

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

Diagnostics guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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This guidance replaces MIB209.

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. But, most studies used EarlyCDT Lung results to classify nodules as benign or malignant. Therefore, most of the existing data does not represent the intended use of the test in updating estimates of lung cancer risk and further validation is needed.

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.

Because of the limited clinical evidence, the cost effectiveness of EarlyCDT Lung was not assessed and 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 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 guidelines recommend 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 mm³ in volume are discharged without follow up. CT surveillance is offered for nodules between 5 mm and 8 mm in diameter or 80 mm³ and 300 m³ in volume. For nodules over 8 mm in diameter or 300 m³ 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, 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 in 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 of the evidence are in the [project documents on the NICE website](#).

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 malignant nodules in people who would otherwise be placed on surveillance, could reduce the number of people on CT surveillance and the anxiety associated with waiting. Malignant nodules could be biopsied and treated earlier, potentially leading to better health outcomes. 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 and accuracy estimates are very uncertain

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, 3 were conference abstracts and only 2

were reported in full. The 2 complete publications had a high risk of bias in terms of patient selection, and the German study (Gonzalez et al. 2021) was also at high risk of bias in the flow and timing domain of the quality assessment. There were also serious concerns about the applicability of the results of these studies to NHS practice because of the position in the pathway where the test was used and how the test was used and interpreted. 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). The committee discussed that the EAG's estimate was uncertain with wide confidence intervals for the sensitivity. It noted that these results are different to the company's estimates, which were based on a single study that had 41.3% sensitivity (95% CI 35.0 to 47.6) and 90.6% specificity (95% CI 87.1 to 94.1; 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 given the uncertainties around the accuracy estimates and the populations studied, 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 Lung 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 Lung 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 heard that the study in China is assessing a different version of EarlyCDT Lung that was specifically developed for the market in China and would therefore not be generalisable to the UK. They also heard that the US study is due to be published in 2022. The committee also discussed the IDx Lung study that started in May 2021. It is unclear from published literature where in the pathway EarlyCDT Lung 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 itself (see [section 3.2](#)) 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 a 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 Lung testing cannot be reliably quantified. There is no robust data to show the clinical utility of EarlyCDT Lung 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 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:

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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.

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