic accuracy, effectiveness, and safety of EarlyCDT-Lung as a screening tool for early lung cancer detection in adults who are at risk of having lung cancer?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
8. Sutton AJ, Sagoo GS, Jackson et al. Cost-effectiveness of a new autoantibody test added to computed tomography (CT) compared to CT surveillance alone in the diagnosis of lung cancer amongst patients with indeterminate pulmonary nodules. PLoSONE. 2020; 15(9): e0237492	**Cost-effectiveness analysis** A decision analytic model consisting of a combination of a decision tree and Markov model was developed to evaluate the cost-effectiveness of the autoantibody test (AABT) in addition to CT surveillance compared to the current practice of CT surveillance alone for patients with indeterminate pulmonary nodules (IPNs). The parameters used in this model can be broadly categorized into prevalence of malignancy, accuracy parameters, transition probabilities between model states, resource use and costs, and utility values. All costs are in pounds sterling (£) for the 2016/17 price year. Discounting was applied at 3.5% for costs and outcomes, with the analysis conducted from the health-care provider perspective. The results are presented using the incremental cost-effectiveness ratio (ICER). Two alternative pairs of test accuracy parameters were considered for the AABT test: Scenario A (sensitivity 41% specificity 93%) compared to Scenario B (sensitivity 28% specificity 98%).		The patient group under examination in this study are 62 year old patients with IPNs. Identified by imaging, these nodules are between 4 and 20 mm in size and carry a risk of malignancy of 10–65%.	AABT (EarlyCDT-Lung) plus CT surveillance	CT surveillance alone	-	**1-Scenario A: sensitivity 41% specificity 93%** At a price of £70 per test, AABT plus CT surveillance is more costly and more effective in terms of QALYs gained than CT surveillance alone (ICER £2,417). *Probabilistic sensitivity analysis*: The cost-effectiveness acceptability curve (CEAC) showed that AABT plus CT surveillance is more likely to be cost-effective at a willingness to pay (WTP) for the QALY of £2,000 and above. At a WTP of £20,000/QALY, AABT is approximately 99% likely to be cost-effective. The price of the AABT can be up to £1,150.37 and still have greater net-monetary benefit (NMB) than CT surveillance alone. There is some value in resolving the uncertainty in the disease related mortality rates, initial patient characteristics (i.e. prevalence and proportion of patients with local and regional disease) and the utility values. **2-Scenario B: sensitivity 28% specificity 98%** Similar to Scenario A, when the price for AABT=£70, and adopting the test accuracy parameters as described for Scenario B, AABT plus CT surveillance is more costly and more effective in terms of QALYs gained than CT surveillance alone (ICER £2,121). *Probabilistic sensitivity analysis*: The CEAC showed that AABT plus CT surveillance is more likely to be cost-effective at a WTP for the QALY of £3,000 and above. At a WTP of £20,000/QALY, AABT is more than 98% likely to be cost-effective. The AABT test can be priced up to £887.28, and be more cost-effective than surveillance alone. There was found to be no value in resolving the uncertainty in any of the parameter groups.	Given that the ICER is well under £20,000, AABT plus CT surveillance can certainly be regarded as cost-effective. .

APPENDIX 5: LIST OF EXCLUDED STUDIES

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