NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics consultation document

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

The National Institute for Health and Care Excellence (NICE) is producing guidance on using EarlyCDT Lung in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on EarlyCDT Lung. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the diagnostics assessment programme manual.

Key dates:

Closing date for comments: 3 November 2021

Second diagnostics advisory committee meeting: 17 November 2021

1 Recommendations

1.1 There is not enough evidence to recommend routine use of EarlyCDT Lung for assessing the risk of lung cancer in solid lung nodules.

1.2 Further research is recommended (see section 4) on:

- 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.

Why the committee made these recommendations

EarlyCDT Lung is used to assess the risk of lung cancer in solid lung nodules. Accurate risk assessment can prevent delayed treatment of malignant nodules or unnecessary biopsies of benign nodules. But, the evidence of how well EarlyCDT Lung works is limited and uncertain.

The company intends for EarlyCDT Lung results to be used to update a person's existing lung cancer risk assessment. Most studies used EarlyCDT Lung results to classify nodules as benign or malignant. Therefore, it is unclear how EarlyCDT Lung results would be used alongside existing risk assessment models.

It is also unclear how EarlyCDT Lung will affect lung nodule management in the NHS. This is because there were no studies to show how EarlyCDT Lung affects clinical decision making for people with lung nodules and there is significant variation in management of intermediate-risk nodules in the NHS.

It is also difficult to assess the impact of EarlyCDT Lung on long-term patient outcomes. This is because there is limited data on the factors that might affect

disease progression, how lung nodules change during CT surveillance and the likelihood and impact of unnecessary biopsy or surgical removal.

The cost effectiveness of EarlyCDT Lung was not assessed because of the limited clinical evidence, so it has not been recommended. Further research is needed on both the EarlyCDT Lung test and on the impact of current lung nodule management. Without more data collection on current management, it will be difficult to quantify the impact of EarlyCDT Lung and other new tests for assessing lung nodules.

2 The diagnostic tests

Clinical need and practice

2.1 In the NHS, lung nodules are managed in line with the British Thoracic Society's guidelines for the investigation and management of pulmonary nodules (2015). The guideline recommends the same diagnostic approach for nodules detected incidentally, due to symptomatic presentation, or through routine screening. People with nodules below 5 mm in diameter or 80 mm^3 in volume are discharged without follow up. CT surveillance is offered for nodules between 5 mm and 8 mm in diameter or 80 mm^3 and 300 m^3 in volume. For nodules over 8 mm in diameter or 300 m^3 in volume, the Brock model is used to calculate risk of malignancy. CT surveillance is offered to people with nodules that are below a 10% risk score using the Brock model.

2.2 The Herder model is used to calculate malignancy risk of nodules after a Brock risk assessment of 10% or above and a subsequent positron emission tomography CT (PET-CT) scan. For nodules with a Herder risk score below 10%, CT surveillance is offered. People with risk over 70% are considered for excision or non-surgical treatment. Within the intermediate group (between 10% and 70% risk of malignancy) the guidelines for subsequent care are more varied, with possible management options including image-guided biopsy, CT surveillance and excisional biopsy. Decisions are based on risk of malignancy and

additional factors such as patient fitness and preferences, and nodule characteristics.

2.3 Accurately differentiating between malignant and benign nodules as soon as possible is important. People have more treatment options and potentially better outcomes when lung cancer is diagnosed in its early stages. However, misdiagnosis of a benign nodule as malignant, could result in further imaging tests (with higher radiation exposure) or invasive procedures, such as biopsy or resection, which carry risks of adverse events.

2.4 EarlyCDT Lung could help identify malignant lung nodules that need immediate treatment or a biopsy. This could result in treatment being offered earlier, potentially giving improved patient outcomes. It could also reduce the number of people on CT surveillance, patient waiting times and radiologist time and enable more efficient use of NHS resources.

The intervention

EarlyCDT Lung

2.5 EarlyCDT Lung (Oncimmune) is a blood test to assess the malignancy risk of solid lung nodules found by chest CT or X-ray. It is an enzyme-linked immunosorbent assay and is available as a CE-IVD kit. EarlyCDT Lung 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). After blood collection, the test is carried out in a laboratory within a secondary healthcare setting. Positive results are reported as 'positive-moderate' if at least 1 of the 7 autoantibodies is elevated above a predetermined 'low' threshold, but all are below the 'high' threshold. If at least 1 of the 7 autoantibodies is elevated above the 'high' predetermined threshold, the test is reported as 'positive-high'.

2.6 EarlyCDT Lung is proposed as a 'rule-in' test to be used in addition to standard care for the detection of lung cancer. A positive EarlyCDT Lung

result would be used to update a pre-test malignancy risk from either the Brock or Herder risk models. The pre-test risk would be unchanged if the EarlyCDT Lung result is negative. The estimated post-test risk is intended to help clinicians make decisions about further testing or intervention.

The comparators

Brock and Herder risk models

2.7 The Brock model is used to calculate a nodule's risk of malignancy, which is based on patient characteristics (such as age, gender and smoking history) and on nodule characteristics. The Herder model is used to calculate malignancy risk after a Brock risk assessment of 10% or above and a PET-CT scan. The Herder model is based on patient characteristics, nodule characteristics, and the degree of F-fluorodeoxyglucose uptake on PET-CT.

3 Committee discussion

The diagnostics advisory committee considered evidence on EarlyCDT Lung for lung cancer classification of solid lung nodules from several sources, including a diagnostics assessment report and an overview of that report. Full details are in the project documents for this guidance.

A test that accurately predicts lung nodule malignancy risk could reduce anxiety in people with nodules

3.1 The patient expert emphasised the importance of people understanding their options based on malignancy risk assessments. A test that correctly identifies high-risk nodules could reduce both the number of people on CT surveillance and the anxiety associated with waiting. However, patient experts were aware of the trade-off between the benefits of earlier diagnosis and treatment, and the risks of overdiagnosis leading to harms from unnecessary biopsies and treatment. The committee acknowledged the potential benefit of EarlyCDT Lung in reducing anxiety and the impact

it could have in helping people, along with their clinician, to decide which further testing or treatment steps are best.

Clinical effectiveness

The evidence on the diagnostic accuracy of EarlyCDT Lung in people with lung nodules is limited

3.2 The external assessment group's (EAG) systematic review found only 5 study populations in which EarlyCDT Lung data on people with nodules was reported. Of the 5 studies, only 2 were reported in full and both had a high risk of bias. The EAG's meta-analysis estimated that EarlyCDT Lung has a sensitivity of 20.2% (95% confidence interval [CI] 10.5 to 35.5) and specificity of 92.2% (95% CI 86.2 to 95.8). These are different to the company's estimates, which were based on a single study (41.3% sensitivity and 90.6 % specificity; Healey et al. 2017). The EAG suggest that the inclusion of case-control data in Healey et al. (2017), where cases were people diagnosed with lung cancer and controls were healthy volunteers, could account for the difference in accuracy estimates. It suggested that poorer diagnostic accuracy among smaller nodules, which are less likely to be present in the confirmed cancer cases, could bias the results. The committee discussed if accuracy data from screening studies was generalisable to this decision question. The EAG commented that the malignancy risk is likely to differ between a screening population – that is people who may or may not have nodules – and a population of people who have nodules. Therefore, the screening data cannot be extrapolated reliably. The committee concluded that further evidence of the accuracy of EarlyCDT Lung in people with nodules is needed (see section 4.1).

The risk model used to calculate post-test malignancy risk from the EarlyCDT result and the pre-test risk needs further validation

3.3 The committee understood that positive EarlyCDT Lung results are intended to be combined with a pre-test risk (using existing malignancy risk assessment models) to give a post-test risk. The EAG's report

highlighted that the risk model (Healey et al. 2017) provided by the company to recalculate risk scores, may overestimate diagnostic accuracy as it was based on evidence from case-control studies (see section 3.2). The committee agreed that combining the tests was an appropriate way to estimate malignancy risk, but also noted that the accuracy data on these test combinations is very limited. The committee recommended that further validation of the model that combines the EarlyCDT result with existing risk models is needed (see section 4.1).

It is unclear whether ongoing studies will provide relevant accuracy data

3.4 The EAG report identified 2 potentially relevant ongoing studies of EarlyCDT Lung: 1 case-control study in China aiming to recruit 1,000 people and the other an observational screening study in the US. The committee also discussed the IDx Lung study that started in May 2021. It is unclear from published literature where in the pathway EarlyCDT is positioned in these trials, and whether it will be used to update risk scores as indicated. The committee concluded that further research is needed on the accuracy of EarlyCDT Lung (see section 3.2) itself and on the accuracy of combining the test results with other risk models (see section 3.3). The committee also noted that the gold standard reference test in a diagnostic accuracy study should be histological confirmation of cancer or minimum 2 years follow up with CT surveillance (see section 4.1).

Evidence on the impact of EarlyCDT Lung on clinical management decisions is limited

3.5 The EAG's report found no evidence on how EarlyCDT Lung testing affects changes in clinical decision making for people with lung nodules. The EAG's simulation study indicated that EarlyCDT Lung is unlikely to significantly impact clinical management in low-risk nodules (below 10%). EarlyCDT Lung may improve clinical management in intermediate-risk nodules, particularly for those with a higher pre-test risk (above 48%). The data feeding into the simulations however was at high risk of bias, and the simulation had to use assumptions because of weak evidence. The

committee discussed that data is needed to demonstrate if a positive EarlyCDT Lung test result changes decision making such as moving from CT surveillance to biopsy or from biopsy to immediate excision without biopsy (see section 4.1).

The likelihood and impact of unnecessary biopsy or resection of indolent and benign nodules is unknown

3.6 The EAG and committee discussed the risk and harms of false positive test results (benign nodules incorrectly identified as malignant). The committee discussed that the safety of biopsy and surgical excision has improved in recent years, but it noted that there may still be adverse effects and anxiety for patients. It also discussed the harms of diagnoses in people with limited life expectancy or with multiple comorbidities, for whom treatment is not possible but the test could cause unnecessary anxiety. The committee discussed that data on the harms of biopsy and excision should be available through existing databases and recommended that it could be obtained as part of a large audit (see section 4.2).

There is limited understanding of how knowledge of nodule malignancy risk and CT surveillance impact health-related quality of life

3.7 In the EAG report no studies of EarlyCDT Lung in the target population reported health-related quality of life outcomes. One screening study (Early Detection of Cancer of the Lung Scotland trial) did report that there were no statistically significant differences in lung cancer worry, health anxiety, illness perceptions, lung cancer risk perception or intrusive thoughts, between people with and without lung nodules at 3 months and 6 months. The committee heard that 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. The committee concluded that EarlyCDT Lung test results could have an impact on anxiety, but that no evidence is available to support this.

A linked-evidence modelling approach would be appropriate to estimate the impact of EarlyCDT Lung on long-term patient outcomes

3.8 No direct trial evidence was found on how EarlyCDT Lung impacts on long-term patient outcomes, such as lung cancer related mortality and morbidity, morbidity associated with other diagnostic tests or procedures, and overall and disease-free survival. The committee noted that this was an important factor to understand, but heard that a randomised control trial for assessing the impact of EarlyCDT Lung on patient outcomes would not be feasible because of the number of patients needed to power the study. The committee agreed that a linked-evidence modelling approach could be used to estimate the impact of EarlyCDT Lung on long-term patient outcomes. This method would link new diagnostic accuracy and decision impact data to existing clinical outcome data on lung nodules and lung cancer (see section 4.1).

Cost effectiveness

Current management practice for intermediate-risk nodules is undefined

3.9 The EAG's report highlighted variation in management practices and lack of evidence around decisions in managing intermediate nodules. Under the British Thoracic Society's (BTS) guidelines for the investigation and management of pulmonary nodules (2015) people with nodules in the intermediate 10% to 70% risk group may be offered CT surveillance, biopsy or surgical excision. A clinical expert explained that in the BTS guidelines, the defined malignancy risk categories for initiating Brock and Herder risk assessment, and for guiding further testing and treatment, were mostly based on evidence graded at a level 3 (non-analytical studies; for example, case reports, case series). The committee recommended that an audit of existing data should be carried out to determine how these nodules are currently managed in NHS practice. It considered that the impact of EarlyCDT Lung and other tests would be difficult to ascertain without first understanding what happens in current clinical practice (see section 4.2).

The clinical consequences of CT surveillance of lung nodules, such as stage progression, are uncertain

3.10 The committee noted that the potential benefit of EarlyCDT Lung is that it could identify malignant lung nodules earlier than standard tests such as CT surveillance. This could lead to earlier treatment and improved patient outcomes. It also noted that there was no evidence that stage progression of malignant nodules happens in the timeframe of CT surveillance. The EAG commented that modelling studies of lung cancer screening strategies often evaluate the likelihood of pre-clinical stage progression over time, but cautioned that the generalisability of this evidence is unclear. The committee noted that it is important to understand if and how lung nodules progress during CT surveillance. This information could then be used in a linked-evidence modelling approach to understand if EarlyCDT Lung could result in meaningful earlier diagnosis of malignant lung nodules. The committee discussed that this data should be available through existing databases and recommended that it could be obtained as part of a large audit (see section 4.2).

Data on patient and nodule characteristics and how different factors impact disease progression would be helpful for future modelling

3.11 The EAG report highlighted that better characterisation of the target population and nodule characteristics is needed for future assessments. It noted that the group of people with lung nodules is heterogeneous and different factors may impact on the speed of progression of malignant lung nodules. The committee agreed that this is important data to collect because it could be used in future modelling of the clinical and cost effectiveness of EarlyCDT Lung or other new tests in this area (see section 4.2).

EarlyCDT Lung is not recommended for routine use in the NHS

3.12 The committee acknowledged that the evidence to support the use of the EarlyCDT Lung to assess the malignancy risk of solid lung nodules is weak. So, the full benefits and potential harms of widespread use of

EarlyCDT testing cannot be reliably quantified. There is no robust data to show the clinical utility of EarlyCDT testing, specifically:

- how well it distinguishes between benign and malignant nodules
- how it influences clinical decision making
- the impact it has on longer-term clinical outcomes.

The committee concluded that it was unable to recommend the widespread use of EarlyCDT Lung testing. It recommended that further research is needed to address the limitations in the evidence (see section 4.2).

A better understanding of the target population and the current diagnostic pathway is needed

3.13 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 (see section 2.3). These issues include:

- How patient and nodule characteristics impact disease progression (see section 3.11)
- How intermediate-risk nodules are currently managed (see section 3.9)
- The clinical consequences of CT surveillance of lung nodules (see section 3.10)
- The prevalence, likelihood and impact of false-positive test results and overdiagnosis (see section 3.6).

4 Recommendations for further research

4.1 Further research is recommended on:

- The accuracy of EarlyCDT Lung, and the validity of the risk models used to combine EarlyCDT Lung results with the Brock and the Herder risk models.

- The impact of EarlyCDT Lung on clinical management decisions.

4.2 A large retrospective audit is recommended to:

- Understand how patient and nodule characteristics impact on malignancy prevalence and disease progression.
- Understand current practice regarding clinical management of people with intermediate-risk lung nodules.
- Determine the clinical consequences of CT surveillance, including the likelihood of disease progression during CT surveillance.
- Determine the likelihood and impact of unnecessary biopsy or resection of indolent and benign nodules

If existing data on these points is limited or not routinely collected, a prospective data collection should be undertaken to obtain it.

5 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 4 into its guidance research recommendations database and highlight these recommendations to public research bodies.

6 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese
Chair, diagnostics advisory committee
October 2021

7 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Matthew Callister

Consultant respiratory physician, Leeds Teaching Hospitals

Phil Crosbie

Senior lecturer in respiratory medicine, University of Manchester

Jesme Fox

Lay specialist

Seamus Grundy

Consultant respiratory physician, Salford Royal Hospital

Helen Johnstone

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NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Vera Unwin

Topic lead

Frances Nixon

Technical adviser

Donna Barnes

Project manager

ISBN: