NICE advice

EarlyCDT-Lung for cancer risk classification of indeterminate pulmonary nodules

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is EarlyCDT-Lung. It is a blood test used to classify the malignancy risk of indeterminate pulmonary nodules (IPN) found by chest CT or X-ray, which would then lead to screening.
- The **innovative aspect** is that it can help early diagnosis of lung cancer in people with high risk.
- The intended **place in therapy** would be in addition to standard care (CT scans) to detect malignant IPN.
- The **main points from the evidence** summarised in this briefing are from 4 studies (1 randomised controlled trial, 2 cohort and 1 case control) involving around 15,000 adults in testing centres in Europe and North America. They show that EarlyCDT-Lung can detect early stage lung cancer and may improve diagnostic performance. The studies including patients from the UK showed a sensitivity of 52% to 57% and specificity of 88% to 90%. EarlyCDT-Lung could be more effective than current risk models at identifying lung cancer.

- **Key uncertainties** around the evidence or technology are that there is no direct comparative evidence with current standard care and limited follow up with people in the trials.
- The **cost** of EarlyCDT-Lung is £600 per test kit (exclusive of VAT) and each kit can run up to 10 samples, equivalent to £60 per test. The **resource impact** will be greater than standard care unless the additional cost of the test is offset by any savings from earlier diagnosis. There is limited evidence to support this.

The technology

EarlyCDT-Lung (Oncimmune) is a blood test that measures a group of 7 autoantibodies (p53, NYESO-1, CAGE, GBU4-5, HuD, MAGE A4 and SOX2) to tumour-associated antigens related to lung cancer. It helps early detection of lung cancer in people with high risk and allows differentiation of benign or malignant nodules. In the early stages of lung cancer, autoantibodies and tumour-associated antigens are produced as the body's immune system's response to cancer antigens. Blood levels of autoantibodies are elevated in the earliest stage of lung cancer and are present at all stages of the disease.

EarlyCDT-Lung test uses a standard enzyme-linked immunosorbent assay (ELISA). EarlyCDT-Lung is available as a CE-IVD kit, from a Clinical Laboratory Improvement Amendments registered laboratory in the US or from laboratories supported by Oncimmune's approved distributor network. Test results are based on a comparison of relative autoantibody levels to fixed thresholds. A sample is positive if at least 1 autoantibody is above a prespecified cut-off. EarlyCDT-Lung has a high specificity and serves as a rule in test to identify people who need interventions such as PET-CT or biopsy. The test may need to be repeated but the best number of times to repeat it is unknown.

Innovations

EarlyCDT-Lung enables earlier and accurate diagnosis in people at high risk of lung cancer. This could mean treatment is offered early, giving improved outcomes. Also, it could save CT scan and radiologist resources and reduce waiting times.

Current care pathway

Pulmonary nodules are small growths in the lung, often found incidentally when having a chest X-ray or CT scan. They may be malignant or benign.

The British Thoracic Society guidelines for the investigation and management of pulmonary nodules recommends that patients with nodules less than 5 mm in diameter or 80 mm^3 in volume should be discharged. CT surveillance is recommended for larger nodules. The guideline recommends using the Brock model for the risk assessment of pulmonary nodules larger than 8 mm diameter or 300 mm^3 volume. Based on an assessment with that model, people whose nodules have a malignancy risk above 10% have PET-CT. Then malignancy risk is recalculated using the Herder model. People with risk less than 10% are offered CT surveillance and those with risk over 70% should be immediately considered for surgery. The guidelines recommend image-guided biopsy or excision biopsy. Or, they recommend CT surveillance guided by individual risk and patient preference for people with indeterminate pulmonary nodules (IPN; 10% to 70% risk of malignancy).

Quite often clinicians must rely on their judgement to assess risk, because validated risk models are only based on a few relevant risk factors.

NICE's guideline on the diagnosis and management of lung cancer recommends sputum cytology for investigation in people with suspected lung cancer who have centrally placed nodules and are unable to tolerate bronchoscopy or invasive tests. A contrast-enhanced chest CT scan is recommended for further diagnosis and to stage the disease. The guideline recommends PET-CT as a first test after CT with a low probability of nodal malignancy (lymph nodes below 10 mm). MRI, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guide fine-needle aspiration (EUS-FNA) are other methods that can diagnose and stage the disease.

Population, setting and intended user

EarlyCDT-Lung will be used in addition to standard care for early detection of lung cancer in people at high risk. It can also be used in the risk classification of people with IPN found by chest CT or X-ray. The test would be offered before deciding about CT surveillance (that is, after initial CT surveillance or after PET-CT). This would mean patients with results showing increased risk of malignancy can begin treatment immediately.

The technology would probably be used in a secondary care setting by a member of the lung cancer multidisciplinary team.

Costs

Technology costs

The EarlyCDT-Lung costs £600 (excluding VAT) per kit and each kit can run 10 samples, so £60 per test. The kit comes with all reagents for testing. The company estimates that staff time for each test will cost £10 for a laboratory running a reasonable volume of tests. This means the per patient cost is £70.

Costs of standard care

Cost of CT surveillance is £90 (NHS National tariff payment system HRG code RD22Z, CT scan of 1 area, with pre and post-contrast, 2019/20 tariff prices). With reporting, the scan is an additional £20.

Resource consequences

EarlyCDT-Lung would be an additional cost to standard care. Resource use may reduce if it helps the early detection of lung cancer.

A National Institute for Health Research-funded study assessed the cost-effectiveness of EarlyCDT-Lung in the cancer risk assessment of IPN compared with CT surveillance. At a cost of £70 for the test, the incremental cost effectiveness ratio is less than £2,500 per quality-adjusted life year (QALY) gained, depending on the test accuracy parameters used.

Edelsberg et al. (2018)assessed the cost-effectiveness of EarlyCDT-Lung in early cancer detection compared with CT surveillance. Results were given of a model-based analysis in a cohort of 1,000 patients who had incidentally detected nodules of 8 mm to 30 mm and an intermediate risk of lung cancer, who were under CT surveillance only. It showed that cost per life-year gained was $18,029 and cost per QALY gained was $24,330. Using EarlyCDT-Lung at a sensitivity and specificity of 28% and 98%, respectively, gave cost-effectiveness ratios of $18,454 and $24,833. The authors concluded that the use of EarlyCDT-lung is likely to be cost saving.

Regulatory information

Early-CDT Lung first received its CE mark as a general in vitro diagnostic in May 2017. Its CE mark was updated in March 2019.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were identified. People with cancer are considered to have a disability and are protected under the Equality Act from the point of diagnosis.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 4 studies summarised in this briefing, involving data from around 15,000 patients.

The studies show the diagnostic accuracy of the EarlyCDT-Lung test and its ability to pick up early stage lung cancer when compared with standard care. The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence for the EarlyCDT-Lung test is of good quality but limited in its scale and scope. There is no long-term follow up of patients past 2 years and the frequency of testing has not been established.

The available evidence shows a variation in values for specificity and sensitivity across the studies and across lung cancer stages. This variation is probably because of different thresholds being applied in each study.

The evidence shows that EarlyCDT-Lung can improve diagnostic yield and prediction of the risk of lung cancer.

Massion et al. (2016)

Study size, design and location

Study of 296 people (from an initial cohort of 1,987 individuals with Health Insurance Portability and Accountability Act authorisation (HIPAA) in a prospective registry in the US.

Intervention and comparator(s)

EarlyCDT-Lung test compared with lung cancer risk models or nodule size (4 mm to 20 mm).

Key outcomes

Presence of lung cancer was confirmed either based on clinician's diagnosis only (inclusive cohort) or based on the availability of CT and pathology reports for people from the inclusive cohort (exclusive cohort). After applying exclusion criteria, 296 patients (221 without cancer and 75 with cancer) were left in the inclusive cohort and 269 (217 without cancer and 52 with cancer) in the exclusive cohort.

Results of model-free analysis showed that for the exclusive cohort, 22 of 68 patients with a positive test result and 30 of 201 of patients with a negative test result had lung cancer, giving a relative risk (RR) of 2.2 (95% confidence interval [CI] 1.3 to 3.5, positive prediction value [PPV] 32%). In the EarlyCDT-Lung test, the RR increased to 2.3 (95% CI 1.3 to 3.9, PPV 40%). For the 4 mm to 20 mm group, addition of a positive EarlyCDT test gave an RR of 2.7 (95% CI 1.3 to 5.7), equal to an increase in absolute risk from 13% to 24%. Results of the nodule-based risk model showed that, for the inclusive cohort, the Gould and Brock models respectively overestimated and underestimated the RR to the actual rates observed ($p<0.001$). The Mayo estimates were closest to those observed ($p=0.54$). For the 4-mm to 20-mm nodules, the receiver operating characteristic curves for the models showed that, as specificity passed 90%, the sensitivity decreased to 30% or less. On adding EarlyCDT-Lung, specificity increased and sensitivity decreased.

Strengths and limitations

The study shows how the test is likely to be used in clinical practice. It was funded by the company. There was no blinding of test assessors, and test results appear to have been interpreted with knowledge of the reference standard. The study authors noted that no formal protocols were followed.

Jett et al. (2014)

Study size, design and location

Cohort study of 1,613 patients from 720 practices across the US who agreed to data sharing through the HIPAA.

Intervention and comparator(s)

Intervention: EarlyCDT-Lung test.

No comparator.

Key outcomes

Based on 6-month follow up of 99% of patients who were tested positive and 93% of those who tested negative, 61 (4%) were identified as having lung cancer, 25 of whom tested positive using EarlyCDT-Lung. This shows a sensitivity of 41%. Of these, 57% when reported were stage 1 or stage 2. A positive test result was associated with a 5.4-fold increase in lung cancer compared with a negative result. The specificity of the test at 6 months was 87%.

Strengths and limitations

A relatively large sample size, which shows the diagnostic power of the test at 6 months. Further follow up would have been useful to show longer-term diagnostic performance. The study would have benefited from a comparator arm that had standard care alone. Some of the authors had conflicts of interest ranging from direct financial or working relationships with the company to consultancy work and research grants.

Lam et al. (2011)

Study size, design and location

Case control study involving 4 separate groups of patients with newly diagnosed lung cancer. There were 122 from a single UK centre with small-cell lung cancer (group 1), 249 from multiple European centres (group 2), 122 from a single centre in Vancouver, Canada (group 3), 82 with no location specified (group 4).

In 3 of the 4 groups (groups 2 to 4) patients with lung cancer were, as far as possible, individually matched by gender, age, and smoking history to control individuals with no previous history of

malignant disease.

These populations were combined with an early validation data set to give 1,077 patients with lung cancer and 1,296 matched controls.

Intervention and comparator(s)

Intervention: EarlyCDT-Lung test.

Key outcomes

Sensitivity 57%, specificity not reported (group 1); sensitivity 34%, specificity 87% (group 2); sensitivity 31%, specificity 84% (group 3); sensitivity 43%, specificity 89% (group 4); sensitivity 38%, specificity 88% (overall); sensitivity 34%, specificity 88% for non-small-cell lung cancer; and sensitivity 50%, specificity 88% for small-cell lung cancer. There was a higher sensitivity for small-cell lung cancer compared with non-small-cell lung cancer ($p \leq 0.001$) but no difference in sensitivity between non-small-cell lung cancer subtype ($p=0.35$).

Strengths and limitations

A large sample and matched control involving several centres across Europe and the US, including a group from the UK. Results include a previous validation sample, with limited reporting. Matching was done on a number of important variables, but there was no reporting on the closeness of matching and consideration of other key variables when matching may also have been appropriate. The study was part funded by the company, 2 of the authors were consultants to the company and 1 of these was also a shareholder.

Sullivan and Schembri 2019

Study size, design and location

Randomised controlled trial of 12,208 asymptomatic adults in Scotland aged 50 to 75 who had a high risk of developing lung cancer over the subsequent 24 months after randomisation.

Intervention and comparators

EarlyCDT-Lung (positive tests were followed by chest X-ray and CT imaging) compared with standard care.

Key outcomes

During the study, 127 lung cancers were diagnosed (56 in the test group and 71 in the control arm). Of the test group, 9.8% had positive EarlyCDT-Lung test results and 3% (n=18) of these people were diagnosed with lung cancer. The rate of late-stage (3 and 4) lung cancer diagnosis was lower in the test group than the intervention group (58.9% compared with 73.2%). More early-stage cancers were diagnosed in the test group (23 compared with 19). The EarlyCDT-Lung test was positive for 12 of the 23 early cancers (sensitivity 52.2%, 95% CI 30.6% to 73.2%) and for 6 of the 33 late-stage cancers (sensitivity 18.2%, 95% CI 7.0% to 35.5%). Although the study was not powered to detect difference in mortality, lung cancer-specific mortality was lower in the intervention arm (17 compared with 24). Further information from the study authors note that EarlyCDT-Lung test showed high overall specificity (90.3%), and moderate sensitivity (52.2%) for detecting early stage lung cancer at 2 years. Sensitivity at 6 months and at 1 year was 77.8% and 69.2% respectively for stage 1 or stage 2 disease, and 38.5% and 30.0% respectively for stage 3 or stage 4 disease.

Strengths and limitations

The study included a large sample size. Power calculations were done to detect the study endpoint. The method of randomisation was stated.

There is limited information in the abstract to judge the study quality.

Sustainability

The company notes that the main body and inserts of the kit are cardboard, which can be recycled. Reagent bottles and other kit contents which may encounter human serum are treated as contaminated waste and cannot be recycled. The company states that this is beyond its control.

No specialist equipment is needed to run the test. For patients with positive findings, there may be a reduction in follow-up CT scans.

There is no published evidence to support these claims.

Recent and ongoing studies

Lung cancer screening study with low-dose CT scan and blood biomarker. ClinicalTrials.gov identifier: NCT01700257. Status: was recruiting, no results published. Indication: lung cancer. Devices: EarlyCDT-Lung test. Location: US.

Specialist comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Three specialists contributed to this briefing, 2 were familiar with the technology and 1 had used this technology before.

Level of innovation

All the specialists agreed that EarlyCDT-Lung has not been superseded. One of them noted that currently no blood test is used to manage indeterminate pulmonary nodules (IPN). One specialist felt the technology is innovative because it can allow early detection of lung cancer. Another specialist felt EarlyCDT-Lung could reduce cases for PET scans and speed up the pathways. This specialist also noted the EarlyCDT-Lung could be used for follow up.

Potential patient impact

One specialist stated that EarlyCDT-Lung can improve IPN management because there is a move towards implementing lung cancer screening. This specialist also highlighted that, although a biopsy is the gold standard diagnostic test, invasive testing is associated with risks such as pneumothorax and bleeding. Two specialists felt that patient exposure to CT scans would be reduced, as well as lessening anxieties over false positive results. Another noted that the early detection of malignant tumour is a potential benefit to the patient. One specialist noted that people with IPN who have comorbidities will benefit from EarlyCDT-Lung. Another felt people in socioeconomically deprived areas will benefit. One specialist noted that it would be interesting to know what effect early detection has on survival rates for people in the Scottish lung cancer screening study that has used EarlyCDT-Lung.

Potential system impact

All the specialists agreed that EarlyCDT-Lung can improve the current pathway for IPN. One noted that if EarlyCDT-Lung can improve precision of estimate from existing risk-based models then patient management can be improved. Another felt earlier diagnosis in 35% to 40% of cases is likely to improve disease management.

General comments

All clinical specialists agreed that there is need for further robust evidence to support the technology. One specialist noted that a reduction in lung imaging may have globally significant implications for case finding and screening for lung cancer in people at high risk of the disease.

Specialist commentators

The following clinicians contributed to this briefing:

- Phil Crosbie, clinical senior lecturer and honorary consultant in respiratory medicine, division of infection, University of Manchester. Has received consultancy fees from the company.
- Frank Sullivan, professor of primary care medicine and director of research, University of St Andrews. Has received research funding from the company.
- Oliveira Pedro consultant in histopathology, the Christie NHS foundation trust. No interests declared.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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