

Lung cancer screening

An update for primary care



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With data from international programs backing the efficacy of lung cancer screening, the Australian National Lung Cancer Screening Program is due to launch in 2025. It will be available to current or ex-smokers aged 50 to 70 years who meet eligibility criteria. The program is anticipated to prevent lung cancer mortality through early detection.

The National Lung Cancer Screening Program (NLCS) is due to commence in July 2025. The program aims to detect lung cancers at an early stage by screening high-risk individuals with low-dose CT (LDCT). This article provides an overview of key concepts in lung cancer screening.

Health impact of lung cancer in Australia

Lung cancer is currently the leading cause of cancer-related deaths in Australia in both men and women. In 2023, there were more than 14,000 new cases of lung cancer and more than 8000 lung cancer-related deaths.^{1,2} Lung cancer has a poor prognosis, with a five-year survival rate of 25.7% compared with an average survival rate of 72.5% from all other cancers in Australia.³

Rationale for lung cancer screening

Lung cancer is typically detected at a late stage, with more than 40% of cases Stage IV at the time of diagnosis.⁴ At this late stage, the lung cancer has spread to other organs and treatment options are limited.⁵ The prognosis of lung cancer varies significantly based

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KEY POINTS

- The Australian National Lung Cancer Screening Program will commence in 2025.
- Lung cancer is the most common cause of cancer-related deaths in Australia. The proposed screening program will aim to reduce lung cancer mortality through early detection in high-risk individuals.
- The Medical Services Advisory Committee has recommended that lung cancer screening be limited to current- or ex-smoking individuals who are aged between 50 and 70 years, have a smoking history of more than 30 pack-years and have quit smoking less than 10 years ago.
- Eligible applicants will be offered a low-dose CT scan of the chest every two years. Patients with pulmonary nodules that are deemed high risk will be recommended for referral for specialist review.
- It is anticipated that within the first 10 years of the lung cancer screening program, 12,000 lung cancer deaths will be prevented and more than 50,000 quality-adjusted life-years will be gained.

on stage, with the five-year survival rate reducing from 67.7% for Stage I lung cancer to 3.8% for Stage IV lung cancer.⁴

Lung cancer screening aims to facilitate early detection and improve survival. National cancer screening programs currently exist for breast cancer, bowel cancer and cervical cancer.⁶ Data from existing screening programs in the USA indicate that this approach is viable, with the five-year survival rate of lung cancers detected in a screening program much higher than that detected outside of a screening program (64% vs 19%, respectively).⁷ In comparison, the advent of immunotherapy using checkpoint inhibitors improved five-year mortality of lung cancer by 14% to 23.7% across all stages.⁸ Therefore, the anticipated benefit from the lung cancer screening program in reducing cancer-specific mortality is at least comparable to recent advances in systemic therapies.

Evidence of lung cancer screening programs

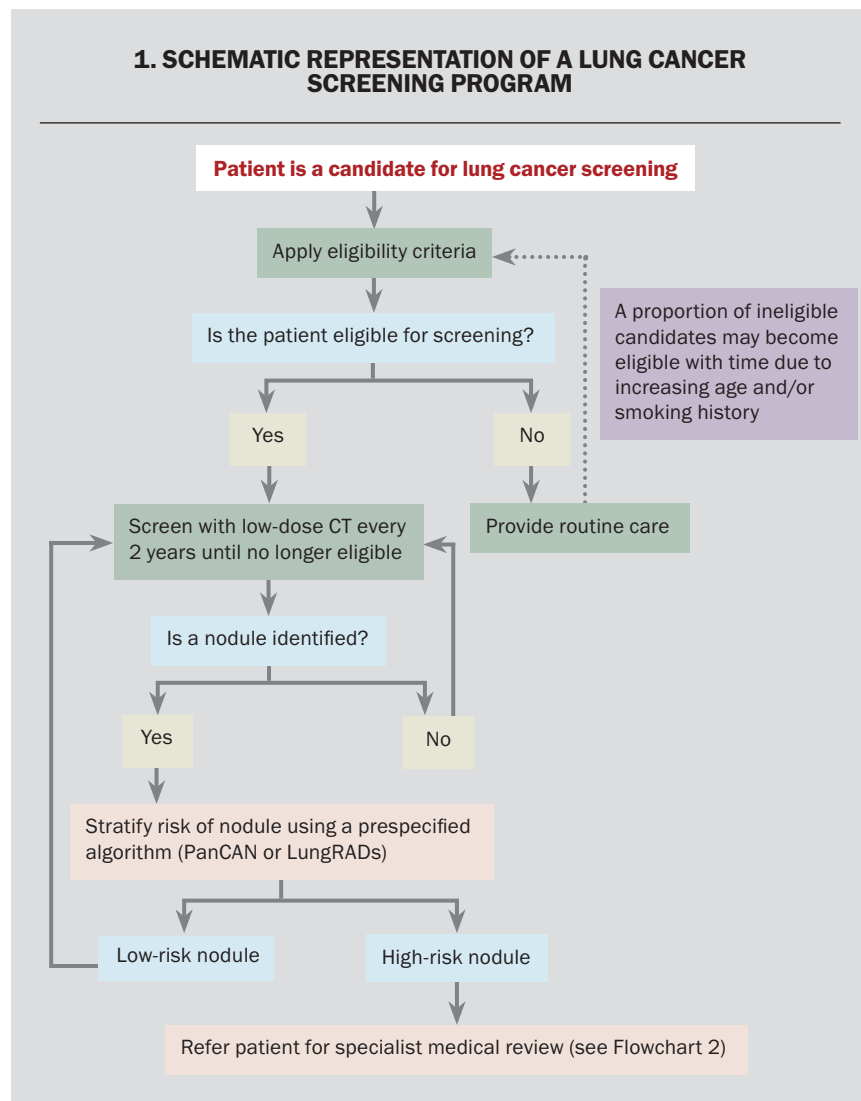
The efficacy of lung cancer screening using LDCT in reducing cancer-specific mortality has been demonstrated in randomised control trials. Findings from four landmark trials in lung cancer screening are presented below. Three of these trials (NLST, NELSON, ILST) investigated lung cancer screening in populations at risk from smoking exposure. The fourth trial (TALENT) investigated the efficacy of lung cancer screening in candidates with non-smoking-related risk factors such as family history. A schematic representation of a program is presented in Flowchart 1.

The National Lung Screening Trial (NLST)

The National Lung Screening Trial (NLST) compared the efficacy of LDCT with that of chest x-rays (CXR) for lung cancer screening in high-risk smoking candidates.⁹ The study found that LDCT was more effective at detecting cancers than CXR. The cohort who underwent screening using LDCT also had a 20% reduction in lung cancer-specific mortality. These results suggest that LDCT is a more effective screening modality than CXR.

The Dutch-Belgian randomised lung cancer screening trial (NELSON)

The NELSON study established the effectiveness of LDCT in lung cancer screening in high-risk smoking candidates.¹⁰ The NELSON study compared outcomes of two cohorts: those who underwent screening using LDCT (intervention arm) and those who underwent no screening (control arm). The study found that LDCT was effective in detecting early-stage cancers, with 46.8% of cancers identified in the intervention arm diagnosed at Stage I compared with only 6.9% diagnosed in the control arm. This was associated with a reduction in cancer-related mortality of 24% in the intervention arm compared with the control arm. The result of this study supports the use of LDCT in lung cancer screening.



The International Lung Screening Trial (ILST)

The International Lung Screening Trial (ILST) is the first screening trial to include an Australian population.¹¹ The study compared the effectiveness of different screening eligibility criteria and nodule management algorithms in lung cancer screening. Preliminary results indicate that risk-prediction models are superior to categorical criteria for selecting candidates for lung cancer screening.¹² The results from remaining outcomes are awaiting publication.

The Taiwan Lung Cancer Screening in Never-Smoker Trial (TALENT)

The TALENT study is a prospective cohort study assessing the efficacy of lung

cancer screening in nonsmoking candidates with at least one risk factor for lung cancer.¹³ The risk factors assessed included family history of lung cancer, passive smoking, environmental exposures, COPD and prior history of tuberculosis, which are not included in most current lung cancer screening eligibility criteria. The study found that participants with a family history of lung cancer had a significantly higher cancer detection rate of 2.6% compared with a detection rate of 1.2% in those without risk factors. This result supports the need to consider broadening lung cancer screening criteria to include high-risk nonsmokers such as candidates with a positive family history.

TABLE. OVERVIEW OF CLINICAL AND RADIOLOGICAL CHARACTERISTICS INCLUDED IN THE PANCAN AND LUNG-RADS NODULE MANAGEMENT ALGORITHMS

PanCan		Lung-RADS
Patient characteristics	Nodule characteristics	Nodule characteristics
Age	Size	Size
Sex	Location	Location
Emphysema	Morphology	Morphology
Family history	Number of nodules	Change on serial imaging

Abbreviations: Lung-RADS = Lung CT Screening Reporting and Data System; PanCan = Pan-Canadian Early Detection of Lung Cancer.

Existing lung cancer screening programs

The effectiveness of lung cancer screening has been evaluated in multiple randomised control studies, with the landmark NLST and NELSON study demonstrating a mortality benefit.^{9,10,14-19} Given this large body of evidence, lung cancer screening programs have been established in the USA, UK, Canada, Poland, China, Taiwan and South Korea.²⁰

The Australian Lung Cancer Screening Program

The Australian NLCSP is currently under development and is due to commence by July 2025. The Medical Services Advisory Committee (MSAC) has published its recommendations for the proposed program.^{21,22} Some key features of the proposed lung cancer screening program are presented below.

Eligibility criteria for lung cancer screening

The MSAC recommends that lung cancer screening be offered to current- or ex-smoking individuals who meet eligibility criteria.^{21,22} Their proposed eligibility criteria require applicants to be aged 50 to 70 years, have at least a 30 pack-year smoking history, either currently smoking or have quit smoking within the past 10 years.²³ The proposed MSAC selection criteria are comparable to those used by the United States Preventative Services Task Force (USPSTF), which uses categorical factors, age and smoking history to select applicants for lung cancer screening.²⁴

Other existing screening programs utilise additional risk factors to select candidates for lung cancer screening. The Canadian Ontario Lung Screening Program and UK-based Targeted Lung Health Check Program both use risk prediction models which incorporate additional risk factors, including ethnicity, education level, personal history of lung cancer and family history of lung cancer, to select screening applicants.²⁵ The Taiwan-based screening program is the first to include nonsmoking participants, provided they have a family history of lung cancer.²⁶ The USPSTF criteria have also evolved over time to address screening inequities, and are now enrolling participants with a broader age range and less intense smoking history, based on local data.²⁴ The Australian lung cancer screening eligibility criteria may also evolve with improved understanding of local lung cancer epidemiology.

Screening intervals

MSAC recommends that eligible applicants undergo LDCT every two years for lung cancer screening.²¹ This recommendation was based on results from the NELSON and Multicentric Italian Lung Detection (MILD) trials.^{10,27} The NELSON study found that a screening period of two years did not lead to a significant increase in the proportion of advanced cancers identified.¹⁰ Similarly, the MILD study found that two-year screening intervals reduced the total number of scans performed without significantly increasing lung cancer mortality or the proportion of advanced cancers identified on

screening.²⁷ Based on these results, a screening interval of two years may reduce health expenditure and radiation exposure without significantly impacting the efficacy of the screening program.

Risk stratification of pulmonary nodules

All lung nodules identified during the screening process will need to undergo risk assessment to determine further action. Nodule stratification algorithms, such as Pan-Canadian Early Detection of Lung Cancer (Pan-Can) and Lung CT Screening Reporting and Data System (Lung-RADS) (Table), stratify nodules based on the risk of malignancy.²⁸ MSAC currently recommends using the PanCan algorithm for nodules detected on baseline screening scans and Lung-RADS algorithm for nodules detected on subsequent screening scans.^{28,29} The PanCan algorithm uses patient (age, sex, family history) and nodule characteristics (nodule size, nodule location, nodule type, morphology) to predict the risk of malignancy.²⁸ The Lung-RADS algorithm uses radiological features of identified pulmonary nodules and the change on serial imaging for risk stratification.²⁹ Depending on the risk profile of the patient and the radiological features of nodules identified, the patient may be discharged, remain within the screening program or referred for specialist respiratory review.

Management of pulmonary nodules identified on screening

Pulmonary nodules have a broad differential that includes benign, infective, immunological and malignant pathology. Therefore, the diagnosis of lung cancer requires histopathological confirmation using tissue obtained via image-guided biopsy, surgery or bronchoscopy.³⁰ Once the lung cancer diagnosis has been confirmed, the patient requires staging to determine the extent of spread, which may require PET-CT, endobronchial ultrasound-guided sampling of lymph nodes and/or biopsy of suspected distal metastases.³⁰ Complex cases require management in a multidisciplinary team that includes thoracic physicians, oncologists, surgeons, radiologists, pathologists

and other medical and allied specialties.³¹ A schematic representation for the diagnostic pathway for the management of patients with high-risk pulmonary nodules is presented in Flowchart 2.

Projected impact of lung cancer screening

The national *Report on the Lung Cancer Screening Enquiry* estimates that within the first 10 years of the lung cancer screening program more than 70% of lung cancers will be diagnosed at an early stage, 12,000 lung cancer deaths will be avoided, and more than 50,000 quality-adjusted life-years will be gained.⁴

Benefits beyond early detection of lung cancer

Opportunities for smoking cessation

Tobacco smoking is the most important modifiable risk factor for lung cancer. The proposed targeted lung cancer screening program offers opportunities to incorporate interventions for smoking cessation. Studies have shown that participation in a screening program increases readiness to quit smoking, increases cessation attempts and improves the chances of success.^{32,33} Therefore, there is a strong incentive to integrate smoking cessation into the lung cancer screening program.

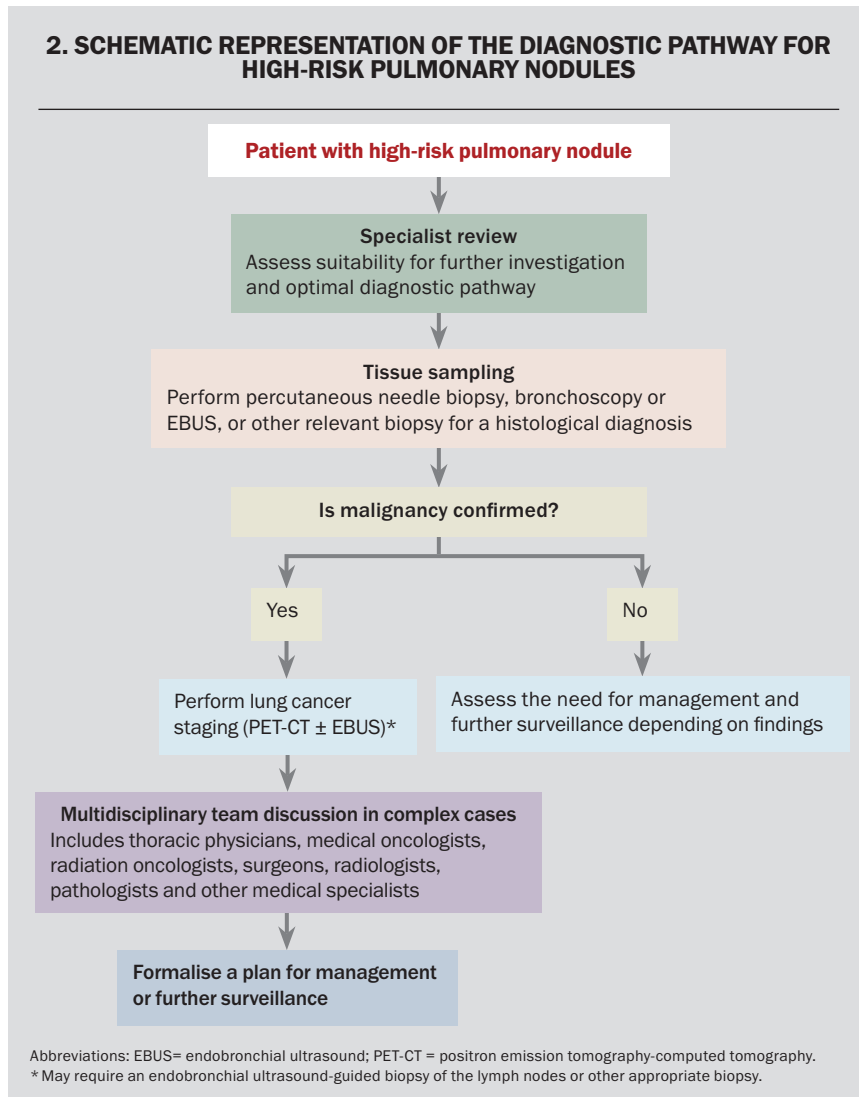
Incidental findings on LDCT

Incidental findings will be identified on LDCT as a part of the screening program. A retrospective analysis of NLST data identified incidental findings in 33.8% of LDCT images, and 89.1% of these findings were deemed reportable.³⁴ The most common findings were emphysema, coronary artery calcification and nonpulmonary mass lesions.³⁴ Therefore, the use of LDCT may also identify other pathologies and allow early intervention.

Potential harms of lung cancer screening

Radiation exposure

CT uses ionising radiation to produce images and cumulative exposure carries



the risk of inducing cancers.³⁵ The LDCT used in the screening program reduces the ionising radiation from 7 mSV (used in conventional CT) to 1.5 mSV.⁴ Based on a single centre study, the number of induced cancers after 10 years of screening with LDCT was estimated to be one cancer per 108 lung cancers identified.³⁵ In the context of a high-risk population, the benefit from a reduction in lung cancer mortality is generally thought to outweigh the risk from radiation exposure.⁴

False positives

False positives refer to the detection of noncancerous nodules during lung cancer

screening. Potential harms from false positives include psychological distress and unnecessary investigations or procedures. Lung cancer screening trials found false-positive rates between 9.6% to 28.9%.³⁶ Data from US screening programs indicate that 0.09% to 0.56% of participants underwent a biopsy and 0.5% to 1.3% underwent a surgical procedure for a false-positive result.³⁶

Psychological burden

Data from existing studies indicate that lung cancer screening is associated with significant psychological burden. Analyses from the NELSON study demonstrated

that indeterminant screening results were associated with an increased level of distress over the short term based on the Impact of Effects Scale (IES).³⁷ Data from the NLST study showed that true positives were also associated with negative impacts on quality of life based on 36-Item Short Form Survey (SF-36) scores.³⁸ Given the potential impacts of screening on quality of life, adequate support services will need to be implemented alongside the NLCSP.

Overdiagnosis

Overdiagnosis refers to the detection of cancers that would not have been clinically significant, and is a concept applied to populations rather than individuals.³⁹ The rates of overdiagnosis in screening trials vary widely between 6.3% to 67.2%.^{21,39} Potential strategies to reduce overdiagnosis include limiting screening to high-risk individuals and effective risk stratification of identified nodules.³⁹

Future directions

Computer-aided detection and radiomics

The Australian NLCSP will generate a large volume of LDCT images. Computer-aided detection (CAD) uses software that aids the radiologist in detecting nodules by removing unwanted background in LDCT images and highlighting findings suspected to be pulmonary nodules.⁴⁰ In doing so, CAD may shorten image reporting times and reduce the risk of missing nodules.

Radiomics software predicts whether an identified nodule is likely to be cancerous. This is achieved by analysing nodule features (size and morphology) to predict the likelihood that a pulmonary nodule is cancerous.⁴¹ Given the lung cancer screening program is likely to generate large numbers of scans, radiomics may become a valuable adjunct in risk stratification of identified nodules.

Optimising eligibility criteria for lung cancer screening

The proposed lung cancer screening program will target current- and ex-smoking

individuals. However, it is known that 10% to 25% of lung cancers occur in people without a significant smoking history and this approach may therefore lead to the exclusion of some high-risk individuals.⁴¹ Epidemiological studies suggest that women and those with a family history of lung cancer are at higher risk of lung cancer, even without a significant smoking history.^{42,43} Most recently, the TALENT study demonstrated that individuals with a family history of lung cancer had a significantly higher cancer detection rate.¹³ The lung cancer detection rate in individuals with a positive family history was 2.7%, which is higher than the overall lung cancer detection rate in the NLST study (1.1%) and NELSON study (0.9%) despite no significant smoking history.¹⁴ Given comparable lung cancer detection rates, the TALENT study supports the need to consider broadening selection criteria for lung cancer screening to include high-risk nonsmokers with a family history. The selection criteria for lung cancer screening may evolve with improved understanding of lung cancer risk factors and epidemiology. The mortality benefit of LDCT lung cancer screening in nonsmoking participants without additional risk factors has yet to be determined.

The role of GPs in lung cancer screening

The Australian NLCSP is under development and the role of GPs has not been formally announced. Based on experience from the US screening program, the roles that GPs could play in the lung cancer screening program include:⁴⁴

- identifying suitable candidates
- shared decision making with patients and multidisciplinary teams
- follow up in patients with abnormal and incidental findings
- maintaining engagement or adherence to the screening program.

Population engagement will be key to the success of the NLCSP. Other Australian cancer screening programs have achieved varying degrees of engagement, with 41%, 50% and 68% of eligible individuals

participating in colorectal, breast and cervical cancer screening, respectively.⁴⁵⁻⁴⁷ The uptake of lung cancer screening programs varies widely across the world. Estimates from existing screening or pilot programs in the USA, South Korea, China, the UK and Japan show varying uptake rates of up to 5.8%, 23%, 31%, 52.6% and 53.4% of eligible candidates, respectively.^{48,49} Some contributing factors to low uptake for lung cancer screening programs include lack of awareness, underestimation of cancer risk, fatalistic view of lung cancer and smoking-related stigma.⁵⁰ Poor uptake will reduce both the number of individuals screened and cancer deaths prevented by the NLCSP.

Australian GPs will likely provide pivotal support for the program. About 82% of the people in Australia have attended a GP practice in the past 12 months, which provides GPs with the greatest coverage of the Australian population among healthcare practitioners.⁵¹ Furthermore, studies have shown that endorsement from a primary care physician is an important motivating factor and increases the readiness of patients to engage in cancer screening programs.⁵² The efforts of Australian GPs to support the NLCSP will be vital to its success.

Conclusion

The Australian NLCSP has the potential to improve patient outcomes through early detection and integration of preventative measures, such as smoking cessation. The success of the screening program will depend on effective implementation and adequate uptake. Although the role of Australian GPs has not been announced, their support will be key to the program's success. **MT**

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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