Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1699 – National Lung Cancer Screening Program

Applicant: **Cancer Australia**

Date of MSAC consideration: **31 March – 1 April 2022**

1. Purpose of application

This application seeks MSAC's advice in relation to a proposed national lung cancer screening program (the Program) for Australia. This application describes the Program components, the clinical and economic evidence supporting the proposal, and the associated financial impact. A key component of the proposed Program is the creation and utilisation of an MBS item for use of low dose computed tomography (LDCT) in asymptomatic high-risk Australians as Program participants.

The proposed Program is based on radiological screening, and encompasses all activities outlined up to the point of referral to a specialist linked to a multidisciplinary team. Although subsequent investigation and treatment of lung cancer sit outside of the Program structure, all downstream consequences and costs were considered in the assessment of the Program. It is proposed that the Program would largely use existing LDCT infrastructure and expertise, however at the implementation planning phase due consideration will be required to ensure appropriate access for participants in more remote or underserviced areas.

Ever-smokers within the eligible age ranges would mostly be identified by their primary healthcare provider. These participants would be assessed to calculate their individual risk of developing lung cancer using a validated risk prediction tool (the PLCOm2012). Individuals with a risk above the defined risk-threshold would be invited for a LDCT scan. Based on the results of the LDCT scan, participants would be classified into different risk profiles, subsequently determining their journey through the screening and follow up assessment pathway.

Pre-ESC and pre-MSAC responses were received from Cancer Australia and the modelling team who conducted the economic evaluation. A pre-ESC response was also received from the Cancer, Hearing and Program Support Division of the Australian Government Department of Health (the Department).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC accepted, with a high level of confidence, that the clinical evidence showed a significant reduction in lung cancer mortality from the proposed

National Lung Cancer Screening Program. However, MSAC considered that the modelled economic evaluation generated a high ICER per QALY (of between $51,501 and $93,470) which did not provide a basis to identify a more cost-effective target population. MSAC also noted the financial model did not fully estimate the downstream implications to the Commonwealth health budget of the proposed Program.

MSAC deferred the application to seek the following information expeditiously:

- clarification regarding the face validity of the Australian modelled economic evaluation
- an investigation of whether a lower ICER is achievable with adjustments to the definition of the population eligible for screening and/or screening intervals
- associated with and contingent on this, a more complete financial analysis of the proposed Program.

Consumer summary

This application was from Cancer Australia to implement a National Lung Cancer Screening Program targeted to people who are at high risk of developing lung cancer. The screening component would be provided primarily through the Medicare Benefits Schedule.

A targeted program means that not everyone would be screened for lung cancer. To be referred for screening, a person would need to be at least 55 years old (50 years old for Indigenous people), have no symptoms of lung cancer and be a current or former smoker. For people who meet these requirements, a regular doctor (general practitioner, or GP) would then further assess their risk using a nominated risk assessment tool which has been specially developed and tested to assess lung cancer risk in current and former smokers. If a person's risk was calculated to be high enough based on this nominated risk assessment tool to meet the program's eligibility requirements, that person would go on to receive a type of imaging scan called low-dose computed tomography. If that person's scan showed no cancer, they would be screened in the same way every 2 years to keep checking for lung cancer, with the last year they would qualify for screening being when they turned 74 years old. If any scan did show signs of lung cancer, then the person would go on to receive more diagnostic tests, and treatment if necessary.

MSAC noted that lung cancer risk is also increased in people who had been subject to large amounts of passive smoke during their life; however, the nominated risk assessment tool does not work for passive smokers. Given this, MSAC considered that it was not feasible to extend the Program to passive smokers as this might expose passive smokers to the increased risk of unnecessary diagnostic tests and treatments (i.e. false positives and overdiagnosis).

MSAC considered that the available evidence showed that the proposed Program would lead to a reduction in the number of deaths caused by lung cancer, but not a reduction in the total numbers of deaths taking into account other causes of death unrelated to lung cancer. MSAC also had questions about the economic model used to assess cost-effectiveness, meaning that MSAC was uncertain if the proposed Program was good value for money. Given the questions about the model, MSAC could not advise on whether the eligibility for the Program could be adjusted to enhance its value for money. Any revised definition of eligibility for the Program is also important because the risk of overdiagnosis and false positives could lead to harmful diagnostic tests and cancer treatments if the wrong people were referred for screening. MSAC wanted more information before it could recommend who should be eligible for screening by the Program.

Consumer summary
MSAC also noted the very large cost to the government to implement the proposed Program and wanted more information so it could be more confident about how much the Program would cost overall. **MSAC's advice to the Commonwealth Minister for Health** MSAC deferred its recommendation on the National Lung Cancer Screening Program pending more information from the applicant. MSAC was not sure if the proposed Program was sufficiently effective and good value for money. MSAC was also uncertain if the proposed Program targeted the correct people.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application is to consider the proposed National Lung Cancer Screening Program, and to advise on its safety, effectiveness, cost-effectiveness and sustainable implementation if funded by the Australian Government. MSAC is asked to assure the government that the policy case for the Program has received robust, independent scrutiny to inform such implementation.

The proposed Program would support the early detection of lung cancer through the delivery of 2-yearly low-dose computed tomography (LDCT) scans in high-risk individuals using existing radiology facilities. MSAC noted that the proposed screening program's clinical management algorithm was complex in that there were several "checkpoints" and test results along the screening pathway that would triage the patients to those who would proceed to the next step in the algorithm. MSAC considered that the initial identification of eligible patients by a general practitioner (GP) to be crucial to the success of the proposed Program.

MSAC noted consumer feedback that people who had been exposed to passive smoke during their lives should also be eligible for screening; however, MSAC also noted that the risk-based tool assessed risk for past or current smokers only, and that the tool was not validated to be used in the passive smoking population. Given this, MSAC considered that it was not feasible to extend the Program to passive smokers without a validated risk-based tool for them as this might expose passive smokers to the higher risk of false positives and overdiagnosis.

MSAC noted the new proposed Medicare Benefits Schedule (MBS) item and descriptor. MSAC noted that the proposed fee ($302.10) was based on the current MBS fee for a CT chest scan.

Category 5 – DIAGNOSTIC IMAGING SERVICES

MBS item *56XXX
Computed tomography, low dose for lung cancer screening, without contrast material(s)
• Where the patient:
  ○ Is aged 55 to 74 years and is in the general Australian population OR is aged 50 to 74 years and is in the Aboriginal and Torres Strait Islander population;
  ○ Is asymptomatic (no signs or symptoms of lung cancer); and
  ○ Receives a request for LDCT lung cancer screening after being identified as at increased risk of lung cancer using the risk prediction tool (PLCOm2012 6-year risk score ≥1.51%).
• Where the service is reported by a specialist in the specialty of diagnostic radiology who:
  ○ Is available to monitor and influence the conduct and diagnostic quality of the examination; and
  ○ If necessary, is available to attend on the patient personally; and
  ○ Is involved in the ongoing supervision and interpretation of chest computed tomography acquisitions in the past 3 years.
• Where the service is performed at a comprehensive practice and the CT:
  ○ Performs LDCT with volumetric CT dose index (CTDIvol) of ≤3.0 mGy (milligray) for standard size patients (defined to be 170 cm and approximately 70 kg) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients; and
  ○ Utilises a standardised lung nodule identification, classification, and reporting system.
• Where the service frequency applicable is in alignment with the screening frequency defined in the lung cancer screening program.
• Where information on the service must be submitted to a Department of Health approved register for each LDCT lung cancer screening performed with details on the patient *(noting the register is still under development)*.
• (R) (Anaes.)

Fee: $302.10 Benefit: 75% = $226.60 85% = $256.80

MSAC noted the comparator (no screening) and considered it to be appropriate.

MSAC concluded that the clinical evidence shows that lung cancer screening reduces lung cancer mortality. MSAC considered that the parameters in the large, randomised NELSON 2003 trial better reflected the Australian healthcare system and the type of screening program being proposed than the large, randomised NLST 2002. In the NELSON 2003 trial, MSAC noted that there was 90% adherence, and lung cancer mortality was 2.6 lung cancer deaths per 1000 patient years in the screening group compared to 3.4 lung cancer deaths per 1000 patient years in the control group for a net reduction of close to 1 lung cancer death per 1000 patient years (this reduction was largely comparable to the NLST 2002, which recorded 2.47 lung cancer deaths per 1000 patient years in the screening group vs 3.09 lung cancer deaths per 1000 patient years in the control group). This reduction is driven by a larger proportion of cancers being detected at Stage 1A and a smaller proportion of cancers being detected at Stage IV in the screening group compared to the control group. MSAC also concluded that the NELSON 2003 evidence shows that, with 1728/13,195 (13%) patients dying in the reported duration of follow-up, lung cancer screening is not associated with a reduction in all-cause mortality (13.93 overall deaths per 1000 patient years in the screening group compared to 13.75 overall deaths per 1000 patient years in the control group for a numerical difference of only 0.17 overall deaths per 1000 patient years, a hazard ratio of 1.01, 95% CI: 0.92 to 1.11, and no apparent divergence of the cumulative all-cause mortality rate per year since randomisation). This may be partially explained by a slight increase in the risk of non-lung-cancer mortality (11.36 non-lung cancer deaths per 1000 patient years in the screening group compared to 10.4 non-lung cancer deaths per 1000 patient years in the control group for a net increase of close to 0.96 non lung cancer deaths per 1000 patient years in the NELSON 2003 evidence). MSAC noted that these results on

all-cause mortality were generally consistent with the findings from the meta-analyses identified by the applicants.[1]

MSAC noted the lack of reduction of all-cause mortality but also acknowledged that a reduction in all-cause mortality may be seen as an unreasonable expectation given that this expectation has not been consistently applied to screening interventions or many other medical interventions. MSAC accepted that the reduction in lung cancer mortality, offered by the Program, even without any changes in all-cause mortality was important to patients and the community.

MSAC considered that introducing the proposed Program would result in several safety or unintended consequences for some individuals screened, including those from:

- overdiagnosis of lung cancers that would not have been detected clinically resulting in unnecessary investigation and treatment (the NELSON trial reported an initial overdiagnosis rate of 19.7% over 10-year follow up [2] that reduced to 8.9% over the extended 11-year follow-up[3] while meta-analyses report overdiagnosis rates ranging from 20%[4] to 30%[5] [6])
- indeterminate test results (reduced in subsequent rounds of screening in NELSON 2003) and false positive test results (shown by a consistent positive predictive value of about 44% across rounds of screening in NELSON 2003), both of which result in unnecessary further testing and diagnostics, including greater radiation exposure from higher dose CT imaging
- the psychological effects associated with these false positive screening results, false negative screening results (resulting in interval cancers, which are clinically detected lung cancers between rounds of screening: 141/344 = 41% of cancers detected in NELSON 2003 were interval cancers), and true positive screening results.

MSAC noted that the modelled economic evaluation was a semi-Markov model with computation by microsimulation which adapted an existing cancer screening model, the MISCAN-Lung to the Australian context. MSAC noted and agreed with the key issues raised in the ESC report regarding the MISCAN-Lung model and in particular that, while the application was transparent regarding the inputs and outputs of the model, the MISCAN-Lung model itself was not transparent. MSAC noted that calibration of the model involved manipulating inputs to ensure outputs matched observed data in the short-term and considered that an inevitable shortcoming of this approach was that various combinations of inputs may lead to the same short-term output but produce different model behaviour in the long-term.

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[1] See for instance the most recent meta-analysis Field J, Vulkan D, Davies M, Baldwin D, Brain K, Devaraj A et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. The Lancet Regional Health - Europe. 2021;100179.

[2] De Koning H, Van Der Aalst C, Ten Haaf K, Oudkerk M. PL02.05 Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. Journal of Thoracic Oncology. 2018;13(10):S185.

[3] De Koning H, van der Aalst C, de Jong P, Scholten E, Nackaerts K, Heuvelmans M et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. New England Journal of Medicine. 2020;382(6):503-13.

[4] Ebell MH., Bentivegna M., Hulme C. Cancer-Specific Mortality, All-Cause Mortality, and Overdiagnosis in Lung Cancer Screening Trials: A Meta-Analysis. The Annals of Family Medicine November 2020, 18 (6) 545-52.

[5] Passiglia 2021. Benefits and Harms of Lung Cancer Screening by Chest Computed Tomography: A Systematic Review and Meta-Analysis. Journal of Clinical Oncology 39, no. 23 (August 10, 2021) 2574-2585.

[6] Hoffman, R.M., Atallah, R.P., Struble, R.D. et al. Lung Cancer Screening with Low-Dose CT: a Meta-Analysis. J GEN INTERN MED 35, 3015–3025.

MSAC also noted two key face validity issues with the model results.

For the first of these, MSAC noted that changing the risk thresholds for eligibility to proceed to LDCT scanning resulted in a U-shaped relationship between the risk threshold and the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) such that increasing the risk threshold above 1.75% led to increases rather than decreases in the ICER per QALY (see Table 48 in the economic evaluation of the Program[7]). From first principles, MSAC considered that increasing the risk threshold for screening would be expected to reduce the ICER per QALY by better targeting more at- risk participants. MSAC noted that the MISCAN-Lung model behaved as expected when applied to the Canadian context[8] (i.e. increasing risk thresholds, in this case measured by pack years of smoking, led consistently to decreases in the ICER per life-year gained (LYG)). MSAC was therefore concerned that the U-shaped relationship found in the application of MISCAN-Lung to Australian data may be an anomalous result. MSAC considered this to be important because the eligibility risk threshold may be the only input variable in defining the Program that could be changed in order to make the ICER per QALY more favourable.

For the second face validity issue, MSAC noted that the sensitivity analysis to investigate the costs and consequences of more recently subsidised immunotherapies (for stage III/IV cancers) found that these immunotherapies led to increased incremental costs (indicating greater use of immunotherapies in the screening arm) and reduced incremental QALYs, indicating greater QALY gains in the no screening arm. Together these impacts led to an increase in the ICER per QALY. MSAC considered these results of the sensitivity analysis to be counterintuitive.

MSAC considered that the pre-MSAC response did not adequately address either of these modelling issues. Other issues which the pre-MSAC response did not sufficiently address were as follows:

- MSAC understood that the model was not dynamic with respect to factors such as risk profiles, smoking prevalence, screening technologies, or anticipated costs and health outcomes of emerging treatments (the pre-MSAC response did state that the model was dynamic for the specific birth cohorts modelled).
- The ICERs estimated were likely biased in favour of screening because they did not take into account the consequences of possible imperfections in Program implementation. The pre-MSAC response was that though the sensitivity analyses were selected to be favourable to screening, the model still revealed low sensitivity (reducing screening tests costs by 50% was the only analysis with a substantial effect) and therefore low sensitivity would also be expected from assumptions which were less favourable to screening. However MSAC considered overall that a more evidence-based response would have been to also supply sensitivity analyses with less favourable assumptions.

MSAC noted the high base case ICER per QALY of approximately $83,545 and that this was on the basis of an optimistic assumption of 100% uptake of the Program. MSAC noted that the sensitivity analysis in the pre-ESC response estimated a lower ICER per QALY of $51,501 based on an assumed 25% reduction in costs for the initial phase and 75% reduction in costs for the continuing care phase for stage I and II lung cancers and no disutility for stage I and II lung cancers in the continuing phase only. However, although noting the view of ESC that this sensitivity analysis relied on more plausible assumptions, MSAC considered that this was likely to

[7] Cancer Australia 2020. *The economic evaluation of targeted lung cancer screening in Australia.* Surry Hills, NSW 2012.

[8] Ten Haaf K, Tammemägi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, Nicholas G, de Koning HJ, Paszat LF. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. PLoS Med. 2017 Feb 7;14(2).

be a best-case scenario and did not account for less than 100% uptake. MSAC considered that a new respecified base case could potentially use the $51,501 estimate as a starting point (with clearer rationale for the revised assumptions) but then take into account an uptake of less than 100% and address the other points detailed below in defining the matters to be addressed by the deferral.

MSAC explored different approaches for putting the proposed Program's ICER in the context of other interventions with similar clinical, economic and budget consequences:

- First, MSAC compared the Program's cost effectiveness to that of other existing screening programs which have had their cost effectiveness estimated in terms of ICER per life-year gained (LYG), which could be compared with an ICER per LYG of $53,414 in the initial evaluation and $43,104 in the pre-ESC response. Though noting that these ICERs may not be directly comparable due to different economic modelling methods used across the models, MSAC observed that another economic evaluation of another lung cancer screening proposal had a relatively high ICER per LYG of $154,776 compared to the National Cervical Screening Program ($16,632 per LYG), the National Bowel Cancer Screening Program ($3,380 per LYG) and BreastScreen Australia ($40,279 per LYG).[9]
- Second, MSAC referred to other related decisions from other similar committees to advise on an acceptable ICER for interventions in similar contexts. MSAC noted that an appropriate ICER threshold in this respect might be for treatments with large patient populations, such as population preventative interventions in asymptomatic individuals including lipid-lowering medicines, anti-hypertensive medicines and vaccines which typically have a large opportunity cost. For instance, MSAC observed that, in March 2015, the Pharmaceutical Benefits Advisory Committee (PBAC) required an ICER of <$15,000 per QALY for direct acting antiviral medicines for hepatitis C. MSAC also observed that, between November 2006 and November 2019, the PBAC also consistently required ICERs in the range of $15,000 to $45,000 per QALY across several applications for human papillomavirus (HPV) and meningococcal vaccines, but considered that interpretation of this range was affected by it being defined as one of the agreed ranges enabling non-specific disclosure of actual ICERs in PBAC's Public Summary Documents.

MSAC accepted these contexts as a starting point and considered that a reliable ICER closer to $20,000 per QALY if possible might be acceptable for a revised Program, noting that the older age group of eligible patients (compared to, for example, the cervical screening program or treatments for hepatitis C) means an overall shortened time horizon and that the benefits would be realised sooner. MSAC also considered it to be reasonable not to require a separate analysis for the Indigenous subgroup of the general population due to the higher unmet clinical need in this subgroup.

MSAC explored possibilities to reduce the ICER for the Program, including increasing the risk threshold to better target the eligible population. (MSAC noted that changing the screening intervals or nodule management protocols made little difference to the ICERs.) However MSAC did not consider that the current model provided sufficient confidence to guide MSAC's decisions because the U-shaped relationship between risk thresholds for eligibility and ICERs called into question whether choosing the risk threshold that gave the smallest ICER was appropriate for this model.

[9] Lew J-B, Feletto E, Wade S, Caruana M, Kang Y-J, Nickson C, Simms KT, Procopio P, Taylor N, Worthington J, Smith DP, Canfell K. Benefits, harms and cost-effectiveness of cancer screening in Australia: an overview of modelling estimates. Public Health Res Pract. 2019;29(2):e2921913.

MSAC advised that the overall financial impact ($157 million over 5 years) was likely underestimated and incomplete, as it included only the costs of LDCT testing and the costs of supporting the Program, but not other related downstream cost consequences such as repeat and additional testing, and treatment costs. MSAC noted that while there was a separate financial cost model that estimated some downstream treatment costs (the 'net costs' model), this was also incomplete, and MSAC considered that the net cost savings it presented were implausible with large discrepancies between its results and downstream treatment costs of the modelled economic evaluation. Because of these problems, MSAC noted that it was unable to rely on the presented information to provide advice on the overall financial net costs to the Commonwealth of the Program. However, MSAC noted that government consideration of funding the Program would require a fully costed policy proposal and this would be prepared subsequent to MSAC's considerations. For this reason, MSAC accepted that only a subset of the financial implications was presented for its consideration.

MSAC noted several possible implementation issues. The program is designed to operate in rural and regional locations using mobile screening units, which MSAC supported as a way to ensure equity of access, but queried if it was realistic for the model to assume that mobile screening costs are the same as static screening costs, and how the additional delivery costs would be handled. MSAC also queried if additional private sector "capacity-building incentives" had been included and queried if there was more information available on the "investment stream" referred to in the policy document to encourage providers to implement mobile screening. MSAC supported creating a lung cancer screening registry as part of the program's implementation and recognised that a separate business case was being prepared to assess the data registry and other implementation components of the Program. MSAC also noted that, once policy around the Program's implementation was closer to being realised, updated costs could then be included in the modelled economic evaluation.

MSAC noted that an Australian-led International Lung Screen Trial is due for completion in December 2023, but considered that the results of this trial would not influence immediate MSAC decision-making mostly because it is not assessing mortality from lung cancer nor, with a relatively small estimate sample size of 2000 participants, is it likely to provide any additional precision around the other relevant clinical effects of lung cancer screening.

MSAC deferred its decision pending further information, which the Department agreed to coordinate with the applicant, Cancer Australia. Specifically, MSAC advised that the applicant:

- revise the model – namely,
    - check the calibration of the Australian MISCAN-Lung modelled economic evaluation
    - address MSAC's face validity concerns relating to the U-shaped relationship between risk thresholds and ICERs and the inclusion of immunotherapies to increase confidence in this modelled economic evaluation
    - more clearly justify the assumptions behind the version of the model generating the pre-ESC response ICER per QALY result of $51,501
    - apply a more plausible uptake assumption than 100%
    - following the above, provide a new, respecified base case using scenario-based adjustments to the definition of the population eligible for screening (starting and stopping age, and other factors predicting risk of lung cancer) and/or screening intervals to result in a reliable ICER closer to $20,000 per QALY if possible (MSAC considered that the associated scenario analyses could reflect the presentation

of options in Table 4 of the application of the MISCAN-Lung model to Canadian data[8]

- when reporting on results from the respecified base case and sensitivity analyses, also report the other outputs of the model that are relevant to decision-making such as number of interval cancers and false positives (MSAC considered that this could reflect the presentation of results in Table 5 of the application of the MISCAN-Lung model to Canadian data[8])
- re-calculate and present a full financial analysis consistent with the respecified base case defined for the MISCAN-Lung modelled economic evaluation (including all affected types of downstream healthcare costs incurred by the MBS and the PBS).

MSAC recognised that some of these re-analyses would be time-consuming. MSAC noted that, contingent on the economic evaluation issues being satisfactorily resolved, then a revised financial analysis should be finalised for the government to consider.

4. Background

On 1 August 2019, the Minister for Health, the Hon. Greg Hunt MP, invited Cancer Australia to conduct an enquiry into the prospects, process and delivery of a national lung cancer screening program in Australia. Cancer Australia released the Report on the lung cancer screening enquiry on its website on 30 November 2020. The Enquiry recommended the establishment of a national lung cancer screening program targeting high-risk individuals (smokers and ex-smokers) aged 55 to 74 years, and high-risk Aboriginal and Torres Strait Islander individuals aged 50 to 74 years.

The 2021-22 Commonwealth Budget tasked the Department and Cancer Australia to work together to establish the feasibility of implementing a national program to inform a fully costed proposal to Government for the detailed design, development, and implementation of a national lung cancer screening program.

The proposed targeted national screening Program would support the early detection of lung cancer through the use of LDCT in asymptomatic high-risk individuals primarily through existing radiology facilities. A risk prediction tool would be applied to those entering the Program to assess their suitability for screening. If a person's risk prediction exceeds a threshold level, they would be offered LDCT screening. Screening would be every two years while they participate in the Program, or until a nodule requiring management is identified. Any suspicious nodule requiring investigation would be managed within existing health services which may or may not lead to a diagnosis of lung cancer.

To enable accessibility and affordability of the Program, the Medicare Benefits Schedule (MBS) is the proposed primary mechanism to fund the risk prediction and LDCT screening components. The use of the MBS would enable the Program to use existing LDCT infrastructure and expertise, necessary to support a national roll-out of the Program, while also helping to deliver broad geographic coverage across Australia for eligible participants.

The proposal seeks the creation of a new Program-specific MBS item for the LDCT screen component delivered by radiology providers. The risk prediction tool would be applied by primary health care providers as part of the usual consultation, without the need for a new MBS item.

The need for MSAC consideration of the new MBS item was flagged by the Department of Finance during the 2021-22 Budget process. This approach was agreed by the Minister for Health, the Hon. Greg Hunt MP, on 20 August 2021. Consideration of this proposal by MSAC is

intended to provide assurance to Government that the policy case for the proposed Program has received robust, independent scrutiny to inform future implementation.

MSAC has not previously considered LDCT for a targeted national lung cancer screening program.

The commentary noted that current Health Assessment MBS items (Items 701, 703, 705, 707) preclude the use of the items for health screening purposes and, in any event, do not include the age range that would be eligible for lung cancer screening. This means that standard consultation items would need to be employed for using the risk prediction tool. If the risk prediction tool takes approximately 10 minutes to complete, only 10 minutes would remain in a Level A or B (<20 minute) consultation to deal with the original issue for the consultation. The lack of a specific consultation item in primary care for applying the risk prediction tool will reduce uptake of the proposed lung cancer screening Program. Examples of existing MBS consultation items that use a risk prediction tool include Items 224, 225, 226 and 227. These can be used to undertake a type 2 diabetes risk evaluation for people aged 40-49 years (inclusive) with a high risk of developing type 2 diabetes, as determined by the Australian Type 2 Diabetes Risk Assessment Tool.

However, in its pre-ESC response, the Department noted that it did not consider that MBS items 224 – 227 are appropriate to facilitate the delivery of 2-yearly low-dose computed tomography (LDCT) scans to detect lung cancer because these items are not GP items and duplicate the services to eligible patient cohorts that are provided by GPs using MBS items 701 – 707 (the same requirements and restrictions apply). Furthermore, the MBS Review Taskforce endorsed a recommendation that a review of the evidence base for current health assessment items be undertaken, including to ensure that the content of health assessment items conforms to appropriate clinical guidelines. Any potential updates to health assessment items would be considered in this context. In relation to the use of general attendance items, the Department noted that Level C and D general attendance items are available for the provision of more complex services, or where more than one kind of service needs to be delivered in order to address a patient's health needs. In general, the Department considered that most services provided by GPs for the proposed Program can be undertaken within the time tiered general attendance framework and it was not appropriate to create new GP items.

5. Prerequisites to implementation of any funding advice

Elements that would need to be in place before establishing a full national Program include:

- necessary quality assurance measures such as established clinical pathways, protocols and accrediting of LDCT machines to ensure they are capable of delivering a low radiation dose CT scan with volumetric assessment
- resources such as decision-aids and training and education requirements for the diverse clinical workforce who would support and operate the screening and assessment pathway
- the establishment of a screening register. Image capture and storage were originally included as requirements of the register. Based on consultation with radiology providers, this register functionality now appears largely unnecessary, particularly as providers already capture and store images. However, requirements to share images when patients move between providers and geographic areas would remain as a key requirement for radiology providers participating in the Program.

- appropriate technology to allow data transfer and communication with participants and health providers
- development and implementation of a Program access strategy to ensure the delivery of screening services in remote parts of each State and Territory, which may include assisting providers and their delivery partners to invest in new mobile service models
- employment of necessary Program implementation personnel and the establishment of governance systems
- information/communication strategies, systems, and tools.

The commentary noted that the proposed intervention (LDCT) does not require any additional TGA approval, as a large number of CT systems are already listed on the ARTG. However, it was not clear which of the above elements are already in place, nor how these elements would be implemented. In its pre-ESC response, the Department noted that it was working in partnership with Cancer Australia to establish the feasibility of the Program including through consulting with key stakeholders to inform the detailed design and implementation of each of the listed Program elements. If supported by government, the development and implementation of the Program elements listed would be undertaken in the initial 12 months to support the first recruitment of participants in the second year.

6. Proposal for public funding

Table 1 presents the proposed MBS item descriptor**.** Subject to MSAC's advice, the fee for the Program-specific MBS item for LDCT is proposed to be set in line with the existing MBS item 56301 *Computed tomography - scan of the chest*, which is currently $302.10. Both the initial and any subsequent LDCT is proposed to be supported through the one item and reimbursed at the same rate. The final item descriptor would also need to define the different age thresholds for the general population and the Aboriginal and Torres Strait Islander population.

The proposed item descriptor requires the service to be performed at a comprehensive practice to provide additional assurance the patient would receive a service meeting the quality standards for the Program. For equity of access, the Program would need to facilitate access to private radiology providers that may not be linked to a medical practice or public hospital. However, while this requirement aligns with the definition currently used for magnetic resonance imaging (MRI) and positron emission tomography (PET) services, it would preclude stand-alone CT practices from participating in the Program. The requirement for a comprehensive practice is not used for CT services; however most diagnostic imaging practices would meet this criterion.

For the purpose of the item descriptor, LDCT has been defined as LDCT with volumetric CT dose index (CTDIvol) of ≤3.0 mGy (milligray) for standard size patients (defined to be 170 cm and approximately 70 kg) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients. This definition aligns with the United States lung screening program, the Targeted Lung Health Checks Programme in the United Kingdom, and the protocol and rationale for the International Lung Screening Trial[10].

The commentary noted that the requirement in the USA by the U.S. Centres for Medicare & Medicaid services requires the CTDIvol to be 3.0 mGy or less for standard sized patients (170 cm and approximately 70 kg, BMI 24.3). In these guidelines, 3.0 mGy is the upper limit of CTDIvol

[10] Lim KP, Marshall H, Tammemagi M, Brims F, McWilliams A, Stone E, et al. Protocol and Rationale for the International Lung Screening Trial (ILST). Ann Am Thorac Soc. 2019.

allowed. Dose index data from a lung cancer screening program in the US were evaluated to ensure compliance with requirements.[11] This study reported that the average CTDIvol for a standard-sized patient was 1.8 mGy. CTDIvol values greater than 3.0 mGy were only observed for overweight or obese patients.

Table 1 Presentation of a newly proposed MBS item

Category 5 – DIAGNOSTIC IMAGING SERVICES

MBS item *56XXX
Computed tomography, low dose for lung cancer screening, without contrast material(s)
• Where the patient:
  ○ Is aged 55 to 74 years and is in the general Australian population OR is aged 50 to 74 years and is in the Aboriginal and Torres Strait Islander population;
  ○ Is asymptomatic (no signs or symptoms of lung cancer); and
  ○ Receives a request for LDCT lung cancer screening after being identified as at increased risk of lung cancer using the risk prediction tool (PLCOm2012 6-year risk score ≥1.51%).
• Where the service is reported by a specialist in the specialty of diagnostic radiology who:
  ○ Is available to monitor and influence the conduct and diagnostic quality of the examination; and
  ○ If necessary, is available to attend on the patient personally; and
  ○ Is involved in the ongoing supervision and interpretation of chest computed tomography acquisitions in the past 3 years.
• Where the service is performed at a comprehensive practice and the CT:
  ○ Performs LDCT with volumetric CT dose index (CTDIvol) of ≤3.0 mGy (milligray) for standard size patients (defined to be 170 cm and approximately 70 kg) with appropriate reductions in CTDIvol for smaller patients and appropriate increases in CTDIvol for larger patients; and
  ○ Utilises a standardised lung nodule identification, classification, and reporting system.
• Where the service frequency applicable is in alignment with the screening frequency defined in the lung cancer screening program.
• Where information on the service must be submitted to a Department of Health approved register for each LDCT lung cancer screening performed with details on the patient *(noting the register is still under development)*.
• (R) (Anaes.)

Fee: $302.10 Benefit: 75% = $226.60 85% = $256.80

7. Population

Target population and participant recruitment

The proposed target population is high-risk individuals (smokers and ex-smokers) aged 55 to 74 years in the general Australian population, and high-risk Aboriginal and Torres Strait Islander individuals aged 50 to 74 years.

Attachment 1 provides a detailed description of the Program including the targeted populations and associated interventions.

The commentary noted that the difference in exclusion criteria between the trials and the proposed Program (as per the MBS item descriptor) means that people with severe health problems would still be eligible for screening in the Australian Program, whereas they were excluded from the trials. Including people with severe health problems in the Program would likely decrease the effectiveness of the Program. However, it may be preferable to retain a broad

[11] Fujii, K, McMillan, K, Bostani, M, Cagnon, C & McNitt-Gray, M 2017, 'Patient Size-Specific Analysis of Dose Indexes From CT Lung Cancer Screening', AJR Am J Roentgenol, vol. 208, no. 1, Jan, pp. 144-149.

MBS item descriptor and encourage the development of separate guidance in Program materials to assist clinicians to identify individuals less likely to benefit from the Program.

The proposed approach to participant recruitment will be multi-channelled to maximise participant recruitment, including for sociodemographic groups at highest risk of lung cancer, from within the target population. Figure 1 outlines the proposed access or entry routes.

Screening presents an opportunity for health education and, thus, smoking cessation is an important component of the Program. It is proposed that smokers entering the Program be offered access to smoking cessation education. Referral to existing State and Commonwealth smoking cessation programs, in particular Quitline, would be the appropriate pathway for smokers in the Program who express a desire to change their smoking patterns.

The commentary noted that combining smoking cessation counselling with the PLCOm2012 (when patients are selected for the screening program) or with LDCT (only including patients with high risk of lung cancer) could improve the effectiveness of the screening program, as it has the potential to lead to a larger mortality reduction due to increased cessation rates. In its pre-ESC response, the Department clarified that smoking cessation counselling is not proposed to be included as an element of the Program itself. However, when undertaking an assessment of eligibility for the Program, there is an opportunity for the primary health care provider to have a conversation with the potential participant and provide information on existing local smoking cessation programs.

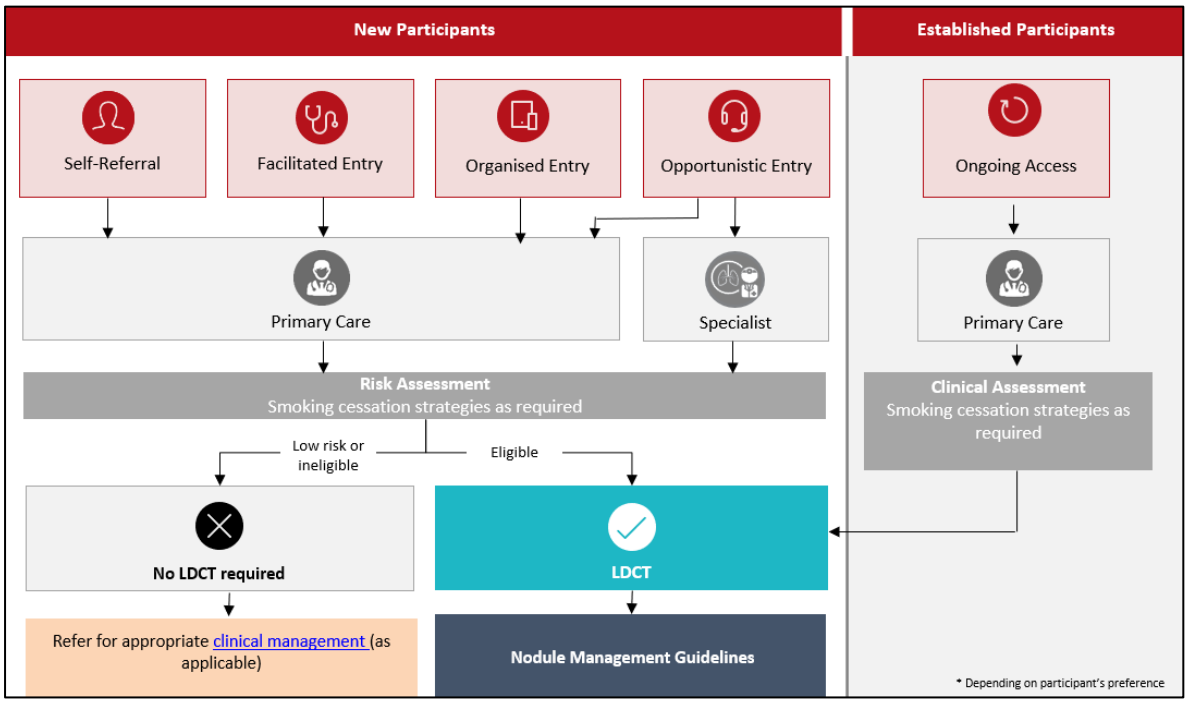

Figure 1 Program entry and access routes

Source: Figure 5, Lung Cancer Screening for Australia: A synthesis of evidence, economics and stakeholder perspectives ("Red report")

Participant eligibility

An essential component of any national cancer screening program is a screening and assessment pathway. Figure 2 diagrammatically describes the proposed screening and assessment pathway.

Screening and assessment pathway

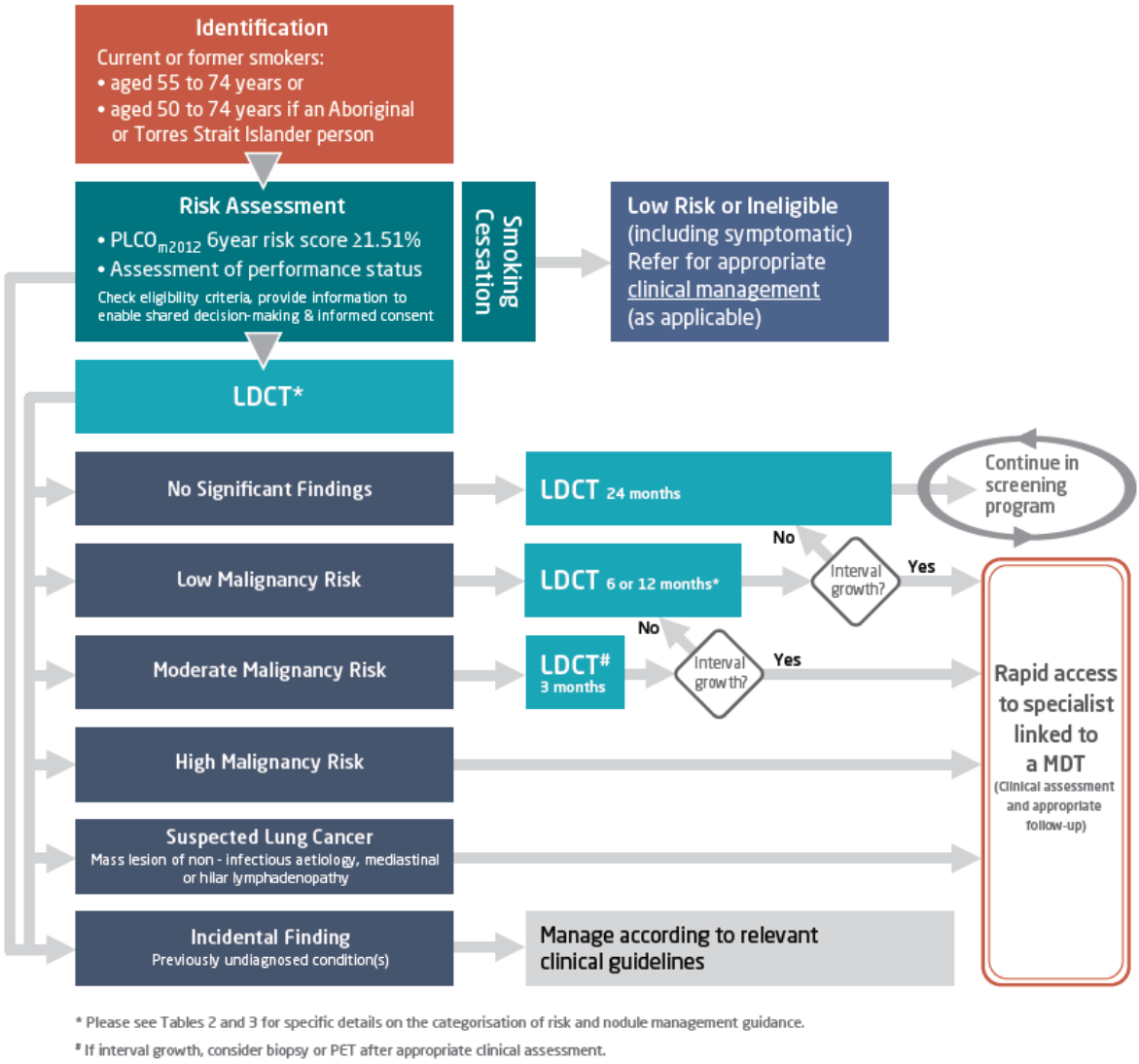

Figure 2 Screening and assessment pathway

Source: Figure 4, Lung Cancer Screening for Australia: A synthesis of evidence, economics and stakeholder perspectives ("Red report")

A two-step eligibility process is proposed. The former is age and smoking history-based, while the latter is through the application of a defined risk prediction tool. Participants aged 55 to 74 years, or 50 to 74 years for Aboriginal & Torres Strait Islander people, at the date of the risk assessment, who are current or former smokers would be identified (see Figure 1 for entry and access routes for the Program) and provided with the opportunity to be assessed by a risk prediction tool called the PLCOm2012 (a lung cancer risk prediction model developed from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial). In order to determine eligibility for the Program, potential participants would complete the risk assessment with an authorised health care professional to determine their PLCOm2012 risk score over a six-year period. If a potential participant aged 55 to 74 years (or for Aboriginal and Torres Strait Islander people aged 50 to 74 years) scores a PLCOm2012 risk of ≥1.51% over 6 years, they would be invited to have a LDCT screening test. Participants assessed as ineligible for a LDCT screening test based on the PLCOm2012 risk prediction tool may be able to be assessed by the PLCOm2012 risk prediction tool again in the future at a specified time. Participants would also be identified as ineligible for a LDCT screening test if they present with symptoms indicative of

lung cancer. Those participants should instead be investigated according to best practice clinical management, using the Cancer Australia GP Guide: *Investigating symptoms of lung cancer: a guide for all health professionals*.

The proposed approach, which focuses on the population group with the highest known prevalence of lung cancer and applies a risk a prediction tool to that population group, is designed to identify the largest number of cancers in the most cost-effective manner. The Program would complement and reinforce existing primary prevention strategies.

Low- dose computed tomography and nodule management

The screening test for the Program is LDCT with volumetric analysis at 2-yearly intervals.

As shown in the screening and assessment pathway, participants' LDCT scans would be classified into the following risk profiles: no significant findings, low malignancy risk, moderate malignancy risk, high malignancy risk and suspected lung cancer. In addition, incidental findings (unrelated to lung cancer) might also be identified. The proposed LDCT reporting would leverage the use of computer assisted diagnostics (CAD) and artificial intelligence (AI). Specifically, the proposed LDCT would employ structured reporting by a radiologist and CAD, with indeterminate results reviewed by a second radiologist. For participants with a LDCT scan showing nodules, the action taken would be determined according to risk of nodule malignancy. For a baseline scan (or T_0 scan), i.e., the first scan used for screening, the PanCan (or Brock University) nodule malignancy probability calculator would be used, noting the most recent version of the PanCan nodule management protocol would be used at the time of reporting. Table 2 outlines how nodules should be managed in accordance with this nodule management protocol.

For any additional scans following the baseline (or T_0) scan, the Lung-RADS 1.1 nodule management classification system would be used, and new nodules managed in accordance with the nodule management protocol outlined in Table 3; noting the most recent version of the Lung-RADS nodule management protocol would be used at the time of reporting.

The commentary noted that the evidence on 2-yearly screening past the first 5 to 6 years is lacking. The benefit and risks of continuous 2-yearly screening of an individual for 20-25 years are unknown. The commentary considered that this meant that any changes in test accuracy over time could have unanticipated consequences.

- Improved LDCT scanners and use of algorithms to detect nodules may alter the test yield and may also result in a greater detection of indolent cancers. If this is the case, overdiagnosis may become a more prominent issue in the Australian setting.
- Improved LDCT scanners may also reduce test specificity and result in a greater number of benign conditions identified.
- A plan for periodically reviewing the accuracy of testing equipment and risk prediction tools, as part of a screening program evaluation, would be beneficial.

Table 2 Nodule management protocol using PanCan calculator for baseline (T0) LDCT scans

Categorisation#	T_0 (baseline LDCT scan)	Interval LDCT scan or referral	Rescreen
No Significant Findings	PanCan nodule risk index <1.5%	N/A	24 months
Low Malignancy Risk	PanCan nodule risk index ≥1.5% & <6%	12 months^	
Moderate Malignancy Risk	PanCan nodule risk index ≥6% & <30%	3 months^^,* and 12 months and review by specialist linked with a MDT	
High Malignancy Risk	PanCan nodule risk index ≥30%	Rapid access to specialist linked with a MDT	If appropriate, continue in screening program (see Table 3)
Suspected Lung Cancer Mass lesion of non-infectious aetiology, mediastinal or hilar lymphadenopathy	Mass lesion of non-infectious aetiology, mediastinal or hilar lymphadenopathy		

Refers to assessment of the nodule. When there is more than one nodule, reference is made to the dominant nodule (highest malignancy risk).
^ Participants with a low malignancy risk nodule will have a repeat LDCT annually for up for two years. Results of this scan are subdivided into two categories – those that show interval growth will be referred for immediate clinical investigation, those that do not show interval growth will receive an LDCT scan at 24 months
^^ Participants with a moderate malignancy risk nodule will have a short term interval LDCT in 3 months. Results from this scan are subdivided into two categories – those that show interval growth (>25% growth in volume) and/or rapid growth (volume doubling time (VDT) <400 days) will be referred for immediate clinical investigation; those that do not show interval growth (<25% growth in volume) and/or VDT>600 days receive an interval LDCT at 12 months.
* For nodules with VDT 400–600 days (intermediate cancer risk), a second repeat CT scan in 3 months should be considered as an initial work-up option.

In its pre-ESC response, the applicant noted that data and research would be core components of the proposed Program. Data would be used to monitor and evaluate screening program performance, with a focus on continuous improvement. This inbuilt program of research would ensure the Program remains contemporary, enabling it to be agile and built to strengthen the evidence base of the Program, this would include ongoing research on participant eligibility criteria, duration of screening and nodule management protocols.

The commentary noted that the PanCan was shown in the study by van Riel et al. to be superior to the Lung-RADS.[12] However, PanCan has only been validated at baseline and therefore the Lung-RADS was proposed to be used for subsequent screens. The commentary agreed that this was reasonable but may need to be re-visited as new information emerges concerning the long-term validity of PanCan.

[12] van Riel, SJ, Ciompi, F, Jacobs, C, Winkler Wille, MM, Scholten, ET, Naqibullah, M, Lam, S, Prokop, M, Schaefer-Prokop, C & van Ginneken, B 2017, 'Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines', Eur Radiol, vol. 27, no. 10, Oct, pp. 4019-4029.

Table 3 Nodule management protocol using Lung-RADS 1.1 calculator for subsequent LDCT scans

Categorisation #	LungRADS 1.1 category descriptor (LungRADS score)	Nodule Type and Size (measure)	Interval LDCT scan or referral	Rescreen
		Volumetry		
No Significant Findings	Negative (1)	No lung nodules	N/A	24 months
Low Malignancy Risk	Benign appearance or behaviour (2)	**Solid nodule(s): < 34 mm³** Non solid nodule(s): < 14137mm³ or ≥14137mm³ and unchanged or slowly growing LungRADS 1.1 Category 3 or 4 unchanged for ≥ 3 months	12 months^	
	Probably benign (3)	**Solid nodule(s): 34mm³ to <113mm³** Part solid nodule(s): total vol ≥ 113mm³ with solid component < 113mm³ OR new < 113 mm³ Non solid nodule(s) (GGN) ≥14137 mm³	6 months	
Moderate Malignancy Risk	Suspicious (4A)	**Solid nodule(s): growing < 268mm³* OR new 113 to < 268mm³** Part solid nodule(s): total vol ≥ 113mm³ with solid component ≥ 113mm³ to < 268mm³ OR with a new or growing < 34mm³ solid component Endobronchial nodule	3 months and review by specialist linked with a MDT	If appropriate, continue in screening program
High Malignancy Risk	Very Suspicious (4B)	**Solid nodule(s): new or growing ≥268 mm³** Part solid nodule(s) with a new or growing ≥ 34mm³ solid component	Rapid Access to specialist linked with a MDT	
Suspected Lung Cancer	Highly suspicious (4X)	LungRADS 1.1 Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy**		

Refers to assessment of the nodule. When there is more than one nodule, reference is made to the dominant nodule (highest malignancy risk).
^ Participants with a Category 2 nodule will have a repeat LDCT annually for up for a specified period, until considered stable.
* Growth: an increase in size of > 2 mm³ ; those that show interval growth (>25% growth in volume) and/or rapid growth (volume doubling time (VDT) <400 days) will be referred for immediate clinical investigation, those that do not show interval growth (<25% growth in volume) and/or VDT>600 days receive an interval LDCT at 12 months. For nodules with VDT 400–600 days (intermediate cancer risk), a repeat LDCT scan in 3 months should be considered as an initial work-up option.
**Category 4X: nodules with additional imaging findings that increase the suspicion of lung cancer, such as growth or new solid component, spiculation, cavitation, GGN that doubles in size in 1 year and enlarged lymph nodes, should be considered for referral.

Based on clinical advice and input, participants with no significant findings would be invited for LDCT scan in 24 months and have an assessment of performance status but not a repeat use of the assessment using the PLCOm2012 risk prediction tool. Participants who are determined to have a high malignancy risk or a suspected lung cancer risk result would be referred by a rapid access process to a specialist linked to a multidisciplinary team (MDT) for further investigation and treatment where appropriate. Participants in the moderate malignancy risk category would receive a three-month follow-up LDCT scan, those in the low malignancy risk category would receive a 12-month follow-up LDCT scan and those with no significant findings would continue with biennial LDCT scans. Incidental findings would be managed outside the Program according to relevant clinical guidelines.

Lung Cancer Screening Register

The establishment of a register is a core component of the proposed Program, being essential to ensuring that national quality assurance standards would be maintained. It would have a central role in the effective functioning of the Program, and include the following core capabilities:

- data collection and storage
- correspondence and management of participants: issuing correspondence to participants, such as invitations and reminders at different parts of the screening and assessment pathway
- data sharing and analytics: feeding data and information to support governance, reporting, research, and evaluation.

8. Comparator

The comparator for the proposed Program is usual care without formal screening, as there is currently no routine lung cancer screening in Australia. Instead, people affected by lung cancer may be diagnosed as a result of exhibiting symptoms or because of other incidental findings.

The commentary noted that for the incremental impact of screening to be equivalent across studies with the same intervention, there must also be similar health care systems and access to care, as this has an impact on the effectiveness of the comparator arm. This means that the magnitude of the benefit of earlier detection through screening will vary by the host health system. Therefore, the applicability of results from health systems similar and dissimilar to Australia should be considered.

9. Summary of public consultation input

Cancer Australia has undertaken comprehensive and extensive stakeholder consultation activities, both before and after the publication of its *Report on the lung cancer screening enquiry*[13]. This has included:

- public consultation via an online consultation hub. Almost 300 responses were received from all States and Territories and a mix of demographics were represented
- targeted consultation with Aboriginal and Torres Strait Islander community and health professionals. This included consultation with 100 Aboriginal and Torres Strait Islander people and a range of health professionals
- in-depth consultations with Cancer Australia's key Advisory Groups
- consultation with expert clinicians and health professionals
- consultation with international experts.

There is strong support from the majority of stakeholders consulted for the introduction of a lung cancer screening program in Australia, primarily due to the acknowledged benefits of earlier detection given the potential for earlier treatment to improve lung cancer outcomes. Some stakeholders go further, reflecting a sense of urgency around the need for such a program. The consultation with Aboriginal and Torres Strait Islander community members affirmed strong concern around the impacts of lung cancer and also referenced the higher incidence of lung cancer and poorer lung cancer outcomes compared to non-Indigenous communities.

In addition, the majority of formal organisational responses referenced international evidence supporting lung screening. Consistent with community perceptions, the overall sentiment from health professionals was that lung cancer screening would be very worthwhile and would be strongly supported.

Reservations principally concerned perceived lack of evidence of cost-effectiveness (from previous published studies), risk of overdiagnosis/over-treatment, and risk of diverting attention from primary prevention. The need to reduce stigma and to implement local initiatives among culturally and linguistically diverse (CALD) communities was also raised.

[13] Cancer Australia, 2020. Report on the Lung Cancer Screening Enquiry, Cancer Australia, Surry Hills, NSW, available at https://www.canceraustralia.gov.au/sites/default/files/publications/report-lung-cancer-screening-enquiry/pdf/report_on_the_lung_cancer_screening_enquiry_0.pdf

Cancer Australia and the Department are together scheduling further consultation on the proposed Program with states and territories. This consultation will focus on health system implications flowing from the proposed establishment of a Commonwealth-managed Program.

10. Characteristics of the evidence base

Cancer Australia commissioned a review presented in a report called the *Evidence review and synthesis for the prospects of a targeted national lung cancer screening program in Australia*. The review focused on a set of eight research questions. A comprehensive, systematic search was undertaken to identify key clinical trials, original studies, program evaluations and economic evaluations. More details on the search and selection methodology are provided in the report, which presents a synthesis of evidence on the clinical effectiveness of lung cancer screening using LDCT, including meta-analyses of randomised controlled trials (RCTs), recently published findings from RCTs, and relevant evidence reported from LDCT-based screening programs in other countries. Human studies published in English between 1 January 2010 and the date of search execution (21 January 2020) were included in the review. Publications prior to 1 January 2010 were only included where a protocol or methodological manuscript detailed a targeted LDCT trial or a program currently in progress. Lung cancer screening trials that exclusively reported on chest X-ray (CXR) and sputum cytology alone were excluded, given that LDCT is the accepted best practice screening test.

The commentary noted that the suitability of the research methods is unclear. In particular, whether "the critical interpretive synthesis (CIS) approach, drawing on realist synthesis methods" adopted by the evidence review are adequate approaches to provide a robust quantitative estimate of the clinical effectiveness of LDCT screening, or identify the limitations of the evidence, remains unclear. The commentary noted that the evidence review does not cite guidelines or methodological literature to explain the CIS or realist synthesis approaches.

Summary of evidence and results – selection of LDCT as the basis for lung cancer screening

Nine main trials (Table 4) inform the clinical evidence base for the safety and comparative effectiveness of LDCT screening compared to no screening. Several recent meta-analyses of the findings of these trials highlight the strong evidence base to support LDCT lung cancer screening. Table 5 summarises the characteristics of these RCTs and assesses the extent to which they are in alignment with the design of the proposed Program.

The commentary noted that not all trials were compared to 'no screening'. The largest trial (NLST) had CXR as the comparator. It was noted that two additional RCTs, as identified in the evidence review were DEPISCAN[14], based in France, and LSS in the US[15].

Table 1 of **Attachment 2** provides more details on the characteristics of these RCTs of LDCT-based lung cancer screening programs. **Attachment 3** provides a summary of the meta-analyses.

[14] Blanchon, T, Brechot, JM, Grenier, PA, Ferretti, GR, Lemarie, E, Milleron, B, Chague, D, Laurent, F, Martinet, Y, Beigelman-Aubry, C, Blanchon, F, Revel, MP, Friard, S, Remy-Jardin, M, Vasile, M, Santelmo, N, Lecalier, A, Lefebure, P, Moro-Sibilot, D, Breton, JL, Carette, MF, Brambilla, C, Fournel, F, Kieffer, A, Frija, G, Flahault, A & Depiscan, G 2007, 'Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR)', Lung cancer, vol. 58, no. 1, Oct, pp. 50-58.

[15] Doroudi, M, Pinsky, PF & Marcus, PM 2018, 'Lung Cancer Mortality in the Lung Screening Study Feasibility Trial', JNCI Cancer Spectr, vol. 2, no. 3, Jul, p. pky042

Table 4 Summary list of targeted LDCT screening RCTs included as the clinical evidence base

Trial ID	Trial full name (or brief description where a formal name could not be identified)
NLST 2002	National Lung Cancer Screening Trial (United States of America)
NELSON 2003	NEderlands-Leuvens Longkanker Screenings ONderzoek (the Netherlands & Belgium)
DLCST 2004	Danish Lung Cancer Screening Trial (Denmark)
DANTE 2001	Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays Trial (Italy)
ITALUNG 2004	Italian Lung Cancer Screening Trial (Italy)
MILD 2005	Multi-centric Italian Lung Detection Trial (Italy)
LUSI 2007	Lung Cancer Screening Intervention Trial (Germany)
UKLS 2011	UK Lung Cancer Screening (England)
AME 2013	Community-based lung cancer screening with LDCT in China (English name not provided)

Table 5 Characteristics of targeted LDCT screening RCTs assessing alignment with the proposed Program

Trial ID	Characteristics in alignment	Characteristics not in alignment
AME 2013		Age range (45-70) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
DANTE 2001		Age range (60-74) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
DLCST 2004		Age range (50-70) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
ITALUNG 2004		Age range (55-69) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
LUSI 2007		Age range (50-69) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
MILD 2005		Age range (49-75) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
NELSON 2003		Age range (50-75) Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
NLST 2002	Age range (55-74)	Eligibility based on smoker history (pack-years) and smoking cessation (years since quit) rather than risk prediction model
UKLS 2011		Age range (50-75) Eligibility based on another risk prediction model (LLPv2 applied at 5% risk of lung cancer risk over 5 years)

LDCT is the recognised screening tool for early diagnosis of lung cancer. It has low radiation dosage compared to conventional CT scans and is more sensitive than chest X-ray (CXR) in the diagnosis of lung cancer. LDCT is the screening intervention used across almost all the lung cancer screening trials (with the comparator being no screening or CXR). CXR was the comparator intervention in the National Lung Cancer Screening Trial (NLST)[16] and in clinical trials from the 2000s that pre-date the NLST.

One of the earliest trials, the PLCO (Prostate, Lung, Colorectal and Ovarian) cancer screening trial (screening completed in 2006), used CXR (versus no screening) as the screening intervention, hence is not included in the RCTs assessing effectiveness of LDCT lung cancer screening. However, data from the PLCO combined with data from the NLST were used as the basis for the economic evaluation using an approach summarised in Section 11.

Although several risk prediction/assessment models have subsequently been developed based on the various trials, Table 5 highlights that all the RCTs used age- and smoking-related eligibility criteria. By contrast, the proposed Program combines age-related eligibility criteria with the PLCOm2012 risk prediction model. For example, the two important international clinical trials, the NLST in the United States of America (USA)[16] and the NELSON trial[2], used eligibility criteria for LDCT screening which were predominantly related to age, smoking history, and years since smoking cessation. The key population selection criteria for the NLST screening eligible cohort were an age range of 55 to 74 years with a smoking history of ≥30 pack-years (i.e., 30 pack-years is equal to smoking 1 pack per day for 30 years), and ≤15 years since smoking cessation. For the NELSON trial, the eligibility criteria were age 50-75 years, 42 pack-years, and ≤10 years since smoking cessation. Using a risk prediction model to select individuals at high-risk of lung cancer improves screening effectiveness and efficiency compared to using age and smoking status/history eligibility criteria (e.g., NLST) alone.

The commentary noted that the PLCOm2012 risk prediction model, however, does take into account criteria related to age, smoking history, and years since smoking cessation. So, in that respect, there is alignment with the trials. However, PLCOm2012 also takes into account a range of other risk factors.

11. Comparative safety

Table 2 of **Attachment 2** provides detailed clinical safety outcomes.

The potential harms of LDCT screening are clearly documented to include radiation exposure, false positives, unnecessary procedures and overdiagnosis, as well as potential psychological harms. More sophisticated means of detecting and classifying nodules are resulting in reductions in false positives, unnecessary procedures for benign conditions and overdiagnosis, for example as observed in the NELSON trial. LDCT screening may be associated with short-term adverse psychological harms, particularly after false positive or indeterminate results, however, RCT and meta-analyses indicate no substantial long-term psychological impacts of participating in an LDCT screening program. Initial evaluations from programs in other countries have reported similar outcomes to the randomised trials of improved early-stage detection and reductions in harms. Thus, when considering a balance of benefits and harms, it appears that the benefits of LDCT screening now outweigh the harms.

[16] Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. New England Journal of Medicine. 2011;365(5):395-409.

The commentary noted that as the rate of overdiagnosis may be higher in the proposed Program (see the section 'Overdiagnosis' below), short-term anxiety may become more prevalent in the Program.

The recently published meta-analysis by Hoffman et al (2020)[6] concluded that 'the estimated risks for false positive results, screening complications, overdiagnosis, and incidental findings, were low.'

Key findings of the evidence review of clinical safety are as follows.

- Although pooled analyses were not reported, Snowsill et al. reported that false positive rates among five trials of targeted LDCT screening ranged from 1.2% to 23%[17]. In the NLST, 23.3% (95% CI: 22.79% to 23.81%) participants received at least one false positive result. In the NELSON trial, the false positive rate was 1.2% across all screening rounds; the trial used volumetric assessment of nodules instead of diameter nodule measurement, which significantly contributed to the reduction in false positives. However, there is an acknowledged difference in false positive rate calculations, due to variation in 'positive test-result' definitions and denominators used (number of total screened versus number of screened positive only) across trials and thus comparisons of these two sets of results should be interpreted with caution.

  The commentary noted that due to the differences in the interpretation of screening results and the lack of detail describing how a lung cancer diagnosis is made, screening metrics such as positive predictive value or false positives may not be similar across the studies and may not be applicable to the proposed Program.

- The proportion of LDCT false negatives results range from 0.1%–1.3% across the results of the NELSON, DANTE, and MILD trials[17]. As such, these are not considered to be a significant harm of targeted LDCT screening, although Snowsill et al. noted that these results should be interpreted with caution due to the low-quality ratings for DANTE and MILD trials. In the Manchester Lung Health Check, a false negative rate of 0.4% across 1337 LDCT scans, and a negative predictive value of 99.6%, sensitivity 89.4% and specificity 97.1%) were reported[18].

  The commentary noted that in the absence of a positive result from screening, a person would most likely be diagnosed clinically at a later point in time – similar to the situation when there is no screening. Conceptually, there may be some danger associated with a false negative test if it provides reassurance to an individual, however this does not appear to be prominent in the literature on screening.

- The current best estimate of overdiagnosis is 8.9% based on an extended (11-year) follow-up in the NELSON trial. The NELSON trial reported an initial rate of 19.7% (95% CI: −5.2% to 41.6%) over 10-year follow up (4.5 years after final screening round) that reduced to 8.9% (95% CI: −18.2% to 32.4%) over the extended 11-year follow-up (5.5 years after final screening round). In cancer screening, the lead time is the average time the diagnosis of a cancer is brought forward through screening. This indicates that, to determine overdiagnosis rates with confidence, these trials ideally need 12 or more years of follow-up[3]. Rates of overdiagnosis would also be positively influenced, i.e.,

[17] Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England). 2018;22(69):1-276.

[18] Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, et al. Second round results from the Manchester a Lung Health Check' community-based targeted lung cancer screening pilot. Thorax. 2019;74(7):700-4.

overdiagnosis reduced, by the introduction of improved selection criteria (that is, risk prediction models) and nodule management protocols.

The commentary noted that in the NLST trial the vast majority of overdiagnoses were reported to be bronchioloalveolar carcinoma (BAC). The overdiagnosis rate was 79% for BAC, the condition has a long lead time (only 25% of screen detected BAC becomes clinically apparent after 10 years). A proportion of the screening population would die of other causes before experiencing symptoms from BAC. It should be considered how people diagnosed with BAC during the screening process should be managed, to minimise the consequences of unnecessary invasive diagnostic procedures and treatments.

The commentary considered that overdiagnosis is a key concern for the proposed Program for several reasons. Compared with the NLST study, Australia does not currently use CXR routinely for lung cancer screening, therefore the proportional increase in BAC diagnoses will be greater. Additionally, LDCT scanners and computer displays are likely to have improved in resolution and image quality compared with those scanners used in NLST from 2001. Finally, the impact of nodule detection software, on the detection of BAC is unknown as it was not used in NLST.

- While morbidities and mortality following diagnostic procedures are important harms to consider, these are likely to be reduced as improvements are made in selecting those people with screen-detected nodules who require invasive procedures. These results should be viewed with caution given the lack of consensus in reporting across studies. The commentary noted that LDCT would identify cases for which invasive follow-up testing (e.g., lung biopsy) would be required and the mortality associated with this follow-up testing is not negligible. However, in its pre-ESC response, the applicant argued that recent trials[19],[20],[21] have shown low mortality rates across pooled analyses. There are also likely to be fewer deaths as improvements are made in selecting those people who require invasive procedures. For example, using volumetric assessment of lung nodules in lung cancer screening has been shown in international trials to increase the accuracy and precision of lung cancer screening, reduce the rate of false positives and therefore limit unnecessary investigations for patients.[8]
- While there is minimal evidence about the long-term impacts of radiation exposure from LDCT screening, radiation exposure and cancer risk from LDCT screening for lung cancer can be considered acceptable in light of the established lung cancer mortality reduction associated with screening. The key study that has sought to estimate the cumulative radiation exposure and lifetime attributable risk of cancer incidence associated with annual LDCT screening is a 10-year, non-randomised, observational trial, known as the COSMOS study. The median cumulative radiation exposure from low dose computed tomography screening over 10 years was 9.3 mSv for men and 13.0 mSv for women. The lifetime attributable risk of major cancers from LDCT screening ranged from 2.6 to 8.1

[19] Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: A systematic review, meta-analysis, and trial sequential analysis. BMC Pulmonary Medicine. 2019;19(1)

[20] Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. 2018;153(4):954-85.

[21] Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, et al. Screening for lung cancer: A systematic review and meta-analysis. Preventive Medicine. 2016;89:301-14.

major cancers per 10,000 participants, according to participant age and sex; one radiation-induced cancer would be expected in every 108 lung cancers detected after 10 years of annual computed tomography screening[22]. The commentary considered that the impact of cumulative radiation exposure of biennial screening on the incidence of lung cancer may have been underestimated. In its pre-ESC response, the applicant argued that radiation exposure and cancer risk from LDCT screening for lung cancer can be considered acceptable in light of the substantial mortality reduction associated with screening. Moreover, continuing advances in LDCT technology will also likely further reduce the radiation exposure risk for patients related to each LDCT scan.[20]

12. Comparative effectiveness

Table 3 of Attachment 2 provides detailed clinical effectiveness outcomes.

The results from two landmark randomised controlled trials – the NLST and the NELSON trial – have demonstrated that targeted LDCT screening delivers substantial reductions in lung cancer mortality. Nearly 70,000 individuals have participated in these sufficiently statistically powered LDCT screening trials, which demonstrate that lung cancers can be detected at an early stage when curative treatments may be offered to people diagnosed with the disease. If implemented, it would enable unprecedented changes in clinical management and help address the poor outcomes (incidence, mortality, survival, psychosocial and quality of life) for lung cancer that have been observed over many decades. These potential improvements in outcomes are central to the prospects for a national targeted LDCT-based screening program.

Key findings of the evidence review of clinical effectiveness are as follows.

- By including longer follow-up results from the NELSON trial and the UKLS trial, the meta-analyses published by Field et al (2021)[23] after the review commissioned by Cancer Australia represents the most recent evidence. This meta-analysis concludes that 'the UKLS trial of single LDCT (and using a risk assessment model to determine the eligible population) indicates a reduction of lung cancer death of similar magnitude to the NELSON and NLST trials and was included in a meta-analysis which provides unequivocal support for lung cancer screening in identified risk groups.'
- Targeted LDCT screening trials demonstrate a reduction of 20-24% in lung cancer specific mortality in the screening group compared with the control group. The results are demonstrated by two statistically powered RCTs (the NLST and the NELSON trial) and in a meta-analysis of pooled trials. In 2011, the NLST demonstrated that LDCT screening reduced lung cancer specific mortality by 20.0% (95% CI: 6.8% to 26.7%; n = 53,454) compared with CXR[24]. In 2020, the NELSON trial showed a lung cancer specific mortality reduction of 24% in men (relative risk = 0.76; 95% CI: 0.60 to 0.91; n = 15,822) and a 39% mortality reduction in women at 10 years (relative risk = 0.61; 95% CI: 0.35 to 1.04) compared with the no screening control group[12]. Field et al (2021) report a 16%

[22] Rampinelli C, De Marco P, Origgi D, Maisonneuve P, Casiraghi M, Veronesi G, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. 2017;356:j347.

[23] Field et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. The Lancet Regional Health – Europe. 2021 published 11 September 2021.

[24] Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243-53.

reduction (relative risk = 0.84; 95% CI: 0.76 to 0.92) in lung cancer mortality with LDCT screening[23].

The commentary noted that few subgroup analyses were available, and there is insufficient evidence to support a substantial variation in the impact of screening by age or sex.

The commentary noted that limitations of the analyses include details relating to case ascertainment (whether death was caused by lung cancer), and whether using evidence with CXR as a comparator was reasonable in the context of the submission. The use of an active comparator meant that the estimated incremental effect of LDCT on mortality gains was likely to be conservative.

- No single trial has been designed with the intention of demonstrating a reduction in all-cause mortality (Field et al 2021)[23], and Huang et al (2019)[19] has previously indicated that targeted LDCT screening trials are not sufficiently powered to detect an all-cause mortality difference. The NLST is the only screening trial that has demonstrated a statistically significant reduction in all-cause mortality of 6.7% (95% CI: 1.2% to 13.6%) detected after a median of 6.5 years of follow-up[24]. While the extended analysis (median of 12.3 years of follow-up data) demonstrated a non-statistically significant all-cause mortality reduction, with a relative risk of 0.97 (95% CI: 0.94 to 1.01)[25], the authors noted that this should not negate the original significant finding (of 6.7%) as the change in mortality benefit over a longer follow-up period would be affected by the length of the original intervention and by the participants (who are/have been heavy smokers) dying from other causes apart from lung cancer[25].

  The commentary considered that this interpretation was reasonable.

  The most recently published meta-analysis by Field et al (2021)[23] included data from 94,834 individuals across nine RCTs and reported a small reduction in all-cause mortality (relative risk = 0.97; 95% CI: 0.94 to 1.00).

  The commentary noted that the evidence from the two largest studies of LDCT for lung cancer screening is not consistent regarding all-cause mortality. In its pre-ESC response, the applicant reiterated that the NELSON trial was not powered to show a favourable difference in all-cause mortality and in general, screening trials have limited power to detect a difference in all-cause mortality, as only a small proportion of individuals in these trials will die from the disease for which is being screened. Modelling analyses indicate that a lung cancer screening trial would require 80,000 individuals to show a significant reduction in all-cause mortality (due to a reduction in lung cancer mortality alone) of 2.5% between 11-13 years of follow-up.[26] This reduction in all-cause mortality would only be detectable within a limited period, as individuals' whose lung cancer death is prevented live longer (gaining additional life-years) but will still eventually die of other causes. Consequently, the applicant observed that while the NELSON trial did not show a significant reduction in all-cause mortality, it is likely that a large-scale lung cancer screening program would yield a considerable number of additional life-years (8.5 life-years per prevented lung cancer death in the favoured scenario). The applicant also

[25] National Lung Screening Trial Research Team. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. Journal of Thoracic Oncology. 2019.

[26] Heijnsdijk EAM, Csanádi M, Gini A, Ten Haaf K, Bendes R, Anttila A, Senore C, de Koning HJ. All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: A review and modeling study. Cancer Med. 2019 Oct;8(13):6127-6138. doi: 10.1002/cam4.2476. Epub 2019 Aug 18. PMID: 31422585; PMCID: PMC6792501.

noted that the NLST is the only lung cancer screening trial that has demonstrated an all-cause mortality benefit of 6.7% over a median of 6.5-year follow-up data.

- LDCT screening significantly increased detection of lung cancer when compared with controls across all trials. The systematic review by Snowsill et al. provided the most comprehensive evidence for lung cancer detection findings. Snowsill reported the range of cumulative lung cancer detection rates among trial participants of six trials (DANTE, DLCST, NLST, NELSON, ITALUNG, UKLS) ranged from 1.7% to 5.2% across all LDCT screening rounds[17]. In a pooled analysis of the DANTE, DLCST and NLST trials with ≥5-years' follow-up, LDCT screening was associated with a statistically significant increase in lung cancer detection when compared with controls (no screen or CXR)[17]. Individual trials also showed a statistically significant increase in lung cancer detection in the LDCT cohorts, although heterogeneity was noted. Most lung cancer detection rates in recent trial results are higher than those observed in earlier trials from the 2000s. Both the NELSON trial and the NLST individually reported statistically significant increases in lung cancer detection in LDCT participants compared with control cohorts. The NELSON trial found 341 of 6583 participants with LDCT-detected lung cancer compared with 304 lung cancers detected in 6612 participants in the control cohort (relative risk = 1.14; 95% CI: 0.97 to 1.33), while the NLST found 1701 of 26,722 participants with LDCT detected lung cancer compared to 1681 of 26,730 CXR-detected lung cancer in the control cohort (relative risk = 1.01; 95% CI: 0.95 to 1.09).

  The commentary noted that the interpretation of cancer detection in screening studies is complex and must be made in the context of other data. An increase in the incidence of lung cancer in the screening arm may reflect earlier diagnosis of clinically relevant lung cancer (stage shift) or may reflect the detection of cancer that would not result in harm (overdiagnosis). In terms of cancer incidence, a beneficial result from a trial of screening (where the screening period is limited) would reflect an early increase in lung cancer incidence followed by a gradual convergence between the arms. The two largest trials (NLST and NELSON) report similar patterns of lung cancer incidence.

- LDCT screening was associated with significantly larger proportions of lung cancers being diagnosed at earlier stages (stage I) compared with controls, as shown in a pooled analysis of seven studies. Two LDCT trials (NELSON and NLST) have recently published updated stage at diagnosis outcomes following the review by Huang et al. Both the NELSON trial and NLST results show a substantial shift to early-stage cancers. Most NELSON LDCT-detected cancers were stage IA or IB (58.9%), with a significantly smaller proportion diagnosed as stage IV (9.4%)[12]. The NLST showed a statistically significant reduction in the diagnosis of late-stage lung cancers (relative risk = 0.79; 95% CI: 0.70 to 0.89)[25]. The dilution adjusted analysis (data through study year-six) of the NLST further confirmed the significant reduction of late-stage cancers (relative risk = 0.72; 95% CI: 0.61 to 0.84).

To assist MSAC consideration, ESC requested that patient-relevant health outcome gains from the two main trials and the economic evaluation be summarised in absolute terms (see Tables 6 and 7).

Table 6 Patient-relevant health outcome gains from NLST and NELSON in absolute terms

	NLST (2011)	NELSON (2020)
Duration	7 years	10 years
Lung cancer detection		
Lung cancer detection rate in LDCT screening group	1060/26455 (0.0401)	341/6309 (0.0540)
Lung cancer detection rate in control group	941/26232 (0.0359)	304/6612 (0.046)
Absolute risk difference in lung cancers detected	0.0042	0.0081
Number of individuals needed to screen per extra lung cancer detected	238	124
Lung cancer mortality		
Lung cancer mortality rate in LDCT screening group	346/26455 [a] (0.0131)	156/6309 (0.0247)
Lung cancer mortality rate in control group	425/26232 [a] (0.0162)	206/6612 (0.0312)
Absolute risk difference in lung cancer deaths averted	0.0031	0.0064
Number of individuals needed to screen per extra lung cancer death averted	320	156
All-cause mortality		
All-cause mortality rate in LDCT screening group	1877/26722 [b] (0.0702)	n/a [c]
All-cause mortality rate in control group	2000/26732 [b] (0.0748)	n/a
Absolute risk difference in all-cause deaths averted	0.0046	n/a
Number of individuals needed to screen per extra death averted	219	n/a

[a] Both the numerator and denominator have been restricted to those who had at least one screening test, so the denominator is less than the total number enrolled in this group as this was the approach described by the study authors in estimating their NNS.
[b] The study authors did not state that the numerator was restricted to those who had at least one screening test and did not provide this adjusted figure, therefore, to ensure the numerator and denominator are aligned, the denominator represents all enrolled in this group.
[c] Though all-cause mortality results were reported for this trial they were not statistically significant.

Table 7 Patient-relevant health outcome gains in absolute terms from the economic evaluation truncated to 10-years of follow-up (calendar years 2021-2031)

		General Australian population (Biennial screening ages 55-74, 1.50% risk)	Indigenous Australian population (Biennial screening ages 50-74, 1.50% risk)
A	Number of individuals ever screened (within the 10-year period) [a]	12,320	26,078
B	Number of LDCT screens	37,285	103,561
C	Number of lung cancer deaths averted (within the 10-year period)	107	277
D	Number of individuals (ever screened) per extra lung cancer death averted (within the 10-year period) = A / C	115	94
E	Number of lung cancer deaths averted (life-time follow-up from those screened within the 10-year period)	171	422
F	Number of individuals (ever screened) per extra lung cancer death averted (life-time follow-up from those screened within the 10-year period) = A / E	72	62
G	Number of overdiagnosed cases (life-time follow-up from those screened within the 10-year period)	74	352
H	Number of individuals (ever screened) per extra overdiagnosis (within the 10-year period) = A / G	166	74
I	Proportion of screen-detected cases that are overdiagnosed	15.6%	30.9%
J	Number of screen-detected cases = G / I	474	1139
K	Number of individuals (ever screened) per screen-detected case [b] = A / J	26	23

[a] The number of individuals ever screened is calculated from 100,000 individuals in the population eligible for the risk prediction tool.
[b] This is not an incremental result over cases detected clinically.

Summary of evidence and results – selection of high-risk individuals for targeted LDCT screening

Attachment 4 summarises the evidence for the selection of the proposed risk prediction tool.

To achieve a favourable balance of benefits, harms, and costs, only individuals at high risk of lung cancer should participate in targeted LDCT screening. As such, accurate participant selection is key to both the effectiveness and efficiency of a targeted LDCT screening program[17,27]. Two main strategies have been applied to the identification of eligible individuals at high-risk of lung cancer in screening trials and program implementation: 1) simple eligibility criteria based on age, smoking history (pack-years) and smoking status (current or former, with specified quit-time for former smokers), and 2) risk-stratification using a lung cancer risk prediction model[28].

Risk prediction models incorporate algorithms to calculate an individual's risk of lung cancer incidence or mortality, based on the combined effects of socio-demographic factors (such as age,

[27] Katki HA, Kovalchik SA, Petito LC, Cheung LC, Jacobs E, Jemal A, et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Annals of Internal Medicine. 2018;169(1):10-9.

[28] Fu M, Travier N, Martin-Sanchez JC, Martinez-Sanchez JM, Vidal C, Garcia M. Identifying high-risk individuals for lung cancer screening: Going beyond NLST criteria. PLoS One. 2018;13(4):e0195441.

gender, race, and education), and other lung cancer risk factors such as smoking duration and intensity, personal history of malignancy or respiratory disease, and family history of lung cancer[29].

Applying a risk-prediction model to select individuals at high-risk also requires specifying a threshold, which is the cut-off point above which people would be offered screening. A model's threshold aims to achieve an optimal balance of benefits and harms.

All LDCT trials used, at a minimum, some core eligibility criteria including age and smoking history, i.e., pack-years and smoking status, with specified quit time for former smokers. Eligibility criteria, even for the same risk factor, were not consistent across trials. For example, the NLST eligibility criteria selected participants aged 55-74 years, who were current or former smokers (within 15 years of quitting), with a cigarette smoking history of at least 30 pack-years[24]. The NELSON trial applied eligibility criteria that selected individuals aged 50-75 years, who were current smokers or former smokers within 10 years of cessation and smoked more than 15 cigarettes daily for over 25 years, or more than 10 cigarettes daily for over 30 years[30].

The commentary noted that Australian rates of smoking have been steadily declining for 20 years or more, from 25% in 1991 to 12% in 2019 (Australian Institute of Health and Welfare, 2021).[31] Given this, it may be that in Australia 55–74-year-old former smokers may well have quit over 15 to 20 years ago (and not within the last 15 years as in the NLST study). This might be an applicability issue. What the impact is of these differences in the screening population is unknown.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) risk prediction model, developed during the US PLCO trial[32] included two models: one for the general population (i.e., never-smokers and ever-smokers), and one for ever-smokers only. Both models estimate risk of lung cancer over a nine-year timeframe. A subsequent version, the PLCOm2012 model[33], has become the most highly recommended risk-prediction model[34,35]. The PLCOm2012 was developed for ever-smokers only and estimates an individual's risk of developing lung cancer over 6 years; a timeframe set to make comparisons consistent with follow-up in the NLST. Risk factors align with those of the PLCO model, with two additional predictors (personal history of any cancer and race/ethnicity), and the removal of one predictor; recent CXR. Furthermore, pack-years smoked was separated into smoking intensity and smoking duration, to incorporate each component more precisely.

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[29] Gray EP, Teare MD, Stevens J, Archer R. Risk Prediction Models for Lung Cancer: A Systematic Review. Clin Lung Cancer. 2016;17(2):95-106.

[30] van der Aalst CM, van den Bergh KAM, Willemsen MC, de Koning HJ, van Klaveren RJ. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch–Belgian randomised controlled lung cancer screening trial. Thorax. 2010;65(7):600.

[31] Australian Institute of Health and Welfare, https://www.aihw.gov.au/reports/australias-health/tobacco-smoking

[32] Tammemagi MC, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst. 2011;103(13):1058-68.

[33] Tammemagi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. New England Journal of Medicine. 2013;368(8):728-36.

[34] Wood DE, Kazerooni EA, Baum SL, Eapen GA, Ettinger DS, Hou L, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(4):412-41.

[35] NHS England. Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography 2019 [Available from: https://www.england.nhs.uk/publication/targeted-screening-for-lung-cancer/].

The PLCOm2012 model has been demonstrated to provide superior performance compared to the NLST eligibility criteria (age, smoking), with improved sensitivity and positive predictive value, with no loss of specificity.

- The PLCOm2012 model, devised and validated in the largest cohort datasets (n=80,375 and n=37,332, respectively), demonstrated promising discrimination on internal and external validation (data from PLCO control and intervention groups)[33]. Within the same validation dataset, the PLCOm2012 demonstrated superior performance in comparison with the NLST eligibility criteria.

- Overall, the PLCOm2012 model identified 11.9% more lung cancers and missed 41.3% fewer cases. Based on the results of this study, Tammemagi et al suggested that, should the PLCOm2012 model have been used in the selection of participants for the NLST, 12 additional deaths from lung cancer would have been avoided, with no change in harms[33].

- The Bach model and PLCOm2012 have consistently demonstrated superior performance to other risk-prediction models in large comparative studies involving validation in external population datasets[27,36,37]. Model comparison studies have also reinforced the superior performance of risk prediction models for selecting high-risk individuals for LDCT screening, compared to selection using age and smoking eligibility criteria[37,38,39,40].

- Li et al externally validated and compared four models (Bach, Spitz, LLP and PLCOm2012) among 20,700 ever smokers in the EPIC-Germany cohort[36]. The Bach model and the PLCOm2012 model had a marginally higher discriminatory power, with the PLCOm2012 model having the best overall calibration. When model performances were compared against the eligibility criteria used in screening trials (NELSON/LUSI, DLCST, ITALUNG, and NLST), the PLCOm2012 model performed systematically better than, or at least as well as, the other eligibility criteria. Overall, the PLCOm2012 demonstrated higher sensitivity, specificity and positive predictive value and identified four additional lung cancer cases than the NLST eligibility criteria (46 versus 42, out of 92, respectively).

- In another study involving nine risk-prediction models using data from two cohorts of ever-smokers representative of US population, the Bach, PLCOm2012, Lung Cancer Risk Assessment Tool (LCRAT), and Lung Cancer Death Risk Assessment Tool (LCDRAT) models demonstrated the best predictive performance, with high discrimination (AUC 0.75 to 0.79) and good calibration (E/O 0.92 to 1.12)[27]. However, not one of the four well-calibrated models achieved both the highest sensitivity and the highest specificity in either validation cohort. Several other tested models including the LLPi, Hoggart and Spitz models, overestimated risk by a factor of 2 to 3.

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[36] Li K, Husing A, Sookthai D, Bergmann M, Boeing H, Becker N, et al. Selecting High-Risk Individuals for Lung Cancer Screening: A Prospective Evaluation of Existing Risk Models and Eligibility Criteria in the German EPIC Cohort. Cancer Prev Res (Phila). 2015;8(9):777-85.

[37] Ten Haaf K, Jeon J, Tammemagi MC, Han SS, Kong CY, Plevritis SK, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med. 2017;14(4):e1002277.

[38] Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. JAMA. 2016;315(21):2300-11.

[39] Tammemagi MC, Church TR, Hocking WG, Silvestri GA, Kvale PA, Riley TL, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLoS Medicine / Public Library of Science. 2014;11(12):e1001764.

[40] Tammemagi MC. Selecting lung cancer screenees using risk prediction models-where do we go from here. Transl Lung Cancer Res. 2018;7(3):243-53.

- Ten Haaf et al also conducted a comprehensive retrospective comparison study investigating the performance of nine risk-prediction models[37]. Again, superior performance was demonstrated by the Bach and PLCOm2012 models, as well as the TSCE incidence model (AUCs >0.68 in the NLST validation dataset, and >0.77 in the PLCO validation dataset). All risk-prediction models demonstrated higher sensitivity and slightly higher specificity, compared to the NLST eligibility criteria.

- The PLCOm2012 is currently the only lung cancer risk prediction model to have been validated in the Australian population[41]. Validated in baseline data from 95,882 ever-smokers in the 45 and Up Study (inclusive of 1,035 lung cancer diagnoses), the PLCOm2012 demonstrated both excellent discrimination (AUC 0.80) and calibration (90th percentile absolute difference between observed and predicted probabilities of 0.006 and 0.016, respectively)[41]. A threshold of ≥1.51% risk was confirmed as appropriate for identifying those at high-risk of lung cancer within 6 years, achieving high positive predictive value and sensitivity in comparison with the NLST eligibility criteria, with only minimal loss in specificity at this threshold. The PLCOm2012 model was determined to perform best among participants aged 55-74 years. At these age parameters, the model estimated 29% of ever-smokers as eligible for screening (450,000 to 700,000 eligible individuals)[41].

  The commentary noted that the financial model estimated 19.9% of ever smokers in the eligible age range to be eligible for LDCT screening.

  The commentary noted that the ethnicity profile in the Australian population differed from the population in which the tool was designed. It is unclear how the tool would be applied or performed in an Aboriginal or Torres Strait Islander population to determine lung cancer risk. In its pre-ESC response, the applicant noted that research to validate the PLCOm2012 risk prediction tool in Aboriginal and Torres Strait Islander people is currently underway. If a program were supported by Government, an initial establishment phase would enable further refinement and implementation of the risk prediction tool before participant recruitment.

In summary, risk prediction models consistently perform better than eligibility criteria based on age and smoking status alone. The PLCOm2012 model has been selected as the preferred risk prediction model for use in the proposed Program because it has performed consistently well in validation studies demonstrating excellent discrimination and calibration results, is referenced in international screening guidelines and program protocols, and is currently the only risk prediction model to be tested in an Australian population.

The PLCOm2012 model was determined to perform best among participants aged 55-74 years and has shown positive interim results in the International Lung Screening Trial (ILST) in a Canadian cohort. Successful implementation of risk prediction models within implemented screening programs indicate promise, however further research specific to the Australian implementation context is essential.

Further evaluations of PLCOm2012 model performance are required in populations inclusive of different racially and ethnically diverse groups, including Aboriginal and Torres Strait Islander people and CALD communities. The evidence review noted significant gaps about Indigenous status and other sociodemographic variables as risk factors for inclusion in risk prediction models. Emerging evidence indicates that while the PLCOm2012 model was found to be

[41] Weber M, Yap S, Goldsbury D, Manners D, Tammemagi M, Marshall H, et al. Identifying high risk individuals for targeted lung cancer screening: Independent validation of the PLCOm2012 risk prediction tool. Int J Cancer. 2017;141(2):242-53.

preferable over the United States Preventive Services Taskforce (USPSTF) criteria in identifying African American ever-smokers for lung cancer screening in the US[42], the PLCOm2012 model may underestimate risk in deprived UK populations[43], and further work on calibration of the model may be warranted.

Summary of evidence and results – selection of nodule management protocols

Attachments 5 and 6 summarise the evidence for the selection of the two proposed nodule management protocols.

Nodule management protocols enable accurate assessment and classification of lung nodules to improve LDCT screening sensitivity and specificity. Current nodule management protocols (e.g., the PanCan and Lung-RADS nodule management protocols) apply certain risk criteria (based on nodule size and other nodule characteristics) to define an abnormality as potentially malignant, benign, or indeterminate, which can substantially reduce the number of false positive findings and the subsequent need for additional invasive diagnostic procedures.

There is no international consensus about which protocol performs best across baseline and screening intervals, however the PanCan and Lung-RADS models have performed well in comparative studies.

Recent studies have sought to compare the performance of different protocols by conducting retrospective analyses of trial datasets.

An Australian analysis of the QLCSS (*Queensland Lung Cancer Screening Study)* dataset by Marshall et al. compared Lung-RADS and PanCan protocols at various nodule size thresholds for baseline and incident scans (one- and two-years post-baseline)[44]. This study found that all protocols were highly sensitive at baseline, with the PanCan protocol having the highest sensitivity (94.8%). A Danish study analysed the Danish Lung Cancer Screening Trial (DLCST) dataset and compared the PanCan, Lung-RADS and National Comprehensive Cancer Network (NCCN) guidelines (version 1.2016) for baseline scans. It found that the PanCan protocol outperformed both Lung-RADS and NCCN guidelines[12]. A Canadian study compared the Lung-RADS and the PanCan protocols as part of the Alberta Cancer Study[45]. The study found that both models performed very well, with the PanCan nodule risk classifications being highly sensitive.

The commentary noted that the PanCan model in the Australian study considered that a risk score of ≥10% was positive.[38] The PanCan model proposed for the proposed Program has four different risk categories. It proposes a risk index of ≥6% and <30% for moderate malignancy risk, and ≥30% for high risk. The management protocol for patients considered to be of moderate risk would be 3-monthly follow-up screening LDCT, whereas patients considered at high risk would be offered a direct referral for a diagnostic work-up. With the different management protocol in the

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[42] Pasquinelli MM, Tammemägi MC, Kovitz KL, Durham ML, Deliu Z, Rygalski K, Liu L, Koshy M, Finn P, Feldman LE. Risk Prediction Model Versus United States Preventive Services Task Force Lung Cancer Screening Eligibility Criteria: Reducing Race Disparities. J Thorac Oncol. 2020 Nov;15(11):1738-47.

[43] Lebrett MB, Balata H, Evison M, Colligan D, Duerden R, Elton P, Greaves M, Howells J, Irion K, Karunaratne D, Lyons J, Mellor S, Myerscough A, Newton T, Sharman A, Smith E, Taylor B, Taylor S, Walsham A, Whittaker J, Barber PV, Tonge J, Robbins HA, Booton R, Crosbie PAJ. Analysis of lung cancer risk model (PLCOm2012 and LLPv2) performance in a community-based lung cancer screening programme. Thorax. 2020 Aug;75(8):661-8.

[44] Marshall HM, Zhao H, Bowman RV, Passmore LH, McCaul EM, Yang IA, et al. The effect of different radiological models on diagnostic accuracy and lung cancer screening performance. Thorax. 2017;72(12):1147-50.

[45] Tremblay A, Taghizadeh N, MacGregor JH, Armstrong G, Bristow MS, Guo LLQ, et al. Application of Lung-Screening Reporting and Data System Versus Pan-Canadian Early Detection of Lung Cancer Nodule Risk Calculation in the Alberta Lung Cancer Screening Study. Journal of the American College of Radiology. 2019;16(10):1425-32.

PanCan model of the proposed Program, the sensitivity of the risk classification approach is therefore not expected to be 94.8%, as in the original study. However, as all patients with ≥6% risk will be offered 3-monthly repeat LDCT screening, the overall impact of the changed criteria, in terms of identifying nodules at risk, is expected to be minimal, although likely more costly.

PanCan was selected as the baseline nodule management protocol based on clinical evidence and clinical consultation. The PanCan nodule management protocol has the highest sensitivity for baseline scans however has only been validated for baseline scans[46]. Therefore, a different nodule management guidance is required to be used for subsequent scans. Lung-RADS 1.1 was selected as the nodule management protocol for subsequent scans based on clinical evidence and clinical consultation.

The commentary considered that this was reasonable.

Lung Imaging Reporting and Data System (Lung-RADS®) is a quality assurance tool designed by the American College of Radiology to standardise lung cancer screening CT reporting and management recommendations, reduce confusion in lung cancer screening CT interpretations, and facilitate outcome monitoring. A complete lexicon and atlas are being developed. The lexicon of lung cancer screening CT terms and the reporting format will standardise the language used in reports. The atlas will include a description of a medical audit and outcome monitoring process.

The Lung-RADS Assessment Categories have been most recently updated in 2019 in version 1.1 of Lung-RADS, including the assessment categories and management recommendations.

As the ILST study includes, as one of its dual aims, an evaluation of the PanCan nodule management protocol compared to Lung-RADS nodule management protocol as the most efficient, the results are eagerly anticipated[10].

Conclusions on applicability

Overall, the commentary concluded that it was unlikely that differences between the proposed Australian screening program and the NELSON and NLST studies would alter the direction of the results in terms of lung cancer mortality or stage shift at diagnosis. However, there were concerns relating to the applicability of published evidence to the proposed Australian program, including differences of:

- eligibility criteria
- duration of screening
- method for detecting nodules
- definition of positive screening findings (nodule management protocols)
- downstream treatment options.

The commentary observed that it is unclear whether translations to account for the identified applicability issues are possible. However, actions to mitigate an increase in harms may be incorporated into the design of the Program. Such actions may include:

- Ensuring that screening participants have a life expectancy that is adequate to benefit from early diagnosis of lung cancer
- Protocols for the investigation of suspicious disease that accounts for the potential harm caused in the context of an increase in the detection of benign conditions

[46] McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369(10):910-9.

- Protocols for the treatment of disease detected that is suspected of being indolent or slower growing (e.g., BAC), to mitigate the risk of surgical mortality or morbidity in a participant that is less likely to die of disease.

Additional eligibility criteria proposed by Cancer Australia include consideration of the general health of patients and, if adhered to, would reduce the number of individuals being screened who are unlikely to benefit on the basis of inadequate life expectancy. These criteria may be a useful tool in combination with education of practitioners likely to refer patients for LDCT screening.

The commentary recommended that, given the key uncertainties associated with differences between the trial screening programs and the proposed Australian screening program, ongoing data collection of screening participants to capture diagnoses, interventions and mortality may permit decision makers to re-visit the parameters of the program in the future.

Clinical claim

The clinical claim is that the proposed Program would result in improved net clinical benefit, specifically that the increased clinical benefits would outweigh the increased clinical harms.

13. Economic evaluation

The form of economic evaluation is a cost-utility analysis commissioned by Cancer Australia[7]. To provide further detail beyond the commissioned report, a set of questions of confirmation or clarification and requests for further information were provided to the economic modelling team and responses were provided.

The cost-utility analysis relied on the MISCAN-Lung model, which is a stochastic, microsimulation model programmed in Delphi. The model was modified to reflect economic costs, from the healthcare payer and patient perspectives, and outcomes of targeted lung cancer (small cell and non-small cell lung cancer) screening with LDCT for high-risk individuals in Australia. A summary of the main components of the model is provided in Table 8, with associated commentary.

Table 8 Summary of the economic evaluation

Component	Description	Justification/comments
Perspective	Health care system perspective. Health care costs incurred by the payer and the patient and health care outcomes associated with the patient. *Note: the financial analyses presented in this Section 12 estimate some of the net costs of the proposed Program from the perspective of the Australian Government health budget.*	*Reasonable*
Population demographics	Australian birth cohorts from 1945 to 1969 remaining alive in 2021.	*Reasonable*
Population risk adjustment	Age, gender and birth cohort specific smoking initiation probabilities, representative for the population under consideration, were used to determine whether an individual initiates smoking and the age of smoking initiation.	These were calibrated using NLST, PLCO and U.S. SEER database. Further adjustments were made to enable the model to predict observed lung cancer incidence in Australia.
Comparator	No screening.	*No formal screening is the appropriate comparator.*
Analysis type	Cost-utility analysis, based on an underlying microsimulation screening analysis model.	*Reasonable*

Outcomes	Payer costs, patient costs, lung nodules detected, lung cancers detected, lung cancer deaths prevented, life-years gained and QALYs gained.	*Additional relevant safety outcomes such as radiation exposure risks, and possible post procedure mortality and morbidity (associated with follow-up procedures after a positive LDCT) were not included in the model.* Pre-ESC response from the applicant: diagnostic procedure effects are mainly relevant to 'overdiagnosed' individuals because diagnostic procedures are just delayed for those who would be diagnosed in the absence of screening. Additional evidence was cited on lung biopsy adverse effects, indicating potentially significant effects, although it was noted that it was unclear whether the patient populations in the evidence are representative of patients undergoing lung biopsy following a positive screening result.
Time horizon	From 2021 – 2069. Estimates of costs and outcomes were extended to 2069 to allow the proportion of the eligible population born in 1969 to reach their maximum modelled age of 100 years, though the final LDCT-based screening for this cohort was 2043 to reflect the upper age limit of screening of 75 years.	*The proposed Program is for ongoing screening. The evidence on 2-yearly screening past the first 5 to 6 years is lacking. The overall benefit and risks of continuous 2-yearly screening of an individual for 20-25 years are unknown.*
Computational method	Microsimulation analysis, specifically the MIcrosimulation SCreening ANalysis Lung (MISCAN-Lung) model which simulates life histories for each individual in the considered population from birth until death, in the presence and absence of screening. Through comparing life histories in the presence of screening with the corresponding life histories in the absence of screening, MISCAN-Lung quantifies the effectiveness of a screening scenario and the accompanying costs. MISCAN-Lung is a semi-Markov model, which generates durations for each state. Individuals are simulated one at a time, which allows future state transitions to depend on past transitions giving the model a "memory". MISCAN-Lung simulates sequences of events by drawing from distributions of probabilities/durations, which makes the results of the model subject to random variation.	*Reasonable*
Generation of the base case	The base case represents the following screening strategy: • screening age eligibility 55 to 74 years (age to start screening 55 years, age to stop screening 75 years) • biennial screening interval • minimum 1.5% 6-year risk of lung cancer (reflecting smoking status, smoking intensity and time since quit smoking, using the simplified PLCOm2012 risk prediction tool) • no exclusion based on years since quitting smoking • 100% uptake of screening.	*Assumption of 100% participation rate in the proposed Program is an overestimate. Participation rate in existing cancer screening programs vary between 43% and 51%. Screening uptake among the eligible indigenous population sub-group is poorer than the general population.*
Health states	Beyond the health states of no lung cancer and death, there are six lung cancer health states: Stage IA, IB, II, IIIA, IIIB, and IV, each of these stages can be preclinical, screen-detected, or clinically detected. Lung cancers are assumed to progress sequentially through stages IA to	*Reasonable*

	IV. The date of death for individuals with lung cancer is set to the earliest simulated date of death (either due to lung cancer or other causes).	
Utilities	A utility of 0.87 was assumed for all pre-clinical health states. A utility of 0.78 was assumed for all clinically detected and screen detected Stage I and II health states, and a utility of 0.69 was assumed for all clinically detected and screen detected State III and IV health states. A utility of 0.59 was assumed for all individuals who enter the lung cancer terminal phase.	*The economic model was sensitive to changes in health state utilities.*
Transition probabilities	The economic evaluation report did not provide the point estimates and distributions for the transition probabilities used in the model.	Transition probabilities were based on distributions. *These could not be validated during the evaluation.*
Discount rate	All costs, life-years and QALYs are discounted at 5% per annum.	*Reasonable*
Software	Delphi	*Reasonable*

QALY = quality adjusted life year, PCP = primary care provider, LUNG-RADS = standardised lung cancer screening CT reporting and management, NLST = National Lung Screening Trial, LDCT = low dose computed tomography

The MISCAN model was first developed in 1985 and has since been adapted to evaluate screening programs for breast, cervical, colorectal, prostate and lung cancers worldwide. The model referred to in this section – MISCAN-Lung – is used to simulate life histories for each individual in the considered population from birth until death, in the presence and absence of screening. Through comparing the life histories in the presence of screening with the corresponding life histories in the absence of screening, MISCAN-Lung is used to quantify the effectiveness of a screening scenario and the accompanying costs.

The MISCAN-Lung model was populated using detailed data describing smoking patterns over the lifetimes of Australian birth cohorts from 1945 to 1969, combined with life tables for these birth cohorts. The Australian data on smoking behaviour came from National Campaign Against Drug Abuse surveys, the National Drug Strategy Household surveys and other published literature, primarily studies by the Australian Institute of Health and Welfare (AIHW). Lung cancer mortality data was obtained from the AIHW for years 1968-2016. These inputs were adjusted to enable the model to predict observed lung cancer incidence rates, whilst maintaining input parameter values that aligned with the observed data and defendable assumptions regarding uncertainties relating to the available data sources. Cost and quality of life (utility) input parameters were then added to the model to predict the incremental effects of screening on costs and QALYs gained over the remaining lifetime of the study population (Australian birth cohorts from 1945 to 1969 remaining alive in 2021). Efficacy of screening and treatment was primarily based on evidence from the NLST, whereas program delivery was informed by a range of sources, including Australia-specific evidence and expertise. However, the NLST compared LDCT screening against CXR, so use of this efficacy data necessitated further adjustments which are explained further in Table 9.

The commentary suggested that a more conservative approach for the calibration process of the model would have been to exclude the PLCO trial data and use the CXR arm of the NLST as a proxy for no screening. However, in its pre-ESC response, the applicant argued that, although CXR screening in the screen arm of the PLCO and the control arm of the NLST may not have led to a significant reduction in lung cancer mortality, CXR screening did affect the incidence and stage distributions within these populations. Thus, the inclusion of the PLCO control arm in the model's calibration process is required to provide unbiased information on the incidence and stage distribution of lung cancer in the absence of screening, which is essential to accurately account for lead-time and overdiagnosis. Furthermore, in contrast to the NLST, the PLCO trial did not have

eligibility criteria related to smoking criteria. The PLCO included a population with a broader range of smoking behaviour compared to the NLST, including never-smokers. Therefore, the inclusion of the PLCO trial data in the calibration process is essential to translate the results of the NLST to populations with broader ranges of smoking exposures and screening programs with alternative eligibility criteria (such as the PLCOm2012 model).

Table 9 Application and alignment of randomised controlled trial results for LDCT screening to the economic evaluation

Randomised controlled trial	Rationale for trial selection in the clinical evaluation	Comparison	Results selected for input into the economic evaluation*	Rationale for input selection	Adjustment to input	Results selected for validating the economic model	Rationale for validation parameter selection	Adjustment to validation parameter
National Lung Cancer Screening Trial (NLST)	High participation in trial, generalisable to community-focussed screening programs in the Australian context.	LDCT screening vs chest X-ray	MISCAN-Lung was calibrated to the NLST based on: (a) the number of screen-detected cancers and relative distribution of histologies/stages (b) the number of clinically detected cancers and relative distribution of histologies/stages (c) lung cancer mortality rates of patients with screen-detected lung cancer (d) preclinical durations in the absence of screening (e) malignant transformation rate by gender (f) LDCT sensitivity by preclinical stage and histology, including effectiveness of CT screening (g) overdiagnosis rates (h) false negative rates (i) false positive rates (j) quality of life data	Calibrating the model to NLST enables analysis of efficacy of screening.	Yes	Estimates from the NLST for results (a) – (c) were validated on NLST-eligible individuals in the PLCO. Estimates for (d) were calibrated to the rates of screen-detected and interval cancers observed in the PLCO. Estimates for (e) were validated against PLCO data, ILST T0 category and SEER program data. Estimates for (i) were validated against ILST T0 screening data (risk category) and SEER program data.	(a) – (c): To calibrate eligibility criteria for the economic evaluation. (d): To align with eligibility criteria. (e): To align with the eligibility criteria and Australian context. (i): To calibrate screening risk category to the Australian context.	(d): Preclinical durations (in the absence of screening) were drawn from Weibull distributions.
Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial	Estimates risk of lung cancer over a nine-year timeframe. Provides understanding of the lead-time achieved by screening.	Chest X-ray vs no screening	(a) Lung cancer incidence parameters to derive eligibility (b) gender specific parameters for malignant transformation (c) risk thresholds used to determine eligibility for screening	Appropriate baseline projections of lung cancer incidence into projection years.	Yes	Lung cancer incidence (NLST-eligible individuals in the PLCO) was further calibrated to AIHW lung cancer incidence data.	To calibrate parameters to observed incidence.	No
International Lung Screen Trial (ILST)	Ongoing prospective study providing insights of targeted screening	CT screening vs no screening	T0 screening data (risk category) from Queensland population (applied PAN-CAN model for baseline screening)	Program delivery	No	Adjusted per NLST comments.	Per NLST comments.	No

	implementations using risk-based strategies to identify participants.							

* The NLST and PLCO cancer screening trial together comprised an indirect comparison of the effectiveness of LDCT vs no screening, with chest X-ray as the common reference.

NLST = National Lung Cancer Screening Trial, MISCAN-Lung = MIcrosimulation SCreening ANalysis Lung model, LDCT = low dose computed tomography, PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial, ILST = International Lung Screen Trial, SEER = Surveillance, Epidemiology and End Results.

The base case for the economic evaluation of LDCT-based screening reflects biennial screening of eligible Australians who enter the model in 2021 as being within the proposed eligible age range of 55 to 74 years and exceeding a PLCOm2012 estimated threshold of 1.5% 6-year risk of lung cancer. The last screening intervention of this population cohort occurs in 2043. Costs and health outcomes are estimated over the lifetime of the eligible population through to 2069.

Given the higher incidence and mortality from lung cancer in the Aboriginal and Torres Strait Islander (Indigenous) population in Australia, a separate analysis of the cost-effectiveness of screening options for the Indigenous population was undertaken. The structure of the MISCAN-Lung model remains the same.

The commentary concluded that the modelling approach used in the report is appropriate. However, the economic model does not capture screening-related radiation exposure risks, and possible procedure-related mortality and morbidity (associated with follow-up procedures after a positive LDCT). Radiation exposure from LDCT is low; however, over a long screening period of 20–25 years may cumulatively result in a non-negligible risk of radiation induced cancers.

The commentary noted that changes in screening technology (resolution of CT scanners and use of automated nodule detection systems) may improve sensitivity for identifying nodules and result in earlier lung cancer detection. However, greater sensitivity may be associated with higher rates of overdiagnosis (which may include the identification of indolent disease or disease at such an early stage that it is unlikely to impact the life expectancy of a subject if treated). If higher sensitivity is accompanied by a reduction in specificity, this may result in more interventions or follow up procedures for benign conditions.

The commentary noted that, as Australian rates of smoking have been steadily declining for 20 years or more, this trend may have several impacts on the applicability of the clinical evidence to the Australian setting. The PLCOm2012 eligibility criteria were trained and validated on populations with different distributions of current vs former smokers, and the performance of the tool when the population is differently comprised may alter. The benefits of a screening program based on the distribution of current and former smokers from up to 20 years ago may not be applicable to a population where most subjects eligible for screening are former smokers. Long-term results from the NLST study reported that current smokers experienced greater benefit from screening than former smokers.[25] It is unclear whether this applicability issue has been addressed in the current economic analysis.

The commentary noted that the economic model assumed a participation rate of 100% for both general population and Indigenous population subgroup in the base case analyses. This is an overestimate and favours the screening arm. In its pre-ESC response, the applicant acknowledged that an assumption of 100% participation is unrealistic but was selected more as a gold standard against which non-perfect participation rate scenarios could be compared. The applicant noted that adherence to screening in those who have had at least one LDCT screen is high, as suggested by the evidence (87.2% to 99.9%, likely close to 90% as shown in a real-world screening). The applicant argued that the primary effect of assuming 100% participation is that the fixed costs of the screening program are spread over a larger number of screens and so the average cost per screen is reduced. The sensitivity analyses around this scenario shows a small effect on the ICER of reducing participation rates.

The effect on the ICER is larger if it is assumed that participation at each screening round is random (e.g., every eligible person has a 65% probability of attending each screening invite), but this scenario is less realistic.

Incremental direct costs in the base case for the general population

Direct costs reported by the economic evaluation include[47]:

- LDCT screen costs: $795 million
- Follow-up LDCT costs: $35 million
- First risk assessment costs: $121 million
- Re-risk assessment costs: $90 million
- True positive diagnostic costs: $113 million
- False positive costs: $140 million
- Treatment costs: $1.446 billion
- Incidental findings costs: $121 million
- Program support costs: $244 million

Total additional payer costs: $3.105 billion

Total additional patient costs: $75 million

A comparison of the Program support components and costs between the economic evaluation and the financial analyses is summarised in **Attachments 7** and **8.**

Additional direct costs in a sensitivity analysis

A sensitivity analysis further explored the contemporary use of targeted therapies/ immunotherapies. The costs reported with the use of immunotherapies for individuals with Stage III/IV lung cancer are as follows[48]:

- Total payer costs: $3.199 billion (+$94 million compared to the base case)
- Total patient costs: no change.

A sensitivity analysis further explored the contemporary use of targeted therapies/ immunotherapies. The costs reported with the use of immunotherapies for individuals with Stage III/IV lung cancer are as follows[49]:

- Total payer costs: $3.199 billion (+$94 million compared to the base case)
- Total patient costs: no change.

Stepped economic evaluation

All results in Table 10 compare the proposed Program to no screening, reporting incremental results for costs, lung nodules detected, lung cancers detected, lung cancer deaths prevented, life years and QALYs.

[47] Table 45 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012.

[48] Derived from Table 51 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012.

[49] Derived from Table 51 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012.

Table 10 Results of the stepped economic analysis[50]

Step	LDCT screening increment	ICER
Step 1 – Incremental cost per extra lung nodule detected by LDCT screening		
Costs of nodule detection (Program costs, LDCT screen costs, first risk assessment costs, re-risk assessment costs, incidental findings costs)	$1.371 billion	
Total screen-detected lung nodules[51]	153,047	$8,958
Step 2 – Incremental cost per extra lung cancer detected by LDCT screening		
Step 1 costs plus confirmatory costs (follow-up LDCT costs, true positive diagnostic costs, false positive costs)	$1.659 billion	
Total screen-detected lung cancers[52]	40,888	$40,574
Step 3 – Incremental cost per extra lung cancer death prevented by LDCT screening		
Step 2 costs plus treatment costs	$3.105 billion	
Incremental lung cancer deaths prevented	14,572	$213,079
Step 4 – Base case (life years)		
Incremental payer costs	$3.105 billion	
Incremental life years gained	58,131	$53,414
Step 5 – Base case (QALYs)		
Incremental payer costs	$3.105 billion	
Incremental QALYs gained	37,166	$83,545

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year, LDCT = low dose computed tomography.

Note: Multiple outcomes may be informative for MSAC decision-making within each step. Figures may not add or compute due to rounding. Patient costs and other unidentified costs not included until Step 4. As the ICERs reported appear to exclude patient costs, patient costs are excluded from the final cost totals.

Overall results of the base case for the proposed general population (biennial screening for those 55 to 74 years of age and exceeding a PLCOm2012 estimated threshold of 1.5% 6-year risk of lung cancer) are presented in Table 11 below. Results for the proposed Indigenous population (biennial screening for those 50 to 74 years of age and exceeding a PLCOm2012 estimated threshold of 1.5% 6-year risk of lung cancer) are also presented. Both sets of results are reported per 100,000 of the eligible population to facilitate a comparison across the two populations.

[50] Derived from Table 45 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012.

[51] This total comprises all true positive and false positive nodules detected by screening. False positives are reported as a model output. True positives can be derived given the 16.44% overdiagnosis rate and the reported number of overdiagnosed cancers (6722).

[52] This comprises all true positive nodules detected by screening. While this figure was not reported as a model output, it can be derived given the 16.44% overdiagnosis rate and the reported number of overdiagnosed cancers (6722).

Table 11 Results of the economic evaluation[53]

Parameter per 100,000 eligible people	General population	Indigenous population
Incremental payer costs (discounted)	$47.036 million	$119.994 million
Incremental life years gained (discounted)	881	1,482
Incremental QALYs gained (discounted)	563	746
Incremental cost per life year gained	**$53,414**	**$80,949**
Incremental cost per QALY gained	**$83,545**	**$160,850**

QALY = quality-adjusted life year, LDCT = low dose computed tomography. ICERs may not equate to increments due to rounding

Key drivers of the model are presented in Table 12 below with commentary in the right-hand column.

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: $83,545/QALY gained
Utilities	The base case assumed that individuals diagnosed with Stage I/II lung cancer experience a maintained utility decrement of 0.09 from the time of diagnosis to the time at which they either progress to Stage III/IV (from which point a further decrement of 0.09 applied) or die from other causes. Individuals may experience disutility during treatment, followed by a recovery in utility the longer they remain disease-free. This is a common assumption in analyses of cancer treatments for early-stage cancer.	High When no utility decrement is applied to individuals with localised lung cancer and the utility decrement for stage III/IV cancer is increased to an overall decrement of 0.22, the ICER decreased to $61,889/QALY.
Discount rates	The recommended discount rate in Australia (5% for costs and benefits) is high relative to that used in other developed countries. Discounting penalises screening programs because costs are incurred more in the early phases of the study time horizon, while the benefits of screening are delayed and hence, discounted more heavily.	High When the discount rate was reduced from 5% to 3% per annum, the ICER decreased to $67,015/QALY.
Cost inputs	Lower LDCT scan item fees for the large volume use of LDCT scans for lung cancer screening have a moderate effect on decreasing the ICER. Uncertainty around the 'continuing phase treatment costs' (i.e., costs following the first-year post-diagnosis and prior to the final year of life) also had an impact on the ICER. There is rationale to suggest that these costs were overestimated.	Moderate When a 50% reduction was applied to the cost of LDCT scans and continuing phase treatment costs, the ICER decreased to $72,382/QALY and $76,431/QALY, respectively.
Eligibility criteria	Changing the eligibility criteria to only include individuals with a 30 pack-year, maximum 10 years since quitting, smoking history	Moderate When the eligibility is limited to this group, the ICER decreased to $78,406/QALY.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year, LDCT = low dose computed tomography

In addition to Table 12, other important aspects of the model include:

- A key driver of the cost-effectiveness of lung cancer screening is the overdiagnosis rate, being the proportion of individuals with screen-detected lung cancers who would have

[53] Table 54 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012. (Note with reference to page 107 that the age range of '50-70 yrs' in Table 55 should be '50-75 yrs'.)

died without their lung cancer being clinically diagnosed in the absence of screening. The overdiagnosis rates estimated by the MISCAN-Lung model for the Australian population are in line with estimates generated by the MISCAN-Lung model for Canadian and Swiss populations. However, in a comparative study of four cost-effectiveness models of lung cancer screening, the MISCAN-Lung model predicted overdiagnosis rates towards the higher end of the range. This would be expected to increase the ICER relative to other cost-effectiveness models.

- The simplified PLCOm2012 risk prediction tool used in MISCAN-Lung assumes individuals are white, have a BMI of 27 with some college education, no COPD, no personal history of cancer, and no family history of lung cancer. Use of the simplified model was necessary due to data limitations and was not considered to be a significant limitation.

The reported univariate and multivariate sensitivity analyses are summarised below. In contrast to the results reported in Table 11, the sensitivity analyses reported below for the general population are not on the basis of per 100,000 of the eligible population and, for the Indigenous population, reflect a base case of biennial screening for those 45 to 70 years of age and exceeding a PLCOm2012 estimated threshold of 1.25% 6-year risk of lung cancer.

Table 13 Sensitivity analyses[54]

Analyses	General population incremental cost ($)	General population incremental QALYs	General population ICER/QALY ($)	Indigenous population incremental cost ($)	Indigenous population incremental QALYs	Indigenous population ICER/QALY ($)
Base case	**3.105b**	**37,166**	**83,545**	**104m**	**770**	**135,449**
One-way sensitivity analyses						
5.5% annual screens	3.149b	37,166	84,720	106m	770	137,127
No performance assessment for rescreens	3.015b	37,166	81,120	101m	770	131,781
No risk or performance assessment for 1st screens and rescreens	2.894b	37,166	77,864	99m	770	128,745
Proportion with investigated incidental findings increased to 25%	3.186b	37,166	85,715	107m	770	138,529
All Program costs reduced by 25%	2.983b	37,166	80,266	102m	770	133,051
Positive screen follow-up costs reduced by 25%	3.042b	37,166	81,839	102m	770	132,526
Out-of-pocket treatment costs reallocated to payer costs	3.147b	37,166	84,669	106m	770	137,430
All treatment costs reduced by 25%	2.744b	37,166	73,819	90m	770	116,510
LDCT cost reduced by 50%	2.690b	37,166	72,382	92m	770	119,508
Stage III/IV costs & QALYs changed to reflect use of immunotherapies[1]	3.199b	35,846	89,427	110m	731	150,981
No utility decrement for stage I/II, reduced utility for stage III/IV	3.105b	50,171	61,889	104m	1,217	85,699
Equal terminal phase treatment costs for all stages at diagnosis	3.068b	37,166	82,547	103m	770	133,952
50% reduction in continuing phase costs for stage I/II	2.841b	37,166	76,431	96m	770	124,497

[54] Total population estimates are derived from Tables 51 and 52 and Indigenous population estimates are derived from Tables 56 and 57 of Cancer Australia 2020. The economic evaluation of targeted lung cancer screening in Australia. Surry Hills, NSW 2012.

65% uptake – random 65% attend each screening round	2.666b	28,518	93,470	75m	532	140,125
65% uptake – the same 65% attend each screening round	2.104b	24,158	87,076	69m	501	138,030
40% uptake – the same 40% attend each screening round	1.388b	14,866	93,381	44m	308	142,641
90% uptake – the same 90% attend each screening round	2.819b	33,450	84,273	94m	693	135,981
3% discount rate	3.429b	51,161	67,015	113m	1,021	110,943
0% discount rate	4.187b	37,166	48,791	134m	770	83,941
No screening related costs (just treatment costs)	1.446b	37,166	38,903	62m	770	80,550
Pack years 30 10 base case	2.448b	31,225	78,406	93m	736	126,623
Multi-way sensitivity analyses						
Equal terminal phase costs + 25% reduced stage I/II continuing phase costs	2.936b	37,166	78,990	99m	770	128,476
+ No utility decrement for stage I/II, reduced utility for stage III/IV	2.936b	50,171	58,515	99m	1,217	81,287
+ No rescreening performance assessment costs	2.858b	50,171	56,961	96m	1,217	78,967
+ Program costs reduced by 25%	2.785b	50,171	55,505	95m	1,217	78,208
+ LDCT costs reduced by 25%	2.577b	50,171	51,370	89m	1,217	73,165

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year
[1] These figures represent corrected results as provided in "Response to MSAC Queries – 2021.11.19 FINAL.docx"

The commentary noted the following:

- The stage shift predicted by the economic model is similar to that observed in the NELSON and NLST trials. However, in comparison to observed Australian data, the model may underestimate five-year survival rates in the non-screening arm. In its pre-ESC response, the applicant provided additional data on the relative 5-year survival rates incorporated in the model and noted that these are generally reflective of the related 5-year survival rates in the Australian population.
- The base-case economic model reported a gain of 37,166 QALYs at a cost of $3.105 billion Australian dollars, representing an ICER of $83,545 per QALY (for the broader Australian population). The ICER reported for the Indigenous population was substantially higher.
- There are notable uncertainties in the economic model. The impact of many uncertainties could not be adequately explored during the evaluation as a fully executable version of the economic model was not available for assessment. However, responses from the economic modelling team, and extensive sensitivity analyses facilitated an estimate of the direction of the effect of some parameter uncertainties.

Program duration

The commentary noted that the proposed Program involves ongoing (up to 20 years) biennial screening. Evidence on biennial screening past the first 5 to 6 years (beyond trial period observation) is lacking. It is unclear whether lung cancer detection rates, and subsequent impacts on lung cancer mortality, can be reasonably extrapolated from the trial period to a 20-year time frame.

In its pre-ESC response, the applicant argued that the incremental benefits will increase over time in a long-term screening program due to a couple of factors:

- The relative proportion of early-stage preclinical cancers is greater after the initial screening round. Given that the successful treatment of lung cancer is highly dependent on the stage at detection, the mortality reduction facilitated by screening is likely to be greater for the incidence screens compared to the baseline screening.
- Due to the variation in screening effectiveness on mortality over time, a continued screening program of 20-25 years is likely to show a greater mortality reduction compared to a clinical trial with a more limited screening period. Within a long-term screening program, the generated mortality reductions will increase in the years after the onset of screening until the largest possible magnitude of benefit is reached and in its steady state (i.e., the "asymptote").

Participation rate

The commentary noted that the economic model assumed a participation rate of 100% for both the general population and Indigenous population subgroup in the base case analyses. This is an overestimate and favours the screening arm due to the fixed costs associated with screening.

Risk assessment costs

The commentary noted that consistent with the MSAC Guidelines' approach to valuing opportunity costs, the economic model includes costs associated with risk assessment (to determine eligibility for the Program). Consistent with the MSAC Guidelines' approach to how these opportunity costs would be realised, the financial analysis has taken a pragmatic view that the higher utilisation of general practice to establish eligibility would not incur additional system costs as demand for GPs is greater than supply. Removal of these costs (i.e., ignoring the expectation that increased GP time associated with risk assessment has no consequence for other patients accessing this GP time) has a moderate impact on the ICER.

New treatments (e.g., immunotherapies)

The commentary noted that the base case of the economic model did not include the use of immunotherapies. The method of incorporating the costs and benefits of immunotherapies into the sensitivity analysis is unclear. The sensitivity analysis results in an increase in incremental costs (indicating greater use of immunotherapies in the screening arm) and yet a decrease in incremental QALYs (indicating greater gains in the no screening arm). This appears counterintuitive and has not been fully explained in correspondence with the economic modelling team. Also noted was that although the methods for incorporating immunotherapies into the model are not clear and may not be appropriate, the impact of immunotherapies on the ICER is both moderate (less than 10%) and overestimated. The costs of immunotherapies applied in the sensitivity analysis are based on the published dispensed prices for the maximum amount, and this is unlikely to reflect the cost to Government.

The applicant's pre-ESC response noted that this was handled as a sensitivity analysis because the screening data against which the model was calibrated did not reflect a period with widespread use of immunotherapies. The applicant stated that for individuals experiencing any of these phases of care, a phase-specific QALY gain was added to the QALYs accrued by these individuals to reflect the incremental benefits of immunotherapies over previously available treatments. This resulted in a decrease in the mean QALY gain of screening because more individuals in the no screening arm receive immunotherapy and hence accrue the additional QALY gains. Additional immunotherapy costs were also applied to patients experiencing any of these phases of care, with costs applied as a function of time spent in the relevant phase of care.

Due to the lead time effects of screening, individuals detected through screening were more likely to spend the full 12 months in the phases of care in which the immunotherapy costs were applied. The applicant argued that this was likely to explain the small increase in the cost difference between the screening and no screening arm in the sensitivity analysis around the effects of immunotherapies. Another factor was the use of immunotherapies by 'overdiagnosed' individuals, who would not have received immunotherapy in the absence of screening. The applicant acknowledged that adaptations to the model may misrepresent the effects of screening on the use of immunotherapies to some degree, but as the impact of immunotherapies are represented on both the costs and benefits side, they would not have a significant impact on the ICER.

Ongoing care costs

The commentary noted that continuing care costs were incurred following diagnosis, continued even in individuals who had achieved remission or cure, and may continue for the lifetime of the model. These costs are likely to be an overestimate and disfavour the screening arm, which is associated with earlier diagnosis and greater long-term remission or cure. ICERs decreased by 16% when continuing care costs were set to zero in a sensitivity analysis.

Health state utilities

The commentary noted that utility decrements in the model for individuals diagnosed with Stage I/II lung cancer were applied inappropriately. The base case applied a maintained utility decrement of 0.09 to the individuals diagnosed with Stage I/II from the time of diagnosis to the time at which they either progress to Stage III/IV (from which point a further decrement of 0.09 applied) or die from other causes. As screening moves diagnoses to a time point that may be several years earlier than would otherwise occur, screening diagnosed individuals are exposed to a substantial decrement in utility despite no difference in clinical symptoms. The model ICER is sensitive to the chosen utility values.

In its pre-ESC response, the applicant acknowledged that this approach was unlikely to reflect the true utility effects of individuals diagnosed with stage I or II lung cancer and referred to the sensitivity analyses in which the utility decrement in the continuing phase is removed.

Key conclusions

The commentary noted that a multivariate analysis with 25% reduction in stage I/II continuing phase costs + no utility decrement for stage I/II, reduced utility for stage III/IV resulted in an ICER of $58,515 per QALY (Table 13). This would reduce further when continuing care costs are set to zero indicating ICERs would be lower than $60,000 per QALY if the base case is respecified by changing the continuous care costs and utility values alone. Removing or reducing screening eligibility costs may further reduce the ICER. The impact of contemporary targeted therapies on ICERs is uncertain. Sensitivity analysis including the costs and QALY gains with the use of more expensive immunotherapies resulted in an indicated increase from the base-case ICERs. The commentary considered that it was unclear how the costs and QALY gains were implemented in the model, and the costs associated with immunotherapy use appear to have directionally different impacts in the economic analysis compared with the financial analysis.

In its pre-ESC response, the applicant reported that consensus was reached between its economic evaluation and financial analysis modelling teams that:

- Some assumptions in the economic evaluation (e.g., treatment costs for localised disease and utility values) resulted in an overestimate of costs in the economic evaluation (this had the effect of disfavouring the screening arm)

    - Screening would be expected to increase the number of life-years in the continuing care phase. However, this may be a conservative assumption adopted in the economic evaluation as it suggests that a person who has been successfully curatively treated for stage I lung cancer still incurs additional costs for years after their treatment, in the continuing care phase. In addition, based on the contemporary treatment pathways for early-stage lung cancer, the initial treatment phase costs for localised disease were overestimated in the economic evaluation. Similarly, the treatment costs in the continuing care phase for localised disease were overestimated.
    - In the economic evaluation, an individual whose stage I lung cancer is cured and who lives for 10 years after this initial diagnosis (dying due to a cause other than lung cancer) still incurs the same level of disutility, over each year of the continuing care phase, as was applied in the initial care phase.
- Some assumptions in the 'net cost' modelling discussed in the next section (e.g., higher early-stage distribution) may have contributed to an overestimate of savings of screening in that analysis (favouring the screening arm).
    - The 'net cost' modelling and the economic evaluation modelling considered different populations in estimating the stage shift expected from implementation of a lung cancer screening program. The 'net cost' modelling sought to determine the budget impact of screening and therefore focussed specifically on the screening population, whereas the purpose of the economic evaluation modelling was to demonstrate benefit/ impact of lung cancer screening to the entire population (birth cohort –1945-1969).
- Cost overestimates in the economic evaluation identified by the applicant's modelling teams aligned with the commentary, in so far as the key drivers of the base case ICER are the treatment cost inputs and utility value inputs.

To reflect contemporary treatment pathways, treatment cost and disutility considerations above, the applicants in their pre-ESC response undertook a range of univariate and multivariate analyses to re-estimate the ICER per QALY, see Table 14 for the complete results.

Table 14 Additional sensitivity analyses in the pre-ESC response from Cancer Australia

	Life-years gained	5% discounted life years gained	5% discounted QALYs gained	Incremental cost per life year gained (payer)	Incremental cost per QALY gained (payer)
Base case (100% uptake)	125,098	58,131	37,166	53,414	83,545
Univariate A: Assume a 75% reduction in costs for both the initial and continuing care phases for stage I and II lung cancers	125,098	58,131	37,166	34,808	54,443
Univariate B: Assume a 50% reduction in costs for the initial phase and 75% reduction in costs for the continuing care phase for stage I and II lung cancers	125,098	58,131	37,166	38,956	60,931
Univariate C: Assume a 25% reduction in costs for the initial phase and 75% reduction in costs for the continuing care phase for stage I and II lung cancers	125,098	58,131	37,166	43,104	67,418
Multivariate A: Assume a 75% reduction in costs for both the initial and continuing care phases for stage I and II lung cancers and no disutility for stage I and II lung cancers in the continuing phase only	125,098	58,131	48,653	34,808	41,590
Multivariate B: Assume a 50% reduction in costs for the initial phase and 75% reduction in costs for the continuing care phase for stage I and II lung cancers and no disutility for stage I and II lung cancers in the continuing phase only	125,098	58,131	48,653	38,956	46,546
Multivariate C: Assume a 25% reduction in costs for the initial phase and 75% reduction in costs for the continuing care phase for stage I and II lung cancers and no disutility for stage I and II lung cancers in the continuing phase only	125,098	58,131	48,653	43,104	51,501

14. Financial/budgetary impacts

A. Utilisation and costs to the MBS for delivering the proposed Program

The utilisation and financial implications to the MBS (incurred by the Commonwealth) of LDCT scanning resulting from the proposed Program are summarised in Table 15.

Uptake of LDCT screening was determined as a function of lung cancer epidemiology adjusted by the proportion of the population eligible for risk assessment by the risk prediction tool, the proportion who agree to use this tool, and the proportion of individuals who exceed the risk prediction threshold. It was assumed that there would be a 100% uptake of LDCT screening by those who are eligible after these three steps.

Specifically, net financial implications to the Commonwealth were calculated using the following methodology, with further adjustment for a hypothetical phased roll-out of recruitment into the Program beginning 1 January of year 2 in 3 PHNs, and with full national roll-out established by 30 June of year 6[55]. The first year of the Program would involve building and implementing the program.

- Estimate the number of individuals in each planned PHN for recruitment for the respective year of roll-out.
- Apply projected population increase to determine PHN population figures in the 55-74 age category.
- Apply estimated percentage eligible for risk assessment (55.8%[56]) to determine the number of individuals aged 55-74 eligible for risk assessment by the risk prediction tool.
- Apply estimated participation rate (60%[57]) to obtain number of individuals participating in this risk assessment.
- Apply estimated percentage eligible for LDCT (19.9%[58]) to obtain number of individuals participating in baseline screening.
- Apply the Cancer Australia screening assessment pathway nodule management protocols, including the percentages of nodule findings in each category[59] to calculate the cascade of services performed each year, broken down into:
    - routine biennial (T2+) screens
    - the number of interval screens at <12 months
    - the number of 12-month interval screens.

[55] In this hypothetical scenario, Year 2 begins with three PHNs recruited for screening; year 3 is designed to have no recruitment, however still provides 12m interval screens for those recruited in year 2; year 4 recruits individuals from all WA and four PHNs, including new screens and T2+ screens and performance assessments for those recruited previously; year 5 recruits all WA, QLD, VIC and NSW for <12m interval screens and 12m interval screens for those recruited in prior years; year 6 involves recruitment from all Australia and includes <12m interval screening costs, 12m interval screening costs and T2+ screening costs.

[56] This percentage is calculated as the number of ever smokers in the 55-74 age group in 2021 which is equal to 55.8% of all people in this age group (total population = 5,218,066; ever smoker population = 2,914,153).

[57] Broadly based on participation rates of other Australian screening programs.

[58] This percentage is calculated as the number of ever smokers in age range that are eligible for screening in 2021, being those with a minimum 1.5% 6-year risk of lung cancer (reflecting smoking status, smoking intensity and time since quit smoking, using the simplified PLCOm2012 risk calculator), which is equal to 19.9% of all ever smokers in this age group (ever smoker population = 2,914,153; total number eligible in 2021 = 579,766).

[59] Per PanCan Classification (T0) and LungRADS 1.1 Classification (T2+) described previously in this application.

- Apply relevant unit costs to each service. The estimated unit cost of each LDCT scan is based on the average MBS benefit paid for item 56301 in 2020-21 of $280.41 (this figure accounts for safety net payments, the bulk billing rate, and the proportion of in-hospital versus out-of-hospital services).[60] The unit cost in each subsequent year and after was then assumed to be subject to an average annual indexation rate of 1.5%.[61]

Table 15 Net financial implications of LDCT screening to the MBS and PBS

Parameter	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology					
Number of people eligible for risk assessment	301,618	No recruitment	509,648	1,923,505	382,999
Number eligible for baseline LDCT screening	36,013	No recruitment	60,852	229,666	45,730
Number who receive baseline LDCT screening	36,013	No recruitment	60,852	229,666	45,730
Number of services of LDCT screening (total screens)	37,828	5,204	100,373	253,201	178,412
Net financial impact to the MBS	**$10.928m**	**$1.526m**	**$29.873m**	**$76.487m**	**$54.703m**

LDCT = low dose computed tomography, MBS = Medicare Benefits Schedule.

Assumptions

The costing estimates presented here do not account for the following:

- people ageing into the Program (i.e., those that turn 55 in the relevant year)
- people who were previously risk assessed and found ineligible being re-risk assessed
- Aboriginal and Torres Strait Islander people aged 50-54 years.

The current costing assumes that no individual receiving the proposed screening item would have otherwise received the existing MBS item 56301. This is a conservative assumption which potentially overestimates the expenditure on LDCT scans via the proposed Program-specific item. In reality, some individuals participating in the proposed Program would likely have received the existing MBS item 56301. However, this small cost offset has not been estimated because all individuals meeting the risk assessment eligibility criteria would be encouraged to switch to the new Program and thus the proposed item.

The estimates also assume the MBS cost is applied to all screens, without consideration of any different costing structure of any other complementary access arrangements such as a mobile screening program. The commentary concluded that this was reasonable, as the MBS fee for providing mobile screening is similar to the fixed facilities. All other operational and setup costs were included in the Program setup costs.

In keeping with usual practice, the financial analysis does not take account of primary care (GP services) costs for undertaking Program-related risk assessments. This is because, in the context of demand outstripping the supply for these services, any marginal changes in utilisation of these

[60] This was derived by dividing the total benefits paid for financial year 2020-21 for MBS item 56301 ($71,876,857) by the total number of services in that financial year (256,326). Figures are available from Services Australia - Statistics - Item Reports (humanservices.gov.au)

[61] The 2020-21 average benefit was 1.6% higher than the average benefit in 2019-20. The MBS indexation rate for July 2020 was 0.9% and the remaining increase would be due to an increase in bulk billing. An assumed indexation rate of 1.5% per annum is therefore a reasonable one because the Program would encourage bulk billing of Program-specific CT scans.

services due to implementation of the proposed Program would be managed by redeploying existing services rather than being realised as financial implications.

Number and cost of LDCT scans to the MBS

Following the methodology described earlier in this section, the total utilisation and net costs of LDCT screening scans over the course of the Program from years 2 to 6 would be:

- individuals eligible for risk assessment: 3,117,770
- individuals eligible for LDCT screening scans: 372,262
- individuals who receive LDCT screening scans: 372,262
- LDCT screening scans provided: 575,018
- financial cost to the MBS: $173.52 million.

B. Utilisation and costs to government for changes in use of downstream health care resources

The "Lung Cancer Treatment Cost Model" (also known as the 'net cost' modelling referred to in the previous section) was constructed to estimate downstream costs in terms of increased or decreased utilisation of MBS and PBS items associated with initial treatment and costs of treating recurrence. This model incorporated contemporary use of immunotherapies for treating Stage III and IV cancers and predicted a substantial cost savings in treatment costs associated with the screening Program (Table 16).

Table 16 Annual treatment costs including recurrence in Stage I and II assuming 100% participation rate (undiscounted)

	Control	Screening	Increment
Year 1	$791,946,863	$778,117,805	–$13,829,058
Year 2	$826,319,225	$800,826,800	–$25,492,425
Year 3	$854,518,815	$770,448,254	–$84,070,561
Year 4	$878,823,697	$738,670,743	–$140,152,954
Year 5	$875,154,941	$731,394,601	–$143,760,340
Year 6	$894,592,898	$753,889,853	–$140,703,045
Year 7	$913,277,693	$773,677,766	–$139,599,926
Year 8	$931,552,398	$791,784,255	–$139,768,143
Year 9	$950,236,327	$809,344,892	–$140,891,436
Year 10	$937,757,332	$800,193,363	–$137,563,968

Note: Negative value represent net cost savings due to the proposed Program.
Source: Annual treatment costs including recurrence in Stage I and II estimated for calendar years 2023 to 2032 during evaluation using Cancer Australia Lung Cancer Treatment Cost Model

The commentary noted that the net cost saving estimated by the 'net cost' modelling was in contrast with the estimated $1.446 billion incremental treatment costs associated with screening in the base case of the economic model. It was not possible to adequately disaggregate healthcare resources used in the economic evaluation, therefore a comparison with the treatment financial model was not possible. The key concerns identified in the financial analysis used to estimate net treatment costs were:

- The initial increased incidence of lung cancer associated with screening was not captured in the estimates.

- The approach of applying observed stage distribution to the incidence cases was not appropriate. The stage shift for screened population would not be apparent immediately from the first year of the screening rollout.
- Costs used in the financial model were underestimated and thus do not represent the costs realised in the Australian healthcare system.
- Treatment costs in the economic evaluation included treatment costs associated with treating the cancer, continuous care costs and terminal phase costs. Continuous care and terminal phase costs were not considered in the financial model. The economic model did not include the cost of more expensive immunotherapies in the base case.

The commentary noted that sensitivity analyses were performed during the evaluation to explore the impact of the issues described above. The annual stage distribution observed in the NELSON study was applied to Australian incidence estimated in the financial model for four cohorts based on the proposed Cancer Australia Roll-out Schedule. The participation rate was assumed to be 100% and all other parameter values remained unchanged. Results of this analysis are summarised in Table 17. Based on this approach, it would be approximately five to six years before treatment costs are neutral for screening.

Table 17 Annual treatment costs including recurrence in Stage I and II assuming 100% participation rate using respecified incidence and 100% participation rate (undiscounted)

	Control	Screening	Increment
Year 1	$22,288,966	$29,286,935	$6,997,969
Year 2	$62,595,896	$72,608,477	$10,012,581
Year 3	$207,501,014	$251,061,485	$43,560,470
Year 4	$252,696,528	$256,511,896	$3,815,369
Year 5	$214,527,922	$208,700,964	–$5,826,958
Year 6	$233,989,147	$237,876,153	$3,887,006
Year 7	$285,605,333	$173,880,988	–$111,724,345
Year 8	$291,947,506	$212,273,214	–$79,674,292
Year 9	$301,218,823	$234,168,473	–$67,050,350
Year 10	$300,631,280	$188,918,986	–$111,712,294

Note: Negative values represent net cost savings due to the proposed Program.
Source: Annual treatment costs including recurrence in Stage I and II estimated for calendar years 2023 to 2032 during evaluation using Cancer Australia Lung Cancer Treatment Cost Model

The commentary noted that in the financial analysis, surgery was costed at $1,496 and chemoradiation was costed at $10,316. The commentary considered these costs to be unrealistically low. As costs associated with surgery and radiotherapy are primarily relevant in Stage I / II diagnoses this underestimate favoured the screening arm.

The commentary considered that the rate of recurrence from Stage I and Stage II used in the net treatment cost model appears very low. Only 10% of Stage I and 33% of Stage II were assumed to recur following treatment. 65% of all recurrences occur in year 3 onwards. This appears to be inconsistent with estimates of 5-year survival for these stages (which may be as low as 50-60%). The commentary considered that while there may be a lower rate of recurrence in the screening arm than in the control arm, there is inadequate justification for the rates applied in the analyses. Higher rates of recurrence would further increase the costs associated with the screening arm.

The commentary noted that in conclusion, based on the approach taken in the sensitivity analysis, it is predicted that there will be a temporary increase in cost to the Australian Government health budget related to downstream treatments. The duration of the incrementally higher costs in the screening arm is uncertain. Cumulatively, the increase may be longer than 10 years, depending on the actual costs of some health resources. In the long term, it is likely that the cost to the health budget would be neutral or even favour the screening arm, however this is subject to substantial uncertainty regarding factors that are not commonly included in financial analyses (such as the future prices of expensive therapies, and the change in the treatments available in earlier stages of lung cancer).

The commentary noted that the approach taken to estimate net treatment costs across economic and financial models varied. Table 18 summarises the differences across the two models.

Table 18 Key differences across economic and financial model in estimating net treatment costs

Description	Economic evaluation	Financial model	Comments
Time horizon	Lifetime of the cohort entering in the model	15 years	Treatment costs in the economic evaluation were accrued for the lifetime (maximum 100 years of age) whereas costs estimated in financial model were immediate treatment costs and costs of treating recurrence within 5 years.
Participation rate	100%	60%	A sensitivity analysis was provided in the economic evaluation for a 60% participation rate; however, the disaggregated treatment costs were not available for comparison.
Lung cancer incidence	Estimated using MISCAN-lung cancer model for the cohort and takes into account the effect of screening	Projected lung cancer incidence in Australia	Incidence across screening and no screening arm was considered equal in the financial model. This is inappropriate as screening will result in increased incidence in first few years as observed in the screening trials. Over a period of about 10 years, incidence will become similar but remain slightly higher in the screening arm due to overdiagnosis and greater lead-time. Therefore, the long-term financial implications may reach a steady state that would not be observed in a short-term analysis.
Application of observed stage shift	Stage shift applied by incorporating probability of detection by screening in each phase	Predicted stage shift was based on long term clinical trial results and was applied from the first year of the screening rollout.	The approach of applying observed stage distribution to the incidence cases was not appropriate in the financial model. The stage shift for the screened population would not be apparent immediately from the first year of the screening rollout.
Recurrence	Based on probability distribution (point estimates not available)	Stage I: 10% Stage II: 33%	Costs associated with recurrence would be captured in continuing care costs in the economic model and may be an overestimate of the treatment costs. Recurrence rates included in the financial model were low and may underestimate the treatment costs associated with recurrence in Stage I/II.
Overdiagnosis	16%	Not included	The economic model may have overestimated the rate of overdiagnosis and related treatment costs. These were not included in the financial analysis.
Treatment costs	Treatments costs were estimated by three phases of care – initial, continuing and terminal	Treatment costs were estimated for initial treatment and treating recurrence	Use of more expensive targeted/immunotherapies in treating late-stage cancers was not included in the base case of the economic model. The impact of contemporary targeted therapies on ICERs is

Description	Economic evaluation	Financial model	Comments
	and by age, stage at diagnosis, gender, and histology. Targeted therapies and immunotherapy costs not included in the base case analysis. MBS, PBS, and hospital costs were included.	within first five years. Targeted therapies and immunotherapy costs were included in the estimates. Only costs associated with utilisation of MBS and PBS services were included.	uncertain. Sensitivity analysis including the costs and QALY gains with the use of more expensive immunotherapies resulted in an increase from the base-case ICER. It is unclear how the costs and QALY gains were implemented in the model. However, the sensitivity analysis results in a net increase in costs (associated with greater utilisation of immunotherapies in the screening arm), which is opposite to the financial implications that report a net decrease in costs (associated with avoided treatments in later stage NSCLC). The financial model did not include continuing and terminal phase costs. Continuing care costs accrued in the economic model are substantial. ICERs decreased by 16% when continuing care costs were set to zero in a sensitivity analysis. Costs associated with surgery, chemotherapy and radiation used in the financial model are an underestimate and do not represent the costs experienced in the Australian healthcare system.

ICER = incremental cost effectiveness ratio; MBS = Medicare Benefits Schedule; NSCLC = non-small cell lung cancer; PBS = Pharmaceutical Benefits Schedule; QALY = quality adjusted life years
Source: Constructed during the evaluation

C. Components and costs to government to support the proposed Program

The proposed National Lung Cancer Screening Program would be administered by the Department on behalf of the Australian Government. Although the Program would be targeted to high-risk individuals rather than being fully population-based, it would complement the existing national population-based screening initiatives for bowel, cervical and breast cancers. Cancer Australia would support Program implementation and operation through the development of Program information and communication materials and clinical guidance, as well as developing data systems and quality standards.

The Department would establish partnerships with the network of 31 Primary Health Networks (PHNs) to facilitate population recruitment and primary care provider participation at the local level. The PHNs would also assist to coordinate the development of clinical referral pathways between primary care, radiology, and specialist providers.

It is intended that the Program would largely be delivered through a private sector model driven by funding through the MBS, with some access to public hospital screening facilities in areas of market failure. Equitable access to screening would also be generated by targeted investment in mobile LDCT screening services in some remote and very remote areas.

A total of $156.6 million of Program support costs over five years was presented by the Department. Program support costs have been defined as those costs related to the operational management of the LDCT screening Program. Costs in this category include: Program management; Program research; workforce development and support; data engagement; development of a register and its operational costs; Program development, information, and communication; national promotion and communication; PHN support and partnership; governance; Program data and quality assurance; monitoring and reporting; evaluation; and mobile screening services.

Program support costs over 5 years have been estimated based on a phased roll-out model consistent with Part A of this section. In the proposed phased roll-out, year 1 would involve

development of the core Program infrastructure, including the register, clinical guidance for the screening pathway and clinical protocols. Partnerships with key stakeholders for initial implementation would also be established. With the core infrastructure in place, the initial recruitment is proposed to begin in three PHN regions in year 2. Program roll-out would then be expanded in two steps, at approximately jurisdictional level for the middle step, with full national roll-out by 30 June in year 6. The approach to Program roll-out and specific geographic coverage may vary if and/or when the Program is established. Final regions chosen would be a decision of Government, informed by further consultation with key stakeholders.

[redacted]

[redacted]

[redacted]

[redacted]

Not all Program support costs were included in the economic evaluation. The economic evaluation was undertaken to inform the Lung Cancer Screening Enquiry report and had an overarching focus on the cost effectiveness of LDCT screening as a function of direct costs and outcomes, rather than supplementary activities. Further, policy development undertaken since the Lung Cancer Screening Enquiry report was delivered has altered some aspects of Program design and determined that a number of items included in the economic evaluation would not be included in the financial costs of the final proposal to Government.

Primary considerations here included:

- Funding for Program-specific research activities was not included in the economic evaluation as it was not seen as a core Program cost relevant to the determination of cost effectiveness.
- The mobile screening costs included in the economic evaluation assumed the Commonwealth would take a centralised service delivery and employment role for related aspects of the Program roll-out. The mobile screening financial costs have been updated to reflect a decentralised approach designed to stimulate the provision of regionally based services while removing the direct costs to support a virtual access hub and a virtual diagnostic hub, and providing greater flexibility to meet equity of access needs.
- The register build and operational costs in the economic evaluation were estimated at a high level based on a percentage of the costs of the existing National Cancer Screening Register. The financial costs have been updated based on policy and scoping work undertaken since the economic evaluation.

Given the phased roll-out approach, and the policy development work undertaken since the release of the Lung Cancer Screening Enquiry Report, it is difficult to undertake a direct comparison between the Program support costs in the economic evaluation and the financial costs that are now proposed for these Program support components. This reflects the different purpose of the economic evaluation in helping to inform the Lung Cancer Screening Enquiry Report, compared to the development of a more fully fledged funding and implementation proposal for Government.

[redacted]

15. Other relevant information

Value of knowing

The table below outlines potential positive and negative psychological implications related to changes in knowledge due to the proposed Program.

Table 20 Summary of psychological implications of LDCT for Lung Cancer Screening Program versus no screening

Positive implications	**Lung Cancer Screening Program**	**No screening**
Psychological impact of a diagnosis of lung cancer following LDCT (true positive)	Access to LDCT would result in diagnosis of lung cancer at an earlier stage in more individuals. This would enable more effective treatments and thus reduce lung cancer morbidity and mortality. Compared with those diagnosed later with lung cancer, people diagnosed earlier would also likely have improved quality of life due to a better experience of care and lower treatment morbidity.	Delayed diagnosis of lung cancer.
Psychological impact of a nodule detected following LDCT with no lung cancer subsequently diagnosed (false positive)	Clinical investigation may result in eventual psychological reassurance once lung cancer is not diagnosed.	Nodule not detected and clinical investigation not required.
Psychological impact of undergoing LDCT and no nodule detected (true negative)	Participant may be provided reassurance that no nodule has been detected, and lung cancer is not present.	No reassurance.
Lifestyle changes	Participation in a lung cancer screening program would provide multiple opportunities for health care workers along the screening pathway to provide lifestyle advice, from the initial discussion with the primary health care worker to the reporting of diagnostic procedure outcomes after a nodule is detected. This would provide increased awareness of risk and information on lifestyle changes. For example, evidence suggests that participating in a lung cancer screening program is associated with better smoking quit rates and reduced smoking intensity.	Delayed lifestyle changes retain risk of receiving a future lung cancer diagnosis.
Access to support	Early diagnosis would permit earlier access to social and clinical support schemes such as cancer care nurses.	Delayed access to support.
Negative implications	**Lung Cancer Screening Program**	**No screening**
Psychological impact of a diagnosis of lung cancer following LDCT (true positive)	Diagnosis of lung cancer earlier may be accompanied by earlier onset of grief and psychological stress.	Delayed diagnosis of lung cancer.
Psychological impact of a nodule detected following LDCT with no lung cancer subsequently diagnosed (false positive)	Detection of a nodule and referral for further diagnostic procedures may be accompanied by initial psychological burden of anxiety and concern given potential for a lung cancer diagnosis.	Nodule not detected and clinical investigation not required.
Psychological impact of undergoing LDCT and no nodule detected however cancer present (false negative)	Psychological stress, anger and grief may arise if it becomes clear that the cancer was present at the time of the earlier scan and earlier diagnosis may have improved outcome, exacerbated by the false reassurance that the screening process would have ruled out cancer.	No false reassurance.

The commentary noted that direct evidence on a lung cancer screening program was available (albeit of questionable applicability) and suggests there may be health benefits from implementing LDCT as a lung cancer screening program. As the proposed intervention is expected to have health benefits (i.e., the purpose of screening is not the "value of knowing", it is earlier diagnosis), the concept of "value of knowing" in this context is less important.

Equity considerations

People living in remote and very remote areas, areas of greatest socioeconomic disadvantage and Aboriginal and Torres Strait Islander peoples are disproportionately affected by lung cancer, with higher lung cancer incidence and mortality in these groups.

As well as being at greater risk of lung cancer, these population groups are also more likely to encounter disparities in access to health services including LDCT compared to the general population. Given these disparities, the proposed Program would have a strong equity of access focus, including to support Program access and engagement for these population groups. This would include a strategy to support accessibility for populations in remote areas and areas with limited LDCT infrastructure. This may include new mobile service models.

In addition, the disparities in access to health services and disparities in health outcomes also lead to lower life expectancies for these population groups for reasons other than lung cancer. This results in increased rates of lung cancer overdiagnosis from screening (because overdiagnosed cases die with cancer rather than from it). For example, the modelled economic evaluation estimates almost five times as many overdiagnosed cases of lung cancer in the Indigenous population than the general population. Ironically, this increased rate of overdiagnosis also increases the estimated incremental cost per QALY gained of screening for this population. In the long-run, broader measures to improve healthcare accessibility (including the provision of lung cancer screening with a strong equity of access focus which raises overall health awareness) may decrease this incremental cost per QALY gained.

Lung cancer is the most frequent cancer diagnosis for Aboriginal and Torres Strait Islander people and the leading cause of cancer death. Incidence and mortality also occur at a younger age than the general population. Although tobacco smoking rates have been declining in Australia, smoking rates for Aboriginal and Torres Strait Islander peoples are higher compared to the non-indigenous population.

The proposed Program would also further emphasise the Australian Government's commitment to working in partnership with Indigenous Australians to close the gap in health outcomes for Aboriginal and Torres Strait Islander people and overcome inequality. Consistent with the Government's commitments under the National Agreement on Closing the Gap, the Program would contribute towards achieving the Target 1: 'Close the Gap in life expectance within a generation, by 2031'. The Program is also being designed in consultation and partnership with Aboriginal and Torres Strait Islander stakeholders, including from the Aboriginal Community Controlled Health Sector, addressing priority one 'Formal Partnerships and Shared Decision Making'.

If implementation is supported, consideration will be given to including the Program as part of the Government's Closing the Gap Implementation Plan.

The Program would therefore include a strong emphasis on targeting Aboriginal and Torres Strait Islander people particularly those in rural and remote communities.

In its pre-ESC response, the Department noted that Aboriginal and Torres Strait Islander representation will continue to be engaged to co-design detailed elements of the Program from an Aboriginal and Torres Strait Islander perspective, including Indigenous data sovereignty, culturally safe and appropriate information and communication materials, methods and channels for participants and health professionals and service delivery. PHN partnerships and communication strategies are also proposed at a local level to identify and address access to LDCT screening in particular communities. Mobile LDCT screening services are being considered, to address potential equity of access issues in rural and remote communities, including for Aboriginal and Torres Strait Islander people. A proposed investment stream would encourage providers to implement mobile screening services in rural and remote areas according to regional need.

Another equity issue would arise if some LDCT screening services are not bulk billed to the MBS. Estimates of the extent and the distribution of such practice may best be derived from the

existing MBS item 56301. Its consequence would be for an affected patient to be charged an out-of-pocket payment, which may result in some patients declining to participate in the Program.

The commentary noted that regular screening with LDCT may incur substantial out-of-pocket costs to individuals. The MSAC may wish to consider mechanisms to address potential equity issues associated with out-of-pocket costs. In its pre-ESC response, the Department noted that under the Constitutional basis for Medicare, it would be difficult to place restrictions on charging practices. Instead, under Medicare, options are usually to incentivise bulk billing. Currently, diagnostic Imaging services (such as CT services) receive a 10% increase in benefit for bulk-billed services – this works out to an increased benefit of $30.20 (from $256.80 to $287.00) for the proposed item. The Department observed that BreastScreen uses a non-MBS funding approach through the National Health Reform Agreement (NHRA) as a cost-shared arrangement with the state and territory jurisdictions, which presents its own issues in terms of transparency of service costs and the related program funding model. The Department noted that the proposed use of the MBS as the primary driver of remuneration for lung cancer screening services, largely through private practice, precludes adoption of the BreastScreen model.

The commentary noted that the accuracy of the risk prediction tool (PLCOm2012) is unknown in the Aboriginal and Torres Strait Islander population. MSAC may wish to clarify how the PLCOm2012 would be applied in the Aboriginal and Torres Strait Islander population and seek to establish the performance of this tool in the target population. In the absence of calibration, there is a risk that Aboriginal and Torres Strait Islander peoples could be over or under diagnosed, leading to false negatives or increased harm associated with inappropriate interventions.

Other relevant considerations

Overdiagnosis: there are several definitions of the term 'overdiagnosis' in screening, including:

- 'when a disease is detected by screening that would not have clinically presented prior to death from other causes in the absence of screening'
- 'when a disease is detected by screening, but death occurs from other causes whilst the disease is being managed'.

Overdiagnosis has been shown to be associated with unnecessary follow up procedures, treatment, harmful psychological impacts, and increased costs that may have a negative impact on wellbeing and life expectancy. Incidental findings resulting from LDCT may also lead to overdiagnosis of other conditions, increasing the potential for psychological harm and negative impact on wellbeing associated with increased costs due to increased treatment.

Stigma: a diagnosis of lung cancer can be associated with social consequences, such as sympathy for people with the diagnosis or a sense of shame in developing a smoking-related disease. The proposed Program would need to be cognisant of these issues and be sensitive to them when communicating with screened individuals, health professionals and the community.

16. Key issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
Uncertainty in magnitude of benefits and harms, and in overall impact on all-cause mortality in the Australian population	Support data collection via the proposed registry for the proposed Program. If this does not extend to recording relevant patient outcomes because it is proposed to be a screening registry only, consider linking to appropriate cancer treatment registries to support the overall data and evaluation framework for outcomes monitoring. Recommend regular evaluation by an independent group that is not connected to the agency responsible for the Program.
Potential for increased harms compared to trial setting, and risk of overdiagnosis	Support the incorporation of the following into the Program design: • protocols for follow-up investigation that minimise the potential harm caused by the incidental detection of benign conditions • protocols for the treatment of detected disease that is suspected of being indolent or slower growing. Overdiagnosis is a risk of many screening programs. ESC suggested that data collection should seek to identify overdiagnosis patterns.
Equity issues in terms of making sure those most likely to benefit can access the service and make informed decisions about screening	Support the Department's work to ensure the proposed Program is co-designed and implemented in partnership with Aboriginal and Torres Strait Islander peoples and people from other target populations.
Risk prediction tool performance and nodule management protocol performance in target populations	Recommend the performance of the risk prediction tool be validated in Indigenous populations, and other target populations, and recalibrated as necessary. Also recommend that the performance of LDCT equipment and nodule management protocols be periodically reviewed as part of the Program evaluation. Results from the International Lung Screening Trial may be informative (with interim results for the PLCOm2012 risk prediction tool published in December 2021 and completed results comparing the PanCan and Lung-RADS nodule management protocols expected in December 2023).
ICERs are high	Plausible ICERs are high and uncertain for a Program proposing to target asymptomatic individuals and that requires a substantial commitment of resources and cost to the health budget portfolio.
Limitations of the economic model	These include issues around the applicability of the clinical trial evidence and the need for an indirect comparison across trials. The calibration of inputs to produce outputs that match observed data is appropriate in the circumstances, but there is uncertainty around extrapolations beyond the observed data. The model, while long-term, does not reflect evolving (longitudinal) factors. The model also could not consider the

ESC key issue	ESC advice to MSAC
	consequences of any possible imperfections in Program implementation.
Cost-effectiveness in Indigenous subgroup	It is reasonable to allow for a higher cost-effectiveness threshold in this relatively small subgroup recognising its greater unmet clinical need, whilst noting that greater rates of overdiagnosis increase the ICER.
Financial implications	There were major discrepancies regarding incremental downstream treatment costs between the economic model and the financial modelling, due to differences in methods and assumptions.
Accounting for full Program costs	Acknowledge that cost estimates might vary to some extent with the creation of new incentives to maximise bulk billing of LDCT screening services, and to provide and operate mobile LDCT units.
Other relevant factors	Consider out-of-pocket payments (co-payment and gap); the opportunity cost of GP time dedicated to risk assessment; and factors that enable reaching remote, lower socioeconomic and Indigenous populations.

ESC discussion

ESC noted that this application is for MSAC to consider the proposed National Lung Cancer Screening Program, and to advise on its safety, effectiveness, cost-effectiveness, and sustainable implementation if funded by the Australian Government. MSAC is asked to assure the government that the policy case for the Program has received robust, independent scrutiny to inform such implementation.

ESC noted the consumer support for the Program, but also noted that all these responses reviewed were from non-smokers who had been diagnosed with lung cancer. ESC was concerned about implementation in rural and remote areas, which would impede peoples' access to the Program in a timely way, especially given the seasonal nature of some of the occupations in these areas, ESC noted that retaining people in the Program could thus be challenging if people need to travel during, for example, harvesting time. ESC also noted that, for people identified as having lung cancer through the Program, access to treatment for those from very remote communities would be problematic. ESC also considered it crucial that patients and clinicians have access to culturally appropriate and health literacy-sensitive decision support tools to facilitate shared decision-making and informed consent. ESC also considered that it may be difficult to implement protocols for follow-up on screening reports and referrals for future tests and/or treatment.

ESC noted the importance of equity of access issues for target populations, including Indigenous populations, lower socioeconomic groups and those in remote areas, ESC noted that the Program was being co-designed with Indigenous input and with input from other target populations.

ESC noted the concern for out-of-pocket costs if the related Medicare Benefits Schedule (MBS) services are not fully bulk-billed and considered that implementation of the Program should consider ways to incentivise bulk billing so that patients are not charged for either the risk assessment or the low-dose computed tomography (LDCT) screening.

ESC noted that a key component of the Program is the creation of an MBS item for use of LDCT in asymptomatic high-risk people. The Program proposes to use existing LDCT infrastructure and expertise, and consideration has been given to how to ensure access for participants in remote

or underserviced areas. ESC queried whether the Program may need to be hospital-based in some of these areas.

ESC noted that the proposed MBS item descriptor for LDCT-based screening allows for asymptomatic people to undergo screening but queried if the interpretation of asymptomatic could be ambiguous. ESC considered it may be appropriate to reflect the symptom-related criteria that was used in the trials to allow for respiratory symptoms that are not strongly indicative of cancer. ESC noted the commentary's suggested extra eligibility criteria regarding the general health of the patient, but ESC considered that these criteria may run the risk of excluding people who may benefit from the Program. ESC considered that an alternative to expanding the item descriptor to address this issue could be to provide more specific guidance in explanatory notes or another document promulgated and maintained by the Program support team.

ESC considered that the proposed MBS item descriptor should specify the proposed risk prediction tool, derived from an American PLCOm2012 tool, and the type of health professional performing the risk assessment. ESC noted that, although recently assessed in the international Lung Screening Trial with interim results published in December 2021, this tool has not yet been evaluated for use in Indigenous or culturally and linguistically diverse populations, or other key target groups for the Program. ESC noted the pre-ESC response that stated that research to validate PLCOm2012 in Indigenous people is currently underway. If this Program is supported, an initial establishment phase would enable further refinement and implementation of the risk prediction tool in this target group before participants are recruited. Related to this, ESC also noted that the International Lung Screening Trial is evaluating the PanCan nodule management protocol compared to Lung-RADS nodule management protocol (completion expected December 2023), which would inform the refinement of these tools as the Program expands its coverage of the proposed eligible population.

ESC noted that the Program is general practitioner (GP) driven, but that the MBS claim for the LDCT will be from a radiologist. ESC noted that any medical practitioner would be able to include a patient in the Program but considered that implementing protocols for follow up and treatment by specialists may be difficult. ESC also noted that the proposal did not include a fee for the primary care risk assessment, but the applicant noted in its pre-ESC response that Level C and D attendance items provide suitable MBS free rebates, and that a risk assessment could be done within this tiered general attendance framework. While noting that a precedent had been set for creation of new GP items for screening programs with the introduction of cardiovascular risk assessment items, ESC considered whether the proposed approach to this aspect of the Program was appropriate to reflect the opportunity cost of GP time dedicated to risk assessment given the constraints faced by GPs relate more to their available time than to the level of the MBS fee. ESC noted that the risk assessment process can be streamlined by incorporating the risk prediction tool into general practice software.

ESC noted the clinical trials and meta-analyses provided to support the clinical evaluation. ESC considered these trials likely have a low risk of bias, but this was not formally assessed during the evaluation. However, ESC acknowledged that given the relative methodological robustness of the two largest and influential trials (Nelson 2003 and NLST 2002), a further independent risk assessment of bias would be unlikely to make a material difference to MSAC deliberations. The assessment group clarified post-ESC that, as noted in the commentary, although formal assessment of these two trials was not undertaken, there were numerous applicability issues and some risk of bias issues that would justify a conclusion of an overall higher risk of bias than a high quality randomised controlled trial for a drug.

In terms of safety, ESC considered the risk of overdiagnosis to be the most significant source of harm from the proposed Program. ESC noted that the Nelson trial has the longest follow-up of all the trials presented and showed that estimates of overdiagnosis decreased over time to 8.9% after 11-years' follow-up. ESC suggested that the design of data collection for the Program should seek to identify overdiagnosis patterns. ESC also noted that the false-positive rate as another

source of harm has also decreased, including from using volumetric assessment of LDCT, which is proposed for the Program.

ESC noted that overdiagnosis can lead to harms from unnecessary surgery and other invasive procedures, and chemotherapy and other cancer treatments as well as psychological harms such as anxiety. The mortality associated with, for example, follow-up lung biopsies is not negligible. ESC noted the paucity of evidence on the long-term impacts from unnecessary radiation exposure from LDCT and from increased radiation doses with other subsequent imaging tests.

ESC noted the following actions that, if included in the Program design, could be used to mitigate an increase in harms:

- Ensure that screening participants have a life expectancy that is adequate to benefit from early diagnosis of lung cancer. At the same time, ESC cautioned that such an action should not introduce bias causing reduced access to screening against whole groups of patients who have lower life expectancies on average, in particular Indigenous patients.
- Implement protocols for investigating suspected disease that minimise the potential harm caused by an increase in the detection of benign conditions.
- Ensure that protocols for treating detected disease that is suspected of being indolent or slower growing are implemented, to mitigate the risk of surgical mortality or morbidity in a participant that is less likely to die of disease.

In terms of effectiveness, ESC noted there was an increase in the numbers of cancer diagnosed at an early stage and a decrease in the numbers of cancers diagnosed at an advanced stage (Table 3, Attachment 2), which indicates that screening would detect at least some clinically important cancers earlier than they would have been without screening. ESC noted that there was a significant reduction in the risk of lung cancer mortality for the two largest trials and meta-analyses, but there were mixed results for overall mortality reduction (most individual trials were not powered to detect a difference in overall mortality). ESC noted that the claim of decreased all-cause mortality is uncertain (as the 95% confidence intervals in the meta-analyses include the null).

To assist MSAC consideration, ESC requested that patient-relevant outcome gains from the two main trials and the economic evaluation also be summarised in absolute terms (e.g., absolute risk reductions and numbers needed to screen). See Tables 6 and 7 in Section 10.

ESC noted that the economic evaluation was based on a semi-Markov model. ESC considered that there were issues with the applicability of the clinical trial evidence and the need for an indirect comparison across trials which resulted in some uncertainty in estimating the incremental effects of screening over not screening. ESC noted that the utilities were pooled from systematic literature reviews and have high heterogeneity. The values do not appear to have validity for causal applications, and this may be overly conservative; however, ESC noted that this had been addressed through a sensitivity analysis.

ESC reviewed the model calibration and noted that while there was good transparency for inputs and outputs, inputs were manipulated for outputs to match comparable observed data, whether at baseline or over the short-term. ESC considered that an inevitable weakness of this approach is that various combinations of inputs may lead to matching the observed data but produce different model behaviour resulting in different outputs over the longer term. However, ESC considered that the approach taken was reasonable in light of limitations of the relevant data available. ESC also noted that, despite its acknowledged plausibility, the model was not dynamic and so could not represent changing factors such as risk profiles, smoking prevalence, screening technologies (which may result in changes in sensitivity and specificity), or anticipated costs and health outcomes of emerging treatments (such as immunotherapy and other targeted therapies).

ESC noted that the observed shifts in the stage of cancer at the time of initial diagnosis, and the increment between the screening and control arm in the proportion of patients at each cancer stage, has limited relevance to the Australian setting unless the control arm reflects the current Australian estimates of lung cancer stage at diagnosis. Therefore, the accuracy of the estimates used in the submission calibrated against earlier Australian data is uncertain.

ESC noted that the economic evaluation results were calculated as the incremental costs per number of lung cancer deaths prevented, percentage of overdiagnosed screen-detected cancers, number of overdiagnosed cases, false-positive screen results, life years gained (discounted) and quality-adjusted life years (QALYs) gained (discounted). ESC noted that the base case incremental cost-effectiveness ratio (ICER) per QALY gained was $83,545 for the proposed general population and $160,850 for the proposed Indigenous population. The ICER for the Indigenous population was higher due to higher incremental costs arising in part from higher rates of overdiagnosis. ESC considered that it is reasonable to allow for a higher cost-effectiveness threshold in this relatively small subgroup recognising its greater unmet clinical need.

However, ESC noted that the reported base case ICERs were based on 100% uptake, which ESC considered to be unreasonable. Adjusted general population ICERs ranged from $84,243 (90% uptake) to $93,470 (65% uptake with random screening attendance). ESC considered these ICERs to reflect more reasonable uptake rates. ESC noted there were also assumptions about utilities and cost inputs in the model that were accepted by both the modellers and the commentary to be conservatively biased against screening and that the pre-ESC response presented some revised ICERs based on less conservative assumptions. ESC considered that the revised ICER per QALY of $51,501 from the pre-ESC response (assuming no disutility for stage I and II lung cancers in the continuing phase only, a 25% reduction in costs for the initial phase of treating stage I and II lung cancers and a 75% reduction in costs for the continuing care phase for stage I and II lung cancers) should be considered a more plausible scenario from the economic evaluation. However, the ESC also considered that all these ICERs from the economic evaluation were also likely biased in favour of screening because they do not take into account the consequences of possible imperfections in Program implementation, such as errors, waste, inaction, mismanagement, poor coordination. Overall, the ESC considered that these reported ICERs are higher than what has usually been accepted for a screening program proposed to target asymptomatic individuals and that requires a substantial commitment of resources and cost to the health budget portfolio. ESC further considered that ICERs for a screening program could be reasonably expected to be lower than conventional ICERs for treatments, due to both a lower urgency of the unmet clinical need compared to that for a treatment, and also anticipating substantial downstream gains from an earlier intervention.

ESC noted the 46 overdiagnosed cases for every 100 lung cancer deaths prevented (6722/14,562), and the high number of false positives (112,159) estimated by the model. ESC reiterated its concerns about the number of overdiagnoses and the number of false-positives (with the number of false-negatives being a lesser concern) but agreed with the way these had been modelled. ESC agreed with the commentary that “effects of false-positive screen results on disutility are expected to be negligible”.

ESC noted the large financial impact to the MBS of the LDCT component of the Program – $10.9 million in year 1 to $54.7 million in year 6, and the associated costs of supporting the Program. ESC considered the LDCT costs to be slightly underestimated because they did not include people ageing into the Program each year by turning 55, people previously ineligible becoming eligible on a subsequent assessment of risk, Indigenous people aged between 50 and 54, and the use of mobile units. ESC noted that the ‘net cost’ modelling estimated downstream treatment costs only, and there was no financial analysis of any other downstream costs after LDCT to manage patients. ESC also noted that there were major discrepancies between this ‘net cost’ modelling and the economic model in their estimates of incremental downstream treatment costs. However, ESC noted the pre-ESC response from the applicant stated “The two modelling

exercises (economic evaluation and estimation of 'net costs') were sequential pieces of work, with the economic evaluation undertaken first followed by the 'net cost' modelling. The two models were based on different assumptions and were conducted for different (now historic) purposes". ESC therefore considered it would be difficult to rely on these financial estimates for budget planning.

ESC expressed concern about the proposal to use mobile radiology facilities for populations residing in areas classified as MM6 and MM7, and whether this is sufficient to ensure equity of access (these two areas accommodate 2.26% of the Australian population). ESC also queried whether the costs proposed sufficiently covered these facilities, and if the fees would remain the same for mobile services. However, ESC noted that assuming a higher cost for these mobile facilities would make no discernible difference to the ICER overall.

ESC discussed the importance of ongoing data collection of screened participants to record relevant patient outcomes in absolute terms as part of the evaluation of the Program. ESC considered that considerable data needed for such evaluation is already captured by GPs. ESC also considered that, in implementing the risk prediction tool for screening purposes, it would be important to record the full result for each patient, not just whether the patient met the 1.51% risk threshold. ESC considered that it would be desirable to extend risk prediction beyond the likelihood of cancer to also the likelihood of a favourable outcome from treatment, should cancer be found. ESC recommended that the data generated should be subject to regular evaluation by an independent group that is not connected to the agency responsible for the Program.

The key indicators for data collection should be reported as population rates (e.g., per 1,000 people screened as the denominator), not as proportion of cancers diagnosed (e.g., 5-year survival rate and stage shift – both use cancer diagnoses as denominator), as the proportion of cancers diagnosed is biased in a screening program setting due to overdiagnosed cases. Data collection could include recalls, screen positives, screen-detected cancers, interval cancers, follow-up interventions (number and mortality from), stage of cancer at diagnosis, lung cancer mortality and all-cause mortality.

To achieve this expansion in data collection and analysis to support the overall data and evaluation framework for outcomes monitoring, linkage to appropriate cancer treatment registries should be explored. ESC noted there is a Victorian Lung Cancer Registry, which collects patient-level information about diagnosis, treatment, and outcomes. ESC queried whether there were plans to expand this registry to a national program, as the registry has received support from the Medical Research Future Fund.

17. Applicant comments on MSAC's Public Summary Document

Cancer Australia appreciates the consideration of the application for a National Lung Cancer Screening Program by MSAC. Working with the economic modellers, further cost-effectiveness analyses and budget impact assessment will be undertaken to address MSAC's advice in relation to the need to:

- clarify the Australian economic model's face validity
- investigate the impact on the incremental cost-effectiveness ratio (ICER) of adjustments to the definition of the population eligible for screening and/or screening intervals
- consider a more complete financial analysis of the proposed Program.

Cancer Australia will submit a response to MSAC's concerns informed by this additional modelling for further consideration by MSAC.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

19. Attachments (see separate document)

Attachment 1: Detailed description of the proposed National Lung Cancer Screening Program

Attachment 2: Tables of RCTs of LDCT-based lung cancer screening programs

- Table 1: Characteristics of RCTs of LDCT-based lung cancer screening programs
- Table 2: Comparative safety outcomes of RCTs of LDCT-based lung cancer screening programs
- Table 3: Comparative effectiveness outcomes of RCTs of LDCT-based lung cancer screening programs

Attachment 3: Meta-analysed results of RCTs of LDCT-based lung cancer screening programs

Attachment 4: Justification of the selection of the risk prediction tool and threshold for referral to LDCT

Attachment 5: Justification of the selection of the nodule management protocol for the assessment of baseline LDCT scans

Attachment 6: Justification of the selection of the nodule management protocol assessment of new nodules identified by subsequent (incident or interval screening) LDCT scans

[redacted]

[redacted]