Rapid Response

Evidence synthesis: Targeted screening for early lung cancer in adults at high risk

Rapid Responses are brief summaries of the best available evidence prepared to inform time-sensitive decision-making. Rapid Responses are not peer reviewed, are current only at time of publication, and do not constitute recommendations. They should be considered alongside existing guidance applicable to NHS Scotland.

For further information on our Rapid Response process and previous Rapid Response outputs, please visit our website.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Targeted screening for early lung cancer in adults at high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of search</td>
<td>12th November 2020</td>
</tr>
</tbody>
</table>
| Referrer | Dr Rebecca Devine  
Specialist Registrar in Public Health Medicine, Scottish Government  
Cancer Policy Team |
| Report published | January 2021 |
| Author | Julie Calvert, Health Services Researcher |

HIS Evidence Conclusions

- High quality evidence showed that screening for lung cancer with low-dose computed tomography (LDCT) resulted in no statistically significant difference in overall mortality compared with no screening.

- Moderate quality evidence showed that screening for lung cancer with LDCT may reduce lung cancer mortality compared with no screening.
What were we asked to look at?

Based on current rates of disease, an estimated 1 in 12 men, and 1 in 13 women will develop lung cancer during their lifetime\(^1\). The stage at which a cancer is diagnosed is generally an indicator of subsequent survival; the earlier the stage, the better the survival\(^2\). Survival from lung cancer is poor with only 9.5% of patients still alive at five years after diagnosis\(^3\).

We were asked to produce an evidence review of targeted screening tools for early lung cancer detection (cancer of the lung, bronchus and trachea). The targeted population are adults without lung cancer (confirmed or suspected) who are at high risk of developing lung cancer. This report is based on an HTA\(^4\) which defines high risk as: people with a history of smoking or current smokers or people with other potential risk factors: exposure to occupational or environmental toxins (for example, radon, asbestos or fine particle exposure), chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, or family history of lung cancer.

The overarching aim of a targeted screening tool in this context is to detect lung cancer at an earlier stage, in order to improve survival and reduce mortality from lung cancer. Due to the overlapping symptoms of lung cancer and COVID-19 infection, and the impact that COVID-19 has had on referral patterns, there is increased urgency to consider targeted screening options (Dr Rebecca Devine, Speciality Registrar in Public Health Medicine, Personal communication, October 2020).

Screening can be done using imaging technologies, including chest X-ray (CXR) and low-dose computed tomography (LDCT), as well as breath or blood biomarkers. Biomarkers are still at an early stage of development. There have been several large RCTs on LDCT in the last few years. The European network for Health Technology Assessment (EUnetHTA) report that, to their knowledge, no European national funding body has supported implementation of lung cancer screening.

Overview of the evidence

We found a relevant, recent (November 2020) and comprehensive EUnetHTA HTA\(^4\). EUnetHTA is a network for HTA across Europe. This HTA asked the same question as our enquiry, and our rapid response is focused almost entirely on this HTA. In addition, the Canadian Agency for Drugs and Technologies in Health (CADTH) recently published an reference list on the clinical utility of screening.

- The absolute effect on overall mortality was estimated to be 5 fewer deaths per 1000 persons (95% CI=-3-12) and for lung cancer mortality 5 deaths fewer per 1000 persons (95% CI=3-8) within about 10 years (for both types of mortality).
- Screening for lung cancer with LDCT (compared to no LDCT) may increase adverse events and lead to harm due to consequences of false positive screening results and of overdiagnosis.
- There is currently insufficient evidence to support the use of biomarkers in clinical practice.
- A large, Scottish trial of the EarlyCDT-Lung test is ongoing. Results for the two year follow up showed the EarlyCDT-Lung test plus CT screening decreased the incidence of later stages of lung cancer at diagnosis. Five and 10 year follow ups are planned.
LDCT as a screening tool

EUnetHTA
The EUnetHTA HTA assessed screening for lung cancer using LDCT compared to no screening or screening using CXR. The outcomes considered were mortality, morbidity, health-related quality of life (QoL), harms resulting from screening itself (e.g. consequences from radiation exposure), or from subsequent diagnostic interventions (for example, invasive biopsy) including overdiagnosis and consequences resulting from false screening results (false positive and false negative) and serious adverse events. EUnetHTA also assessed evidence on screening for lung cancer using biomarkers in addition to LDCT (compared to LDCT alone); either for selecting patients for screening or to characterise undetermined nodules found in LDCT.

The methodology used by the EUnetHTA group was robust. For the investigation of LDCT, the authors based their evidence on a recent German national benefit-harm assessment. The EUnetHTA authors selected one or more (number not stated) high-quality and up-to-date systematic reviews (no detail available to assess how these were selected) from which primary studies were identified based on the specific inclusion criteria of the report. This was supplemented by their own systematic search for RCTs for the predefined time period outside of the German report. Sources searched included MEDLINE, Embase and the Cochrane Central Register of Controlled Trials, as well as study registries, checking reference lists, documents made available from consultation procedures and author inquiries (no detail available to allow description of how the EUnetHTA authors made inquiries). The last search was carried out in June 2020. For the research question on biomarkers + LDCT, the authors carried out systematic literature searches for RCTs or systematic reviews in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews as well as following sources of study registries and checking reference lists. The selection of studies was carried out by two people and included studies were rated for quality using standardised tools. In addition to a systematic review and meta-analysis the HTA authors:

- contacted patient organisations for COPD from Germany and Ireland. However they were not able to obtain participation. The EUnetHTA report did not provide any more detail on this.
- involved external experts in the field of epidemiology, oncology, radiology, and screening programmes who reviewed the HTA project plan and the assessment draft.

Characteristics of the studies included in the assessment
The HTA identified nine relevant randomised trials involving current or former smokers. Of these, eight relevant studies with useful data available for extraction were selected. Two ongoing studies, one planned study, one completed study without reported results and four studies with unclear status were noted, but not included.

In six of the eight of the RCTs the subjects were either assigned to screening by LDCT or no screening. These six studies are: DANTE (Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays), DLCST (Danish Lung Cancer Screening Trial), ITALUNG (Italian lung cancer screening), LSS (Lung Screening Study), MILD (Multicentric Italian Lung Detection), NELSON (NEderlands Leuven's Longkanker Screenings ONderzoek), NLST (National Lung
Screening Trial), LUSI (Lung tumor screening and intervention trial). These studies were conducted in Europe (Italy, Denmark, Germany, Netherlands and Belgium), the number of participants ranged from 3,000 participants, rising to 16,000 and 53,500 participants in the studies NELSON and NLST and the total number of participants was 90,836. The screening phase was between 1 and 6 years, with the planned follow-up period between 5 and 10 years (in the LSS study no information was available on the duration of follow-up). Both men and women were included in the studies, with the exception of the DANTE study, which only examined men. In two of the eight RCTs (United States) LDCT screening was compared to screening using CXR.

The risk of bias at the study level was low for four studies (DLCST, ITALUNG, LUSI and NELSON) and high for four studies. High risk of bias was due to lack of clarity on: allocation concealment (DANTE, MILD and NLST), whether reporting was independent of result (LSS) and significant differences in baseline characteristics between the intervention and control groups (MILD study). At the outcomes level, the risk of bias for overall mortality and lung cancer mortality, consequences of false screening results and overdiagnosis was rated as low for three studies (DLCST, ITALUNG and NELSON). A high risk of bias was found for all outcomes in the LUSI study and for adverse events in the DANTE study. No further outcome-specific bias assessments were carried out for those studies classed as high risk at the study level.

Clinical effectiveness
All studies reported evaluable data on mortality (overall mortality and lung cancer mortality) and overdiagnosis.

For overall mortality, data from three studies with a low risk of bias (DLCST, ITALUNG, NELSON) and three studies with a high risk of bias (DANTE, MILD, LUSI) were included. The observation period ranged from 8 to 11 years from randomisation. A random-effects meta-analysis of the six studies (n=33,703) showed no statistically significant effect in favour of screening (IRR (incidence rate ratio): 0.95; 95% CI=0.88-1.03; p=0.164). The finding of no statistically significant difference remained for a meta-analysis of the three studies at low risk of bias (IRR: 0.93; 95% CI=0.69-1.26; p=0.434). Findings were similar for the comparison of LDCT screening versus CXR screening. Sensitivity analysis from two studies (LSS and NLST n=90,473) with high risk of bias showed no significant difference (IRR: 0.97; 95% CI=0.92-1.02; p=0.168).

For lung cancer mortality specifically, data from the same six studies were included. The observation period ranged from 8 to 11 years from randomisation. A random-effects meta-analysis of the six studies (n=33,703) showed a statistically significant effect in favour of LDCT screening (IRR: 0.81; 95% CI=0.72-0.91; p=0.004). However, when only the three studies with a low risk of bias were combined, there was no statistically significant difference between the groups (IRR: 0.80; 95% CI=0.60-1.06; p=0.076). For the comparison of LDCT screening versus CXR screening, analysis based upon two studies with high risk of bias (LSS and NLST) showed a significant difference (IRR: 0.89; 95% CI=0.82-0.96; p=0.010).

To explain why overall mortality was not significantly different for screening, but lung cancer mortality was, albeit it only when all studies were included, the HTA authors suggested that some of the screening patients saved from lung cancer death may have died from other tobacco-related diseases. The authors estimated the absolute effect for overall mortality to be 5 deaths less per 1,000 persons (95% CI=3-12) and for lung cancer mortality 5 deaths less per 1,000 persons (95% CI=3-8) within about 10 years.
Screening can cause harm through false screening results and overdiagnosis. There was no data available on the quantity or impact of false negative results. Data from three studies with a low risk of bias (DLCST, ITALUNG, NELSON) and three studies with a high risk of bias (DANTE, MILD, LUSI), suggested that screening for lung cancer with LDCT leads to harm due to consequences of false positive screening results compared with no screening. Effect estimates from the individual studies showed that between 0.1% and 1.5% of the participants in the studies experienced a consequence of false positive findings (invasive diagnostic work-up or surgery).

With regards to overdiagnosis (from the resulting invasive clarification diagnostics and treatment including the associated complications and side effects), data from three studies with low risk of bias (DLCST, ITALUNG, NELSON) and three studies with a high risk of bias (DANTE, MILD, LUSI) were available for comparison of LDCT and no screening. For the comparison of LDCT screening versus CXR screening, data from two studies (LSS and NLST) with high risk of bias were available. From the eight included studies, the overdiagnosis risk was determined in relation to all participants invited to screening. In two of the six included studies comparing LDCT screening versus no screening, (ITALUNG, MILD) no overdiagnosis was found. The risk of overdiagnosis ranged from 0.6% to 2.2% in the LDCT vs. no screening studies and in the two studies comparing LDCT screening versus CXR screening, overdiagnosis risks were 1.2% and 0.1%.

The overdiagnosis risk in the presence of a lung cancer diagnosis during the screening phase was assessed in five studies. The range was wide; an overdiagnosis risk of 63.2% (DLCST), 28.6% (LUSI) and 16.2% (NELSON) respectively, was found. In one study no overdiagnosis could be detected (ITALUNG). An overdiagnosis risk of 2.8% was found for comparison against CXR screening (NLST).

**Adverse events**
The EUneTHTA HTA reported that screening for lung cancer with LDCT may increase the incidence of adverse events compared with no screening. One study (DANTE) with a high risk of bias reported adverse events. The observation period was 8 years post-randomisation. There was a statistically significant difference in the number of adverse events after surgery for suspicious findings to the disadvantage of LDCT screening (OR 3.48; 95% CI=1.41-8.62; p=0.004). For adverse events with a severity ≥3 (scale not specified), there was a statistically significant difference between the two study groups to the disadvantage of LDCT screening (OR 4.25; 95% CI=0.92-19.69; p=0.046).

**CADTH**
In addition to the EUneTHTA HTA, an Oct 2020 evidence report on the clinical utility of screening (any screening method) for lung cancer in adults at high risk of lung cancer compared to a different screening method, or to no screening was compiled by CADTH. They carried out a limited literature search of key resources (including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search) published during the last 5 years. They found five health technology assessments, 10 systematic reviews (six with meta-analyses), and 14 randomised controlled trials. They identified a recently published systematic review and meta-analysis on the impact of lung cancer screening by LDCT which included seven RCTs. All seven were included in the EUneTHTA HTA. The systematic review included all seven trials in the meta-analysis, while the EUneTHTA chose to separate those studies that had used CXR in the control group. The CADTH findings were similar to the EUneTHTA report which found no significant effect on overall mortality together with a reduction in lung cancer mortality. Results from the CADTH meta-analysis showed a statistically significant relative reduction of lung cancer-specific mortality of 17% (risk ratio
(RR) = 0.83, 95%; CI=0.76-0.91) and a relative risk reduction of overall mortality of 4% (RR=0.96, 95% CI=0.92-1.00) in the screening group compared with the control group.

**Biomarkers**

Biomarkers are used to identify risk of lung cancer in certain patients undergoing screening to allow further refinement of screening selection criteria, independent of age and smoking, and to limit the costs of lung cancer screening. Biomarkers can also be used to characterise undetermined nodules identified during computed tomography (CT) screening. In particular, biomarkers may be helpful for patients with nodules that need closer surveillance or to inform decisions on whether to perform a biopsy.

**EUnetHTA**

The EUnetHTA report carried out a systematic literature search for RCTs or systematic reviews on the benefit and harm of using biomarkers in addition to LDCT, compared to LDCT screening alone, within the process of screening for lung cancer in at risk groups. They did not identify any RCTs or systematic reviews that matched their inclusion and exclusion criteria. The authors did identify studies which addressed the use of biomarkers in the diagnosis of lung cancer but that didn’t compare LDCT and biomarkers with LDCT alone; a recent systematic review on the diagnostic performance of blood and serum-based biomarkers and the ITALUNG RCT.

A well-conducted systematic review, identified three phase 3 studies on the diagnostic performance of blood and serum-based biomarkers for lung cancer screening and their impact on lung cancer-related mortality and all-cause mortality. The literature search covered the period from 2000-2015. Two of the studies investigated the use of biomarkers alone (EarlyCDT-lung, miR-Test), while one study investigated the test properties of combined screening using biomarkers and LDCT compared to LDCT alone (micro-RNA signature classifier (MSC)). It is not clear why this did not meet EUnetHTA inclusion criteria). MSC, when used with LDCT for lung cancer detection, achieved a positive likelihood ratio of 18.6 if both LDCT and MSC were positive, and a negative likelihood ratio of 0.03 if both LDCT and MSC were negative. The authors concluded that biomarkers may be a promising complement to LDCT in lung cancer screening, but that the current evidence is insufficient to support the use of biomarkers in clinical practice.

A multimodal screening approach using a biomarker panel was investigated in a 2017 study (ITALUNG). Using biomarkers, the blood samples of participants in the LDCT screening arm with screening-detected lung cancer (n=517) were compared to people without a lung cancer diagnosis. A post hoc analysis of multimodal screening with biomarker and LDCT showed a higher specificity of 90% compared to 74% with LDCT screening alone.

**CADTH**

The CADTH review identified; a 2016 systematic review (and meta-analysis) which assessed LDCT, CXR and sputum cytology (SC) and a 2020, Scottish RCT on a blood-based autoantibody biomarker. The 2016 systematic review and meta-analysis of screening for lung cancer in adults at average to high-risk, assessed CXR, SC and LDCT. The review authors identified seven RCTs on CXR screening with or without SC. They found no significant benefits for lung cancer mortality or all-cause mortality in the pooled analyses that included trials using CXR screening, with or without SC, and follow-up from 5 to 20.5 years.
The Early Diagnosis of Lung Cancer Scotland (ECLS) Team reported results of a recent (2020), phase IV RCT (n=12,208) which evaluated the ability of the EarlyCDT-Lung test (a high specificity blood-based autoantibody biomarker) and any CT scanning, to identify people at high risk of lung cancer. This was a community based trial conducted in socioeconomically deprived areas in Scotland. The outcome was the incidence of patients identified to be at stage III/IV/unspecified lung cancer at diagnosis compared with those identified during standard clinical practice. Patients who tested positive on the EarlyCDT-Lung test received LDCT scanning six-monthly for up to two years, those with a negative result and control arm participants received standard clinical care. At two years, in the intervention arm, 33/56 (58.9%) lung cancers were diagnosed at stage III/IV compared to 52/71 (73.2%) in the control arm. The absolute risk reduction in stage III/IV/unspecified lung cancer diagnosis was 0.3% (95% CI=0.01 to 0.6). The hazard ratio for stage III/IV presentation was 0.64 (95% CI=0.41-0.99, p=0.0432). A comprehensive cost-effectiveness analyses will be presented in a subsequent article. This trial will continue with follow up after 5 and 10 years.

**NICE**

In addition to the EUnetHTA and CADTH reports, we identified a 2020 NICE Medtech innovation briefing (MIB)\(^6\) on the EarlyCDT-Lung test used for cancer risk classification of indeterminate pulmonary nodules. The briefing identified four studies, two of which have been described above (including the Scottish ECLS data\(^9\) and a study within a systematic review\(^8\) cited by EUnetHTA). The included studies involved around 15,000 adults in testing centres in Europe and North America. The studies showed sensitivity values of 52% to 57% and specificity values of 88% to 90%. Two economic studies suggested that EarlyCDT-Lung would be an additional cost to standard care. NICE concluded that the evidence for EarlyCDT-Lung test is of good quality but limited in scale and scope. There was variation in specificity and sensitivity, likely due to differences in thresholds set by the studies.

**Targeted Lung Health Checks (TLHCs) NHS England**

A targeted lung screening programme, which uses LDCT to identify early-stage lung cancer in high risk participants, is underway across 14 sites in NHS England\(^6\). The programme will run until 2023 and is currently being piloted and evaluated. The evaluation will look at the impact of the screening programme on patient health outcomes, experience and wider health inequalities and will support the longer-term strategy for a wider roll out. We were not able to find any evaluation data at a national level. We found four local preliminary reports published in peer review journals\(^10-13\) and one flash report on a charity website\(^14\). Participant uptake, detection rates, lung cancer risk models to determine eligibility for CT scanning, cost effectiveness and estimated impact on mortality were assessed.

**Ongoing work**

A systematic review and network meta-analysis, which will assess evidence on LDCT compared with other screening strategies for lung cancer was due for publication in May 2020, but has been delayed and no publication date given\(^15\).
References

## Appendix: literature search

<table>
<thead>
<tr>
<th>Resource</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIS projects</strong>&lt;br&gt;Check if any team within HIS has conducted/ is conducting work on this topic.</td>
<td>0</td>
</tr>
<tr>
<td><strong>Guidelines International Network (GIN)</strong>&lt;br&gt;Check for UK guidelines e.g. Royal College Physicians</td>
<td>0</td>
</tr>
<tr>
<td><strong>Secondary literature and economic evaluations</strong>&lt;br&gt;Cochrane library&lt;br&gt;Check for Cochrane reviews</td>
<td>0</td>
</tr>
<tr>
<td>Dynamed</td>
<td>0</td>
</tr>
<tr>
<td>TRIP database&lt;br&gt;Check for guidelines/ reviews</td>
<td>NA</td>
</tr>
<tr>
<td>BMJ Best Practice</td>
<td>NA</td>
</tr>
<tr>
<td>Medline&lt;br&gt;Check for systematic reviews, meta-analyses, economic evaluations. Use the SIGN search filters for these study designs.</td>
<td>0</td>
</tr>
<tr>
<td>EMBASE&lt;br&gt;Check for systematic reviews, meta-analyses, economic evaluations. Use the SIGN search filters for these study designs.</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Other relevant databases</strong>&lt;br&gt;The Knowledge network lists other relevant databases that may be useful</td>
<td></td>
</tr>
<tr>
<td>Manchester&lt;br&gt;<a href="https://thorax.bmj.com/content/74/4/405">https://thorax.bmj.com/content/74/4/405</a></td>
<td></td>
</tr>
<tr>
<td>Nottingham</td>
<td><a href="https://www.roycastle.org/research/nottingham-lung-health-check/">https://www.roycastle.org/research/nottingham-lung-health-check/</a></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Primary studies (only if insufficient secondary evidence found)</strong></td>
<td></td>
</tr>
<tr>
<td>Medline</td>
<td>Use the SIGN search filters for these study designs.</td>
</tr>
<tr>
<td>Cochrane library</td>
<td>Check for RCTs in the trials database</td>
</tr>
<tr>
<td><strong>Ongoing secondary research</strong></td>
<td></td>
</tr>
<tr>
<td>PROSPERO database</td>
<td>Check for recent systematic review protocols.</td>
</tr>
<tr>
<td><strong>Ongoing research (only if insufficient secondary evidence and primary studies found)</strong></td>
<td></td>
</tr>
<tr>
<td>Clinicaltrials.gov</td>
<td>Check for ongoing studies that have recently closed or are due to complete in the next 6-12 months.</td>
</tr>
<tr>
<td><strong>Unpublished research</strong></td>
<td></td>
</tr>
</tbody>
</table>

Search concepts used:

Screening, lung cancer, early stage, biomarkers, low-dose computed tomography

© Healthcare Improvement Scotland

**January 2021**

This document is licensed under the Creative Commons Attribution-Noncommercial-NoDerivatives 4.0 International License. This allows for the copy and redistribution of this document as long as Healthcare Improvement Scotland is fully acknowledged and given credit. The material must not be remixed, transformed or built upon in any way. To view a copy of this license, visit [https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/)