EarlyCDT Lung blood test for risk classification of solid pulmonary nodules: systematic review and economic evaluation

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Declared competing interests of authors: Marta Soares reports membership of the Health Technology Assessment General Committee (2020 to present).

Published December 2022
DOI: 10.3310/IJFM4802

Scientific summary

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Health Technology Assessment 2022; Vol. 26: No. 49
DOI: 10.3310/IJFM4802

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Background

Pulmonary nodules are small growths in the lung, often found when having a chest computerised tomography (CT) scan. These nodules may be cancerous, and so require treatment. In the UK they are generally managed in accordance with the British Thoracic Society (BTS) guidelines.

For very small nodules, people are discharged with no follow-up. For smaller nodules with < 10% risk of malignancy, patients are offered regular surveillance using CT. For larger nodules, the Brock model is used to assess risk of malignancy. If risk is low (< 10%), people will be offered CT surveillance. For higher-risk nodules, positron emission tomography–computerised tomography (PET-CT) is recommended, and the nodule risk is then recalculated using the Herder model. For people with 10–70% risk of malignancy, biopsy, excision biopsy or CT surveillance may be used. People with a risk of > 70% are considered for excision or non-surgical treatment.

EarlyCDT Lung (Oncimmune Holdings plc, Nottingham, UK) is a blood test that could potentially be used to assess the malignancy risk of people at risk of lung cancer. The test measures the presence of seven autoantibodies. A blood sample is considered to indicate malignancy when at least one of the seven autoantibodies is elevated above a predetermined cut-off value. Oncimmune proposes that the EarlyCDT Lung test result is used to update a patient's estimated risk of malignancy, with a positive test result increasing the risk.

Objectives

The aim of the project was to appraise the existing evidence on the potential clinical effectiveness 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.

Methods

Diagnostic accuracy and clinical effectiveness

A systematic review was conducted to identify all published studies of EarlyCDT Lung. Comprehensive database searches of MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), EMBASE, Cochrane Central Register of Controlled Trials, Science Citation Index, EconLit, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database, NHS Economic Evaluation Database (NHS EED) and the international Health Technology Assessment database were carried out on 8 March 2021. Further database searching was performed to identify evidence on other parts of the diagnostic pathway, specifically Brock and Herder models, CT surveillance, PET-CT and biopsy methods.

The key inclusion criteria were as follows:

- persons with solid pulmonary nodules identified by CT scanning, who may be eligible for further diagnostic testing
- use of EarlyCDT Lung, or other procedures listed above

- malignancy confirmed by biopsy or surgical resection; benign nodules confirmed by clinical follow-up of at least 1 year
- studies reported diagnostic accuracy data, or any data on the clinical impact of the technology.

Data on study and patient characteristics and results were extracted. Data were also electronically extracted from figures. Data from relevant studies with multiple publications were extracted and reported as a single study. The quality of the diagnostic accuracy studies was assessed using the quality assessment of diagnostic accuracy studies-2 tool.

Given the limitations of the evidence, a narrative synthesis approach was used, summarising evidence from each study using tables and figures. Meta-analysis of diagnostic accuracy data (sensitivity, specificity and area under the receiver operating characteristic curve) was used when there were sufficient data. Data on diagnostic accuracy for EarlyCDT Lung were combined with data on lung cancer prevalence and nodule risk based on the Brock and Herder models to simulate the potential clinical impact of using EarlyCDT Lung.

Cost-effectiveness

Cost-effectiveness evidence on EarlyCDT Lung for the diagnosis of lung cancer was identified by the abovementioned database searches; the evidence was narratively summarised and tabulated. Studies were appraised for their quality and appropriateness to the decision problem defined by the National Institute for Health and Care Excellence Diagnostics Assessment Report scope. In addition, structural and evidential aspects of the decision models were highlighted.

Additional pragmatic literature searches were conducted to identify evidence to support the development of a conceptual model. These searches aimed to identify cost-effectiveness studies evaluating (1) other diagnostic strategies for lung cancer and (2) screening approaches for lung cancer. The studies identified were also narratively summarised to highlight structural and evidential aspects of the decision models (aspects that could be of relevance to the current assessment).

We conceptualised a decision model to inform future evaluations of the cost-effectiveness of use of EarlyCDT Lung, based on the learnings from the literature searches and on clinical advice. The results of the conceptualisation were recorded using influence diagrams, and evidence requirements and uncertainties were highlighted throughout. The conceptualisation process was structured to identify value drivers and value components that could be of relevance for establishing the cost-effectiveness of EarlyCDT Lung in the diagnostic pathway for solid pulmonary nodules.

Results

Systematic review and meta-analysis of EarlyCDT Lung studies

The searches identified a total of 3233 unique records, of which 47 were included in the review, representing only six distinct patient cohorts among whom EarlyCDT Lung was used. No cohort explicitly underwent EarlyCDT Lung after identification of pulmonary nodules. For five of the cohorts, the diagnostic accuracy of EarlyCDT Lung among patients with nodules was reported. Only two of these five cohorts have been fully published as journal articles. The results from both published cohorts were considered to be at high risk of bias.

The summary sensitivity of EarlyCDT Lung from a bivariate meta-analysis was 20.2% [95% confidence interval (CI) 10.5% to 35.5%] and the specificity was 92.2% (95% CI 86.2% to 95.8%). Based on the hierarchical summary receiver operating characteristic (HSROC) curve, EarlyCDT Lung has around 26% sensitivity at 90% specificity, or 12% sensitivity at 95% specificity. The area under the HSROC curve was 69.4%, suggesting poor to moderate overall diagnostic accuracy. There were few data on diagnostic accuracy by nodule size, or on diagnostic accuracy when combined with other tests, such as Brock risk.

The diagnostic accuracy from the Evidence Assessment Group (EAG) analysis was lower than that claimed by Oncimmune (around 41.3% sensitivity at 90.6% specificity). Consequently, EAG modelling found that the increase in predicted risk of malignancy if Early CDT Lung is positive may be smaller than in the model produced by Oncimmune.

Comparator tests

A meta-analysis of eight studies reporting data on the Brock risk model found it to have very good diagnostic accuracy [area under the curve (AUC) 92%, 95% CI 90% to 95%], but with some evidence of heterogeneity across studies ($I^2 = 90\%$). A meta-analysis of five studies reporting data on the Herder risk model found it to have good diagnostic accuracy overall, with an AUC of 84% (95% CI 77% to 92%). There was substantial heterogeneity ($I^2 = 87\%$).

Although several meta-analyses of the use of PET-CT among patients with pulmonary nodules were identified, the studies included in these meta-analyses did not report the performance of PET-CT based on nodule size or on pre-test likelihood of malignancy, as categorised in clinical guidelines.

Evidence on CT surveillance was limited, with one study reporting diagnostic accuracy data. That found that volume doubling time and nodule volume had very high diagnostic accuracy to detect malignant nodules.

There was adequate evidence providing diagnostic accuracy estimates for CT-guided transthoracic needle biopsy. Better-quality studies of radial probe endobronchial ultrasonography-guided transbronchial lung biopsy may be needed, although they are probably less widely used than CT-guided biopsy.

Clinical impact of EarlyCDT Lung

No evidence was found on the clinical impact of using EarlyCDT Lung to diagnose pulmonary nodules. Instead, the EAG used simulation methods to investigate the possible impact of using EarlyCDT Lung. As the simulation was based on limited evidence, and required a number of strong assumptions to be made, its results should be treated as suggestive only.

The simulation concluded that EarlyCDT Lung is unlikely to offer meaningful clinical improvement for low-risk nodules (0–10%), as adding EarlyCDT Lung to Brock risk appears to result in little change in diagnostic accuracy over using Brock risk alone. It appears to identify few additional genuinely malignant nodules and may lead to more false-positive results than true-positive results.

At the 70% risk threshold, adding EarlyCDT Lung to Herder risk may improve sensitivity for only a small decline in specificity. Consequently, a large proportion of malignant nodules in the intermediate-risk group (10–70%) might be correctly identified by EarlyCDT Lung, and mostly reclassified to having a new risk of > 70%, with comparatively few false-positive reclassifications.

Cost-effectiveness reviews

The review of existing cost-effectiveness evidence identified two relevant studies. Neither of these was considered suitable to inform the current decision problem because of important differences, namely in the patient population, the position and use of EarlyCDT Lung within the diagnostic pathway, and the diagnostic accuracy evidence used to inform it.

The additional reviews to support conceptualisation identified eight diagnostic cost-effectiveness studies, and 34 screening studies; a sample of nine screening models were reviewed. These reviews highlighted that all evaluations relied on a common value mechanism of earlier diagnosis of lung cancer (at an earlier stage of disease). The reviews also identified structural assumptions and parameter estimates that could be used as alternatives to those implemented in the EarlyCDT Lung cost-effectiveness studies.

Conceptualisation of cost-effectiveness model

The conceptualisation process identified three core components for a future cost-effectiveness assessment of EarlyCDT Lung: (1) the characteristics of the subpopulations (reflecting the proposed positionings for EarlyCDT Lung in the current diagnostic pathway), (2) the way EarlyCDT Lung test results affect subsequent clinical management decisions and (3) how changes in these decisions can affect outcomes.

There is limited evidence on the subpopulations of interest. Existing evidence, however, highlights that these are likely to differ in characteristics that drive value (such as prevalence of disease), and that there may be further heterogeneity (e.g. on outcomes).

The evidence on how EarlyCDT Lung test results are expected to affect subsequent management decisions indicates that this depends on the test's positioning, on nodule and patient characteristics (determining eligibility for subsequent management options), and the level of variation in clinical practice.

Changes in management decisions may affect clinical outcomes in two ways (two components of value). The first relates to short-term impacts (costs and adverse events) of escalating the current pathway to more interventional investigations/treatments (including the possibility of intervention on indolent malignant and benign nodules), and the potential for increased radiation exposure. The second relates to longer-term health benefits and cost implications of earlier and/or increased detection (and treatment) of lung cancer. The evidence linkage mechanism for this component of value encompasses:

- the identification of differences in the time to diagnosis between current and proposed identification strategies, and mapping of these differences against likelihood or time to preclinical stage progression, to define the level of stage shift
- the linking of the stage distributions, with and without stage shift, to expected long-term outcomes conditional on disease stage.

There is little evidence on the time to diagnosis and the likelihood of stage progression under CT surveillance (and on heterogeneity on this), and on the potential for stage shift of EarlyCDT Lung. Linkage to health outcomes requires evidence on survival, health-related quality of life and costs conditional on disease stage at diagnosis. Our reviews identified UK-specific evidence on these components. Future cost-effectiveness models also need to consider other determinants of outcomes (such as age or histology), primary tumour treatment, the need for adjustments for lead and length time biases (typically associated with stage-shift mechanisms), and the adequacy of the data in reflecting contemporary treatments for lung cancer.

Conclusions

Implications for health care

The EAG concludes that the current evidence on EarlyCDT Lung is insufficient to determine its clinical value. This is because of the limited size of the relevant evidence base, and uncertainties as to whether or not current evidence generalises to the UK diagnostic pathway.

It appears that EarlyCDT Lung has poor diagnostic accuracy when used in isolation to diagnose pulmonary nodules, with low sensitivity to detect malignancy. It is therefore unclear what it can add to existing diagnostic methods, such as Brock and Herder risk assessments and the use of CT surveillance.

No evidence on the clinical impact of using EarlyCDT Lung was identified. Based on results from the EAG's limited simulation study, EarlyCDT Lung may have little clinical benefit when diagnosing low-risk or smaller nodules, as it appears unlikely to appropriately change clinical management decisions.

EarlyCDT Lung may possibly have clinical value when identifying malignancy in intermediate-risk nodules (10–70% risk), by correctly identifying high-risk nodules that are malignant, and so might benefit from prompt excision.

There is no relevant evidence on the cost-effectiveness of EarlyCDT Lung and there is currently insufficient evidence to support explicit quantifications of the clinical and economic value of EarlyCDT Lung. We have identified key components and drivers of value that would need to be quantified in a future assessment of the clinical and economic value, and present considerations to support the conceptualisation of a future decision model.

Evidence requirements for a future assessment of EarlyCDT Lung

Large, independent, prospective cohort studies are required, in which EarlyCDT Lung is used among patients with identified pulmonary nodules, and in which patients are diagnosed and managed in line with the BTS diagnostic pathway. Studies should estimate the diagnostic accuracy of EarlyCDT Lung in isolation, and in combination with Brock and Herder risks. These studies should be used to validate, or update, the risk model proposed by Oncimmune.

These cohort studies should also assess the clinical impact of EarlyCDT Lung by reporting outcomes including the following:

- impact on risk classification
- change in clinical management
- timing and tumour stage at detection and treatment of malignant nodules
- avoidance of unnecessary CT or PET-CT
- promotion of unnecessary PET-CT, biopsies or surgical excisions.

Ideally, a randomised controlled trial should be performed, in which patients with identified pulmonary nodules are randomised either to standard BTS management or to BTS management plus EarlyCDT Lung. However, the EAG acknowledges that this may not be feasible.

Currently, the broader evidence base on the whole BTS diagnostic pathway is limited. Large well-designed and UK-based prospective cohort studies are particularly needed to investigate the following:

- the diagnostic accuracy and clinical impact of using the Brock and Herder risk models
- the clinical consequences of CT surveillance
- how patient and nodule characteristics determine malignancy prevalence; eligibility for alternative clinical management options; likelihood of, and time to, detection under CT surveillance; and patient outcomes.

A well-designed cost-effectiveness study is required, integrating emerging relevant evidence with the recommendations in this report to appropriately justify the value components considered and their translation into a relevant model structure.

Study registration

This study is registered as PROSPERO CRD42021242248.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 49. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

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The research reported in this issue of the journal was funded by the HTA programme as project number NIHR133496. The contractual start date was in April 2021. The draft report began editorial review in September 2021 and was accepted for publication in June 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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