Title of the project

EarlyCDT Lung for lung cancer risk classification of solid pulmonary nodules: a systematic review and conceptual economic model

Name of External Assessment Group (EAG) and project leads

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Plain English Summary

People may undergo X-ray investigations or computed tomography (CT) scans of their lungs for a variety of medical reasons. These scans may identify lung nodules which might be cancerous. When this happens doctors may want to carry out further tests to see whether the patient may or may not have lung cancer. Currently this additional testing consists of CT scans, or alternatively Positron Emission Tomography (PET-CT) scans of the lung nodules, which are combined with patient characteristics (such as age, sex, smoking history, and other risk factors) to predict the risk that the nodule is cancerous. If lung cancer is diagnosed, or strongly suspected, urgent treatment may be required.

EarlyCDT Lung is a new blood test that detects substances in the blood associated with having cancer cells in the lungs. It could potentially be used in the NHS to assess the lung cancer risk of nodules seen on CT or PET-CT images. The test could help doctors in deciding the next course of action. Patients will already have a risk of lung cancer calculated from their CT or PET-CT scan and personal characteristics. The EarlyCDT Lung test result updates this risk, because if the test is positive the risk that a lung nodule is cancerous is substantially increased. This test could help doctors make decisions about whether to treat immediately, carry out further tests, or monitor the nodule over time to see whether it grows or changes shape.

The purpose of this project is to thoroughly investigate the evidence on the potential clinical and economic value of the EarlyCDT Lung test for lung cancer risk classification. To achieve this we will first search for all relevant published studies on EarlyCDT and reanalyse the reported data to see whether use of the EarlyCDT Lung test might be clinically valuable. There appears to be too little clinical evidence on EarlyCDT Lung to fully investigate whether it could potentially be considered a cost-effective use of NHS resources. This project will therefore review the existing evidence on its economic value, and identify what evidence would be needed to fully assess the cost-effectiveness of the Early CDT Lung test.

Decision problem

The purpose of this assessment is to investigate the evidence supporting the use of the EarlyCDT Lung test in the assessment of malignancy risk of solid pulmonary nodules. This includes nodules at high risk of being malignant which may require immediate intervention; nodules at intermediate risk that may require excision, further diagnostic assessment or surveillance; and nodules at low risk requiring longer-term surveillance or no further action.

This assessment will consider existing evidence (and identify potential evidence gaps) on whether the Early CDT Lung test has potential to be a clinically useful and cost-effective addition to current diagnostic strategies (including CT surveillance for lower-risk nodules, or PET-CT and diagnostic biopsies for intermediate-risk nodules) for determining future health care choices, such as CT surveillance, or confirmatory diagnosis and treatment.

The existing published evidence base on EarlyCDT appears to be too small to fully assess the clinical and economic value of the test. This assessment will therefore review the extent of the existing evidence and provide a common understanding of the evidence requirements and evidence linkages required for a full assessment of the value of EarlyCDT Lung to the NHS.

Interventions

Early CDT Lung test

EarlyCDT Lung is a blood test that can be used to assess the malignancy risk of people at risk of lung cancer. The test can, in principle, be used on any at-risk person; this assessment will consider its use in persons with solid pulmonary nodules found by chest CT scan or X-ray. [1-3] Incidental finding of pulmonary nodules in asymptomatic individuals, when performing CT scans for other medical purposes, or during lung cancer screening, is an increasingly common clinical dilemma encountered by lung cancer clinicians. EarlyCDT Lung could be used as part of the standard diagnostic pathway for early detection of lung cancer, where it might result in treatment being offered earlier, giving improved patient outcomes.

EarlyCDT Lung uses a standard enzyme-linked immunosorbent assay (ELISA) method. It is manufactured by Oncimmune and is available as a CE-IVD marked kit. The test measures the presence of autoantibodies to a panel of 7 lung cancer associated antigens (p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4 and SOX2). [1] A blood sample is considered positive when at least one of the 7 autoantibodies is elevated above a pre-determined cut-off (Table 1). Elevated levels of these autoantibodies may indicate current (or past) malignant disease. The thresholds were set to give a high test specificity with the aim of reducing false-positive results that would lead to unnecessary and potentially invasive diagnostic procedures. The EarlyCDT Lung test results are interpreted by skilled medical professionals in combination with other clinical information. In particular, it is suggested that its results be used to modify the risk of malignancy estimated by existing nodule risk calculators, including the Brock model and the Herder model. [4, 5]

Table 1 Recommended cut-offs for autoantibodies measured using EarlyCDT Lung

Autoantibody		Low cut-off value		High cut-off value	
CAGE		4.25		5.27	
GBU4 5	**No significant level of autoantibodies detected**	4.36	**Moderate level result**	5.92	**High level result**
NYESO 1		3.02		4.27	
p53		5.79		6.47	
SOX2		5.48		5.58	
MAGE A4		6.19		7.94	
HuD		7.31		8.15	

Oncimmune have described EarlyCDT Lung as a "rule-in" test to help identify pulmonary nodules that may benefit from earlier diagnosis and treatment. Results of EarlyCDT Lung tests are reported as one of three options:

- No significant levels of autoantibodies detected
  (if no autoantibody is above the low cut-off level)
- Positive-moderate
  (if at least one autoantibody is above the low cut-off level, but below the high-cut-off level)
- Positive-high
  (if at least one autoantibody is above the high cut-off level)

A patient will have a pre-test risk of lung cancer predicted by their sex, age, smoking history, and other risk factors alone, calculated by the Brock (or Swensen/Mayo) nodule malignancy risk calculator. If a person is being assessed after PET-CT scan their risk may be assessed using the Herder malignancy risk tool.

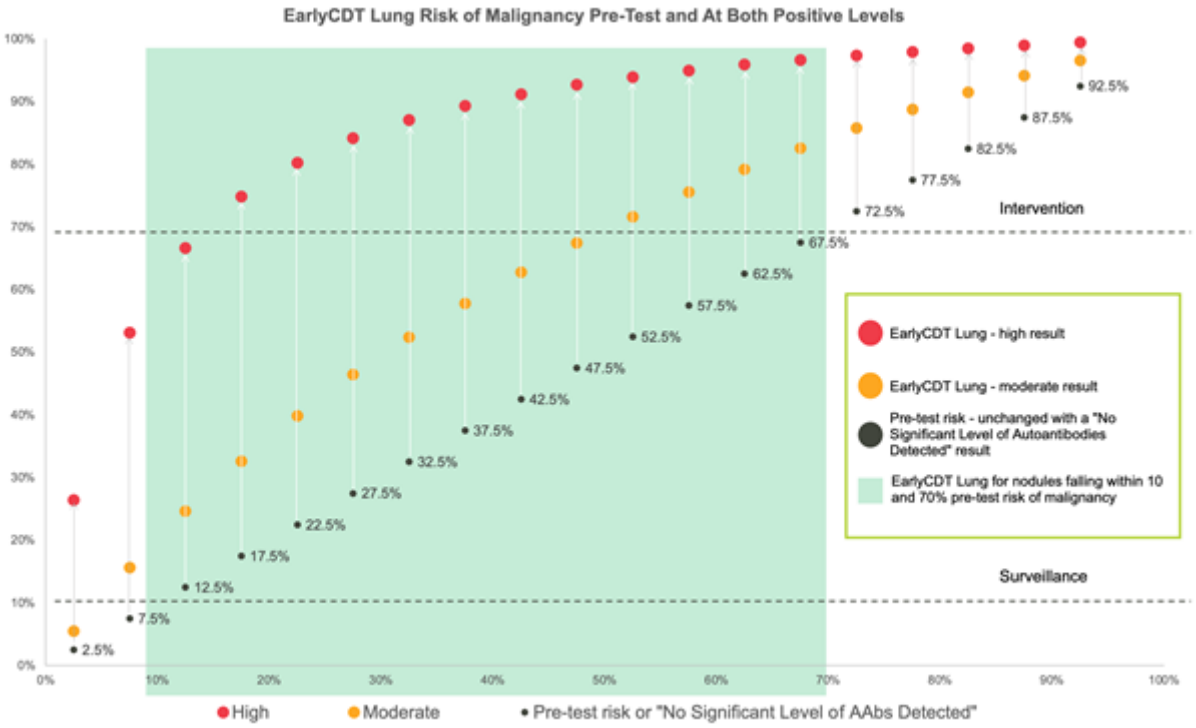
The company proposes that the EarlyCDT Lung test result is used to update these estimated risks of malignancy. For people who test negative with EarlyCDT Lung, the company recommends that the estimated risk is left unchanged from the pre-test risk – in this way defining this test as a 'rule-in' test. Statistically, a patient with a negative test result should see their risk scores downgraded, but this is not proposed for this assessment. Clinical management in these individuals would then proceed in line with the pre-test risk.

A positive-moderate result would lead to a moderate increase in the chance of malignancy from the pre-test risk. If the increase in risk is large enough it might suggest that further diagnostic testing is needed, such as image-guided biopsy. A positive-high result would lead to a substantial increase in the chance of malignancy from the pre-test risk. This might suggest that further diagnostic testing is needed, or if the new risk estimate is sufficiently high, that the person should proceed directly to surgical resection of the nodules.

Oncimmune have produced a graph detailing how the pre-test risk could be modified given a positive-moderate or positive-high EarlyCDT test result (Figure 1). The calculation of post-test mortality risk from the baseline risk obtained from the Swensen/Mayo calculator and the EarlyCDT

Lung test result is described in Healey et al. (2017). [6] The company proposes applying this calculation to pre-test risks derived with both Brock and Herder models.

Figure 1 Impact of EarlyCDT on lung cancer risk assessment



The EarlyCDT Lung test should not be used in people with a previous history of cancer of any type, except for basal cell carcinoma, as other cancers may lead to elevated levels of autoantibodies, and hence to false-positive results. It should also not be used in people known to have diseases that result in an elevated level of serum total protein, for example, myeloma, amyloidosis, and monoclonal gammopathy of undetermined significance.

Other autoantibody tests

No other autoantibody tests will be considered.

Other tools for assessing malignancy risk

No other lung cancer risk assessment tools will be considered.

Diagnostic technologies and pathways

Diagnosis of lung cancer

Lung cancer is often diagnosed later and at a more advanced stage than for other cancers. Early detection is critical for improving outcomes. Diagnosis of lung cancer requires more than one investigation. Initial investigations involve history taking, an assessment of clinical symptoms and signs to exclude other illnesses, such as chest infections.

NICE guidance on diagnosis and management lung cancer 2019 makes several recommendations that optimise the diagnostic pathway and allow flexibility for managing symptoms of lung cancer in a range of people. The guideline recommends that patients with suspected lung cancer should be urgently referred for a chest X-ray. If the results suggest lung cancer, a contrast-enhanced CT scan of the chest, upper abdomen and lower neck is performed.

Further investigations to confirm a diagnosis and to provide information on the stage of the disease are then carried out. These investigations generally include a biopsy for histological confirmation and subtyping but may also include positron emission tomography-computed tomography (PET-CT). This is recommended as a first test after CT with a low probability of nodule malignancy (lymph nodes below 10 mm). [7] Other methods that can diagnose and stage the disease are MRI, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guide fine-needle aspiration (EUS-FNA) [8]. This helps with diagnosis and choosing the best treatment.

Diagnostic pathway for pulmonary nodules

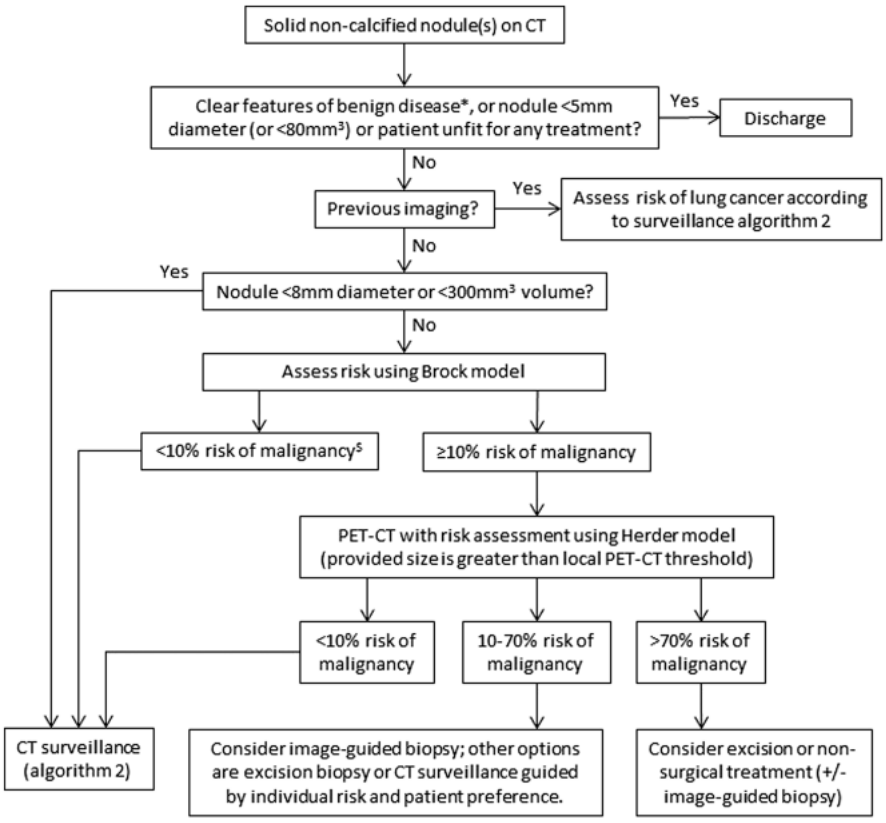
Pulmonary nodules are small growths in the lung, often found when having a chest X-ray or CT scan; for example, when performing a CT scan for conditions unrelated to cancer (incidental findings), when patients are referred to the diagnostic pathway from symptoms, or as part of lung cancer screening. They may be malignant or benign and are managed in accordance with the British Thoracic Society Guidelines for the investigation and management of pulmonary nodules (2015) [7]. In America, the Fleischner Society Guidelines for management of solid nodules (2005) [9] are widely used, but these are not often followed in the UK. Figure 2 provides a recommended pathway for the initial approach to solid pulmonary nodules.

For nodules smaller than 5 mm in diameter (or 80 mm^3 in volume), the British Thoracic Society recommend that people should be discharged with no follow up. People with nodules of 5 to 8mm diameter, or under 300 mm^3 in volume, which are expected to have lower than 10% risk of malignancy, are offered CT surveillance. This involves repeat scanning at 3 months and 1 to 2 years to assess nodule volume doubling time. The frequency and duration of CT scans is determined by nodule size, characteristics, and patient risk factors.

For larger nodules (over 8mm in diameter) the Brock model is used to assess risk of malignancy. If risk is low (<10%) people will be offered CT surveillance. For pulmonary nodules at above 10% risk after Brock model assessment, PET-CT is recommended, and the nodule risk is then recalculated based on the Herder model. The Herder model predicts the risk of malignancy in solid pulmonary nodules using patient characteristics, nodules characteristics, and the degree of F-fluorodeoxyglucose uptake on PET-CT. [10]

For people with 10-70% risk of malignancy using the Herder model, image guided biopsy, excision biopsy or CT surveillance guided by individual risk and patient preference is used. People with risk over 70% are considered for excision or non-surgical treatment (see Figure 2 for more information).

Figure 2 Initial approach to solid pulmonary nodules (British Thoracic Society guidelines 2015)



Population and relevant subgroups

The population is any persons with solid non-calcified pulmonary nodules identified by CT scanning, whether received for conditions unrelated to lung cancer, as part of a cancer diagnosis procedure for people with possible lung cancer symptoms, or as part of a lung cancer screening programme. Specifically, the assessment will examine:

1. People with a nodule of 5-8mm in diameter or 80-300mm^3 in volume
2. People with <10% risk of malignancy using the Brock model after initial CT scan or using the Herder model after PET-CT scan
3. People with 10-70% risk of malignancy using the Brock model, or the Herder model (after PET-CT scan)

People with other cancers, or who have had a cancer diagnosis in the past five years, are excluded from consideration: EarlyCDT is not recommended for such persons.

In all populations, patients would receive an EarlyCDT Lung test and proceed to excision or surgery if deemed to be at high risk of malignancy (>70%). At lower risk of malignancy (<70%) patients would go on to CT surveillance, or possibly biopsy or excision for patients at intermediate risk (10-70%).

Subgroups of interest are:

- Reason for receiving a CT scan
    - Symptomatic
    - Incidental (other medical conditions)
    - Lung cancer screening or lung health check

Further subgroups may be considered, dependent on clinical advice

Place of the intervention in the care pathway

Lung cancer is often diagnosed at a more advanced stage than other common cancers. National Cancer Registration and Analysis Service data show that almost half of all lung cancers are diagnosed at stage 4. Late diagnosis, where curative treatment is not possible, is a contributing factor to poor survival rates for people with lung cancer. Early detection is key to improving outcomes.

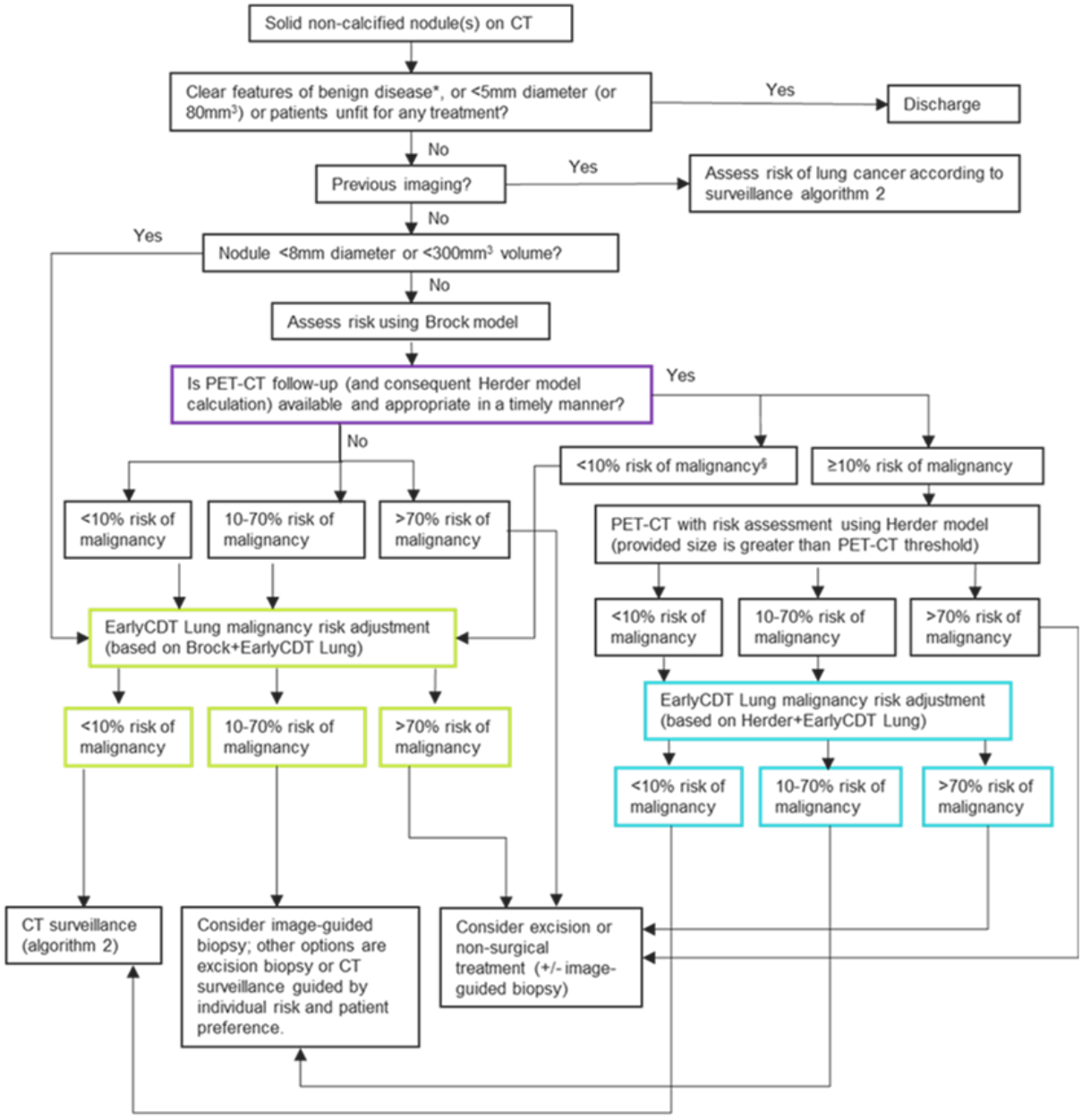
The proposed position of EarlyCDT Lung test within the current British Thoracic Society pathway for solid pulmonary nodules (British Thoracic Society guidelines 2015) is shown in Figure 3. This pathway includes an option where PET-CT scans are not available. Clinical opinions received at scoping suggested that lack of access to PET-CT is not of concern for the NHS. This assessment will therefore only consider the part of the pathway where PET-CT is available, unless evidence or clinical advice emerges to suggest the contrary.

The position of EarlyCDT Lung has been stated to be after the first CT scan, or post PET-CT when the result suggests intermediate risk. EarlyCDT Lung could be used to assess people with nodules <8mm diameter or 300mm^3 volume and those with <10% risk of malignancy using the Brock model. The test could also be used for people in the 10-70% risk of malignancy using the Herder model. If the EarlyCDT Lung test is positive, the malignancy risk is increased and people with a post-test risk of greater than 70% could then be moved into the intervention pathway immediately, without the delay caused by CT surveillance, or further diagnostic testing.

This assessment will consider the following specific locations in the diagnostic pathway where EarlyCDT could be used, the feasibility and relevance of the proposed placements will be established based on clinical advice:

1. For people with nodules 5-8mm in diameter or 80-300mm^3 in volume
2. People that have <10% risk of malignancy using the Brock model after initial CT scan
3. People that have <10% risk of malignancy using the Herder model after PET-CT scan
4. People that have 10-70% risk of malignancy using the Brock model (with EarlyCDT preceding PET-CT)
5. People that have 10-70% risk of malignancy using the Herder model, after PET-CT scan

Figure 3 Proposed position of EarlyCDT Lung within the current BTS pathway for lung cancer



Key

* e.g. hamartoma, typical peri-fissural nodule

§ Consider PET-CT for larger nodules in young patients with low risk by Brock score as this score was developed in screening cohort (50-75 years) so performance in younger patients unproven.

Action after risk assessment

Under the current diagnostic pathway (Figure 2) persons with small nodules or a low malignancy risk (<10%) are offered CT surveillance, with regular CT scans to check for growth of the nodules. Persons with high-risk nodules (>70%) proceed directly to excision or treatment, if suitable, with a biopsy for confirmation, where required. For persons with intermediate risk (10-70%) there are a wider range of options. These include: image guided biopsy or excision biopsy, or CT surveillance. The exact choice of approach will depend on the estimated risk, clinical opinion, and patient preference.

EarlyCDT is proposed to update the individual's risk, but it is currently unclear if or how clinical decision making, conditional on the updated risk score, would be altered. Clinical advice received suggests there may be some uncertainty or difference of opinion. For example, whether patients with small nodules but a positive EarlyCDT test could undergo biopsy, as the nodule may be too small to biopsy effectively; or what level of risk to change from CT surveillance to image-guided biopsy. This assessment will investigate the following possible pathway after EarlyCDT assessment, but will seek for further evidence and clinical judgement on relevant alternatives.

- For small or low risk nodules where risk is below 10% risk after EarlyCDT
    - Offer CT surveillance in accordance with standard pathway
- For small or low risk nodules where risk increases to 10%-70% risk after EarlyCDT
    - Consider PET-CT scan
    - Consider image-guided or excision biopsy (may not be feasible for smaller nodules)
    - Offer CT surveillance (possibly at higher frequency)
- For small or low risk nodules where risk increases to over 70% risk after EarlyCDT
    - This may not be possible given working of risk algorithm
    - Receive PET-CT scan and/or biopsy prior to deciding on surgery
- For intermediate risk nodules still at 10%-70% risk after EarlyCDT
    - Proceed as for standard pathway, although choice of action may be influenced by any change in estimated risk
- For intermediate risk nodules where risk increases to over 70% risk after EarlyCDT
    - Proceed directly to excision or treatment
    - May require PET-CT or biopsy

Objectives

The aim of the project is to appraise existing evidence on the potential clinical and cost-effectiveness of the EarlyCDT Lung test for lung cancer risk classification of solid pulmonary nodules, and to develop a conceptual economic model to provide a common understanding of the evidence requirements and evidence linkages required to undertake a robust cost-effectiveness analysis. To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review and, if feasible, a meta-analysis of the diagnostic accuracy of EarlyCDT Lung for lung cancer risk classification of solid pulmonary nodules.
- To perform a narrative systematic review of the clinical impact and practical implementation of using the EarlyCDT Lung test.
- To perform a scoping review of the evidence on EarlyCDT Lung for uses outside the specified diagnostic pathway (e.g. as a lung cancer screening tool), where this will inform the overall review.

Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of EarlyCDT Lung for lung cancer risk classification of solid pulmonary nodules.
- To review cost-effectiveness models for other surveillance and diagnostic strategies for the identification of malignancy in solid pulmonary nodules, and UK specific cost-effectiveness models of screening strategies for lung cancer.
- To conceptualise a decision model structure to provide a common understanding of how the cost-effectiveness of EarlyCDT Lung for lung cancer risk classification of solid pulmonary nodules in the different positions of the diagnostic pathway proposed for the technology can be quantified.
- To scope existing evidence that could support the implementation of the conceptualised decision model, highlighting key evidential and structural uncertainties.

Methodology

Systematic review of diagnostic accuracy and clinical effectiveness

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement [11, 12].

Literature searching

Comprehensive searches of the literature will be conducted to identify all studies relating to the EarlyCDT Lung test. As the literature is anticipated to be limited, all publications considering EarlyCDT Lung will be searched for.

Focussed and pragmatic searches will be performed to identify literature on the diagnostic accuracy, clinical impact and cost-effectiveness of diagnostic and risk prediction tools for lung cancer, including the Brock and Herder models for assessing the risk of malignancy in pulmonary nodules.

The following bibliographic databases will be searched: MEDLINE, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, and EconLit.

Ongoing and unpublished studies will be identified by searches of ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations & Theses A&I, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. The manufacturer will be contacted to provide details of all complete and ongoing studies they have conducted.

An example search strategy for Ovid MEDLINE is included in Appendix 1. The MEDLINE strategy will be translated to run appropriately on the other databases and resources. No language or date restrictions will be applied to the searches. A study design search filter will not be used.

Reference lists of relevant reviews and studies will be scanned in order to identify additional potentially relevant reports.

Additional literature searching

In order to identify and appraise existing evidence on the clinical and cost-effectiveness of Early CDT Lung, and inform the conceptualisation of a decision model, it is anticipated that sources of evidence on the diagnosis, management and treatment of pulmonary nodules will be required, beyond that reported in the literature on EarlyCDT.

Systematic database searches for additional evidence on clinical effectiveness, cost-effectiveness and quality of life data will therefore also be undertaken. The exact nature of the searches will depend on the extent of the EarlyCDT literature, and what is required to assess the general clinical and economic impact of the test.

Anticipated areas for searching include, but are not limited to:

- UK evidence on the population characteristics of people receiving CT scans which may identify pulmonary nodules (including those under investigation due to incidental findings, the presence of symptoms or from pilot Lung Cancer Screening Programmes), and on the subset of those with pulmonary nodules. Characteristics of interest will include, but are not restricted to, the underlying prevalence of lung cancer, the distribution of stages of disease for those diagnosed with lung cancer and the proportion of indolent cancers.
- Diagnostic accuracy for other tests and investigations used in the diagnostic pathway (e.g. image-guided biopsy)
- Progression of lung cancer in people undergoing CT surveillance, which is likely to be related to the speed of disease progression prior to diagnosis, for example, via nodule volume doubling time,
- Evidence on the treatment and prognosis of lung cancer after diagnosis, including morbidity and mortality according to nature and timing of diagnosis

Database searches will initially focus on identifying systematic reviews in these areas. If systematic reviews are not available, more specific searches to identify studies of relevance to UK practice will be undertaken.

Further, pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence.

Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any titles and abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements will be resolved by consensus or, where necessary, by consulting a third reviewer. Conference abstracts will be eligible and attempts will be made to contact authors for further data, if required.

The following eligibility criteria will be used to identify relevant studies:

Participants

Persons with solid non-calcified pulmonary nodules identified by CT scanning, who may be eligible for further screening or diagnostic testing, including using the EarlyCDT Lung test.

Subpopulations will be people with:

1. nodules between 5-8mm in diameter or 80-300mm^3 in volume
2. nodules over 8mm in diameter and over 300mm^3 in volume with a risk of malignancy estimated to be under 10% (using either Brock or Herder model)
3. nodules over 8mm in diameter and over 300mm^3 in volume with a risk of malignancy estimated to be between 10% and 70% (using either Brock or Herder model)

Persons who have had a previous cancer diagnosis will be excluded. Persons with a malignancy risk above 70% (before EarlyCDT test) are also excluded, as they are recommended to proceed directly to surgical excision, and would not benefit from further testing.

Interventions

The EarlyCDT Lung test. The test will be considered in three possible locations in the diagnostic pathway:

1. In isolation, for nodules between 5-8mm in diameter or under 300mm^3 in volume
2. In combination with the Brock test, where the Brock test suggests a malignancy risk of <10%
3. In combination with the Brock test, and/or Herder test after PET-CT scan, where an intermediate malignancy risk (10 – 70%) is estimated.

No other interventions will be considered

Comparators

The broad comparator will be diagnosis and management of pulmonary nodules using current BTS guidelines (as in Figure 2). Specifically, this will include diagnosis and management of nodules using:

1. The Brock model
2. The Herder model (after PET-CT)
3. No risk assessment (for nodules between 5-8mm in diameter or 80-300mm^3 in volume)

Reference standard

Confirmed diagnosis of a malignant or benign tumour by image-guided biopsy, excision biopsy or surgical resection. For confirming the absence of malignancy, confirmed stable nodule volume after one year, or stable diameter after two years, will also be accepted.

Outcomes

Outcomes of interest will be:

- Diagnostic accuracy
    - Sensitivity, specificity, positive and negative predictive values, diagnostic likelihood ratios, areas under ROC curves
    - For EarlyCDT in isolation and in combination with Brock and Herder models

- Short-term clinical outcomes
    - Impact of test on risk classification
    - Impact on clinical decisions relating to diagnostic or treatment pathway
    - Further tests used
        - Including PET-CT and image-guided or excision biopsy
    - Adverse events during or after testing
- Longer-term clinical outcomes
    - Lung cancer mortality
    - Lung cancer related morbidity
    - Morbidity associated with other diagnostic tests or procedures
    - Overall and disease-free survival
- Patient-focussed outcomes
    - Health-related quality of life
        - SF36, EQ-5D
    - Impact on anxiety and cancer concern
        - False-positive tests
        - Unnecessary biopsies or other procedures
        - Overdiagnosis of tumours not requiring immediate treatment
        - Delay in diagnosing treatable cancers
        - Understanding and communication of test results
- Implementation of test
    - Time to obtain results
    - Laboratory capacity
    - Training requirements
    - Clinical variation in interpreting and using results

Given the limitations of evidence identified in initial scoping searches, it is expected that data will not be available for many of these outcomes. They are listed here to present a complete list of outcomes of interest.

Study designs

Due to the anticipated small number of studies and publications likely to be eligible, all study designs will be included, provided they report evidence on the outcomes listed above.

All forms of evidence will be considered, including both quantitative data and qualitative evidence.

Data extraction

Data on study and patient characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. Where feasible, data will be electronically extracted from figures presented in publications.

Data from relevant studies with multiple publications will be extracted and reported as a single study. The most recent or most complete publication will be used in situations where we cannot exclude the possibility of overlapping populations.

Quality assessment strategy

The quality of the diagnostic accuracy studies will be assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies), modified as necessary to incorporate review-specific issues. QUADAS-2 evaluates both risk of bias and study applicability to the review question. Suitable quality assessment tools such as ROBINS-I will be used for studies of other eligible clinical outcomes and study designs not assessing diagnostic accuracy.

The quality assessments will be performed by one reviewer and independently checked by a second reviewer. Disagreements will be resolved through consensus, and where necessary, by consulting a third reviewer.

Synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables, and plotted in figures where feasible, and as a narrative summary, grouped by population and test characteristics.

Initial searches suggest that the literature on the EarlyCDT Lung test is small and may not be sufficient to perform meta-analyses. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques as described below; however, it is anticipated that a narrative approach to synthesis will be required for most outcomes.

Meta-analysis and narrative synthesis of diagnostic accuracy

Using extracted diagnostic accuracy data from 2 x 2 tables, or reported diagnostic accuracy results, estimates of sensitivity and specificity will be calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. Positive and negative predictive values will also be calculated and presented in figures and tables.

Where three or more studies are available the hierarchical summary ROC (HSROC) model will be fitted to produce summary meta-analysis estimates of diagnostic accuracy and summary ROC curves.

If meta-analysis is not feasible the diagnostic results from different studies will be compared and synthesised using a narrative approach. This will account for the differing study conditions, nature of participants and study quality.

Synthesis of clinical outcomes

Quantitative data on short and long-term clinical outcomes will be tabulated or plotted. Data on survival outcomes will be extracted from Kaplan-Meier curves, where available, and new Kaplan-Meier curves constructed. Where there are sufficient studies reporting the same clinical outcomes, results will be synthesised using standard random-effects meta-analyses.

Where data are insufficient for meta-analysis a narrative synthesis will be performed, by comparing the tabulated results across studies to identify broad evidence of effectiveness.

Synthesis of patient-focussed outcomes and implementation evidence

Any quantitative data on these outcomes will be meta-analysed or synthesised narratively, as described for clinical outcomes.

Qualitative evidence for these outcomes, such as commentary, opinion pieces, research recommendations or the conclusions presented in publications, will be summarised in suitable tables. A broad thematic synthesis will be used to identify key issues arising from the extracted evidence, including key areas of agreement or disagreement across the included literature.

Investigation of heterogeneity and subgroup analyses

For diagnostic accuracy data, we will visually inspect the forest plots and ROC space to check for heterogeneity between study results. To investigate sources of heterogeneity, we will incorporate relevant covariates in the HSROC models, where possible. Where data permits, subgroup analyses will be conducted, by performing separate HSROC models in defined subgroups of studies.

For clinical outcomes where meta-analyses are performed, heterogeneity will be investigated by examining forest plots, considering the I^2 statistic, and if feasible, by performing separate meta-analyses in different subgroups of studies or participants.

Sensitivity analyses

We will carry out sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS-2 or ROBINS-I domain results (for example, by excluding studies with high risk of incorporation bias) and study design (for example, in-procedure versus retrospective evaluation of index test results). This will be performed for diagnostic accuracy and clinical outcomes, where there are sufficient data to permit it.

Where participants from several studies are recruited from the same cohorts and significant overlap is suspected, data from only one study with the most reliable reporting will be included in the main analyses. The impact of studies where substantial overlap is suspected, or where only a composite outcome is reported, will be explored by including/excluding them from the main analyses.

Scoping of EarlyCDT Lung evidence outside the main diagnostic pathway

The database searches will identify all published literature on the EarlyCDT Lung test. Some of the literature will not eligible for the main review, by not meeting the inclusion criteria, or falling outside the proposed diagnostic pathway for the use of EarlyCDT Lung (for example, where it is used as a lung cancer screening test).

This additional literature will be summarised in tables. Where this literature informs understanding of the clinical impact of EarlyCDT Lung, or informs the economic analysis, a narrative summary of the evidence will be produced.

Additional clinical evidence

To support the conceptualisation of the decision model on EarlyCDT Lung, we expect additional reviews to be required (See section “Additional literature searching” above).

Systematic reviews (or UK-relevant studies in the absence of reviews) will be summarised using narrative synthesis. If relevant and feasible, results from individual studies will be pooled using standard random effects meta-analysis. Findings will be summarised in suitable tables and figures and compared to the findings for the literature on EarlyCDT Lung.

Systematic review of cost-effectiveness evidence and conceptualisation of a decision model

Given the restricted decision problem for this assessment, this component of the work aims to:

- Systematically review and critically appraise existing cost-effectiveness evidence on the use of EarlyCDT lung for people with solid pulmonary nodules who are referred to the diagnostic pathway for lung cancer, and
- Conceptualise a decision model on EarlyCDT lung for lung cancer risk classification of solid pulmonary nodules, compared to current clinical practice, with appropriate consideration for:
    - relevant diagnostic pathways of lung cancer in the UK and potential placement(s) of EarlyCDT-lung,
    - the nature of the evidence linkages of intermediate outcome measures, such as diagnostic accuracy, to final health outcomes including morbidity and mortality associated with the diagnosis and treatment of lung cancer, that would be required to inform a formal cost-effectiveness analysis,
    - the identification of existing evidence to inform the model, highlighting data gaps and limitations in the available evidence.

Systematic review of cost-effectiveness evidence

Database searching

The results of the searches carried out for the systematic review of clinical effectiveness will be used to identify any relevant studies of the cost-effectiveness of EarlyCDT lung for lung cancer risk classification of indeterminate pulmonary nodules.

A broad range of studies will be considered, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included.

Cost-effectiveness evidence identified by the search will be appraised for quality and summarised.

Synthesis of existing evidence

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison. In particular, information will be extracted on:

- The comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling) and primary outcome specified for the economic analysis;
- Details of adjustment for quality-of life, categories of direct costs and indirect costs;

- Estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

Preliminary scoping searches identified two relevant publications for this decision problem. [13, 14] Neither of these studies refer to direct evidence on outcomes for EarlyCDT Lung. Instead, both use accuracy evidence for the technology within a linked evidence approach to reflect the indirect mechanism of value accrual arising from tailoring treatment decisions (or other courses of action that impact on patient outcomes) to patient characteristics.[15] Both studies evaluate the use of EarlyCDT-Lung to route patients to confirmatory diagnosis/treatment instead of CT surveillance, and in both the additional value of EarlyCDT-Lung arises from earlier diagnosis of malignancy. The link to impacts on long term costs and health relies on assumptions over the identification of disease at earlier stages (stage-shift) and the extent of misclassification. Neither of these studies seem to fully model treatment pathways (we will seek for further clarification on this), but instead use real world evidence assumed to be reflective of current practice in the setting of interest.

The review will examine in detail the assumptions underpinning the modelling / evidence-linkage approaches, with the aim of identifying important structural assumptions and relevant data sources. Key areas of uncertainty will be highlighted and considerations given to issues and challenges in generalising from the results of existing models.

The appropriateness of previously developed models will be assessed based on:

i) Consistency with the decision problem being considered in this assessment;
ii) Relevance of outputs for decision making (i.e. to estimate long-term NHS costs and QALYs based on morbidity and mortality associated with a more accurate and timely diagnosis of lung cancer); and
iii) Flexibility to address different routes of referral to the diagnostic pathway for lung cancer (pilot Lung Screening Programmes currently underway in the UK, referral via symptoms, and referral from incidental findings from investigation on unrelated conditions).

Additional targeted searches for cost-effectiveness studies

To allow a fuller critical appraisal of the assumptions and data sources used in the existing cost-effectiveness studies and to assist in the conceptualisation of a new decision model, further targeted literature searches for cost-effectiveness studies will be undertaken to identify a broader set of approaches (including relevant sources of evidence) for the evidence-linkage. These will aim to identify cost-effectiveness models evaluating other diagnostic strategies for lung cancer (such as those relating to the use of the Brock and Herder models or of PET-CT scan), and UK specific cost-effectiveness studies on screening approaches for lung cancer. Screening occurs upstream from diagnosis of lung cancer and, in common with the existing EarlyCDT Lung cost-effectiveness studies [13, 14], UK cost-effectiveness models on screening (such as Griffin et al. 2020 [16]) use a mechanism for evidence linkage (based on stage-shift). It is hence important to consider this broader evidence as part of the conceptualisation and development of the new decision model.

Studies identified in these targeted reviews (both of diagnostic and screening models in lung cancer) will not be subject to a formal assessment but we will describe the assumptions and data sources underpinning the linked-evidence approach, with particular emphasis on the modelling of long term health outcomes and costs. If the linked evidence approaches and data sources from these models are considered appropriate, contemporary and relevant for the current decision problem, these studies will be used in the conceptualisation of an analytical model, to support the identification of important structural assumptions and parameter estimates. The appropriateness for the current decision problem of the evidence linkage mechanisms and data sources used in these previously developed models will be assessed as specified in the 'Synthesis of existing evidence' section.

Conceptualisation of the decision model and identification of evidence requirements for future appraisals

This component of work will focus on the conceptualisation of a decision model, structured according to good practice recommendations[17, 18] , to quantify the broader consequences to health and overall NHS and PSS costs associated with the use of EarlyCDT Lung (i.e., its cost-effectiveness). The model will be specified to comply with the NICE reference case. [19] The key outputs of this element of work will be:

- the development of an appropriate model structure accompanied by a description of key structural assumptions and of the nature of the evidence linkages required, and
- an outline of key parameter inputs required, including an assessment of the strengths and limitations of existing evidence and possible data gaps that would need to be addressed in future research.

We will also consider how the conceptualised model would need to be implemented and whether a discrete event simulation (DES), as opposed to a more conventional state-transition modelling approach, would be required.

The conceptualisation process will combine problem-oriented and design-oriented elements (see Table 2).[18] These activities will assist in translating the shared understanding of the decision problem towards a model-based solution.

Table 2 Elements of model conceptualisation

Elements of conceptualisation	Aims
Problem-orientated	• To ensure a common understanding of how the model will capture the impact of EarlyCDT Lung on costs and health outcomes. • To ensure that the proposed model will be clinically relevant - that all relevant events, resources, costs and health outcomes have been included and that these reflect current knowledge of disease and treatment systems.
Design-oriented	• To provide a common understanding regarding model evidence requirements prior to model implementation. • To provide an explicit platform for considering and debating alternative model structures and other model development decisions prior to implementation. • To provide the conceptual basis for reporting the methods and assumptions employed within the final implemented model • To provide a basis for comparison and justification of simplifications and abstractions during model development.

The problem-oriented element of the conceptual modelling will describe: (i) current clinical understanding of the clinical condition and important events; and (ii) clinical pathways through which patients are detected, diagnosed, treated and followed-up. The design-led element of conceptual modelling will identify potentially feasible and credible model choices to represent the events and pathways deemed relevant in the problem-oriented element, considering the availability of existing evidence.

Mapping value drivers for EarlyCDT Lung

The mapping of current diagnostic pathways and the potential placement(s) for EarlyCDT Lung (Figure 2 and Figure 3) will be initially extended to identify how EarlyCDT Lung can be used to guide clinical decisions, and establish the mechanisms for clinical and economic impact of this technology (including any potential consequences of suboptimal treatment decisions in those misclassified) – i.e., the value drivers for EarlyCDT-Lung in this decision problem. In terms of health effects, this entails, for example, identifying: [20]

- any direct health effects of the technology,
- effects derived indirectly by altering clinical decision on further tests or treatments,
- effects on the timing of decisions and actions, or
- influence on patient and clinician perspectives.

In terms of costs, both implications for resource use and the processes of health care service provision of the use of the test in relation to its alternative(s) will be established.

The identification of value drivers for this technology will be done in close collaboration with clinical experts and with appropriate consideration for existing heterogeneity in clinical practice.

Evidence linkage

To identify possible mechanisms for evidence linkage (for reflecting the consequences of diagnostic test accuracy as final cost and health outcomes), we will use the findings from the cost-effectiveness model reviews. This will involve consideration of how each diagnostic pathway impacts on the identification of lung cancer and its timing, linking this to the possibility of curative and non-curative treatment for lung cancer and its health and resource outcomes. We will consider the possibility of misdiagnosis and overdiagnosis, both leading to unnecessary tests, biopsies and excisions which have resource and health implications.

Scoping searches for additional evidence

The conceptualisation process will also be assisted by targeted searches to scope evidence on key components of the decision problem. These will include the searches described in the *Systematic review of diagnostic accuracy and clinical effectiveness* section for population characteristics, diagnostic accuracy, progression of lung cancer in people undergoing CT surveillance and treatment and prognosis of lung cancer. Whilst the full definition of these components will have to await the findings of the systematic review of cost-effectiveness evidence, we are likely to conduct further searches on:

- Adverse events associated with tests and invasive procedures (e.g., needle biopsy with or without excision),
- Resource utilisation, costs and health-related quality of life implications of:
    - Tests, including EarlyCDT and CT surveillance, and follow-up tests in the diagnostic pathway including imaging and histopathology costs, such as PET-CT scans. For costing, this will include relevant aspects such as throughput, costs of staff and of any required training in the use of the technology;
    - Subsequent invasive tests and procedures, such as biopsy, and their complications;
    - Other forms of lung cancer treatment and longer-term outcomes and costs associated with disease progression after initial treatment, and
    - Health and cost implications arising from false positive test results and overtreatment of indolent nodules, including follow-on diagnostics and inappropriate treatment.

Software

Any required data management and statistical analyses will be conducted in R using standard R libraries, the *meta* library for meta-analysis, and in-house code for diagnostic meta-analysis.

Handling information from the companies

Any confidential information or data supplied to the EAG by the company, or any other agency, will be held on a secure server accessible only to the EAG. Confidential information will be clearly marked as either academic in confidence or commercial in confidence in the EAG report and all other project documentation.

Competing interests of authors

None of the authors have any conflicts of interest.

Timetable/milestones

Milestone	Date to be completed
Submission of final protocol	26 February 2021
Submission of progress report	7 May 2021
Submission of draft Diagnostic Assessment Report	21 June 2021
Submission of final Diagnostic Assessment Report	19 July 2021

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Appendix 1: MEDLINE search strategy

With subsections to identify EarlyCDT studies, autoantibody studies and studies in lung cancer

Ovid MEDLINE(R) ALL <1946 to February 12, 2021>

1 EarlyCDT.af.
2 Early CDT.af.
3 Early-CDT.af.
4 Early cancer detection test.af.
5 1 or 2 or 3 or 4
6 ECLS trial$.af.
7 5 or 6

8 Oncimmune.af.
9 7 or 8

10 exp Autoantibodies/
11 (autoantibod$ or auto-antibod$ or AABT or AAb or AAbs).ti,ab.
12 10 or 11

13 exp Lung Neoplasms/
14 Solitary Pulmonary Nodule/
15 ((lung$ or pulmonary or bronchial or bronchogenic) adj3 (neoplas$ or carcinoma$ or cancer$ or nodule$ or tumor$ or tumour$ or malign$ or adenocarcinoma$ or blastoma$)).ti,ab.
16 NSCLC.ti,ab.
17 SCLC.ti,ab.
18 ((lung$ or pulmonary) adj2 (lesion$ or mass or masses)).ti,ab.
19 ((noncalcified or non calcified) adj2 (nodule$ or lesion$ or mass or masses)).ti,ab.
20 NCPN.ti,ab.
21 ((ground-glass or solid or part-solid or subsolid or sub-solid) adj2 (nodule$ or lesion$ or mass or masses)).ti,ab.
22 ground glass opacit$.ti,ab.
23 (GGN or GGNs or GGO).ti,ab.
24 ((benign or malignant or indeterminate) adj2 nodule$).ti,ab.
25 coin lesion$.ti,ab.
26 (IPN or IPNs).ti,ab.
27 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 12 and 27
29 9 or 28
30 exp animals/ not humans.sh.
31 29 not 30