Australian Government

Medical Services Advisory Committee

Attachments to the Public Summary Document

Application No. 1699 – National Lung Cancer Screening Program

Applicant: **Cancer Australia**

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

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

Program component	Proposed option	Key source (published and/or consultation)	Alternatives to proposed option considered	Rationale and evidence base for proposed option (may include a cross-reference to a table below)	Proposed option subject to sensitivity analysis in clinical evaluation (Y/N)	Proposed option subject to sensitivity analysis in economic evaluation (Y/N)
Age threshold for starting screening	55 years	NLST[1] Weber et al (2017)[2]	<50 years 50 years	Older age is associated with higher lung cancer risk. In terms of optimal screening age, increasing the starting age is expected to inflate the model discrimination, yet leads to fewer life-years gained[3,4] . Conversely, lowering the starting age increases the sensitivity and yields more life-years gained, but at the cost of specificity and the number of required screens[5,3]. Analyses suggest that harms associated with starting screening before age 50 can exceed the benefits of lung cancer mortality reduction[4], and microsimulation cost-effectiveness analyses have suggested that screening before the age of 55 may not be cost-effective[6]. Validation of the PLCOm2012 risk prediction tool in an Australian population (Weber et al 2017)[2] indicated that the model was determined to perform best among participants aged 55-74 years. The two main RCTs, the NLST and the NELSON trial used an eligible age range of 55-74 years and 50-75 years respectively. The age range eligibility criterion for the NLST was 55-74 years, and this age range has been used in many of the cost-effectiveness studies, including that in Australia by Wade et al (2018)[7], in the US by Kumar et al 2018[8], and in Taiwan (Yang et al 2018)[9], all of which have shown cost-effectiveness using this screening age range in a variety of models. The lower age threshold of 55 years is recommended internationally, based on the substantial evidence base. A lower age of 50 years is recommended in the National Cancer Center Network (NCCN) guidelines, but these eligibility criteria also include the presence of 'an additional risk factor' in addition to a 20 or more pack-year smoking history.	No	Yes (Table 50 in economic evaluation report)
Age threshold for starting screening (Aboriginal and Torres Strait Islander people)	50 years	Australian Institute of Health and Welfare 2018. Cancer in Aboriginal & Torres Strait Islander people of Australia. Accessed April 2020; https://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/table-of-contents	45 years 55 years	For Aboriginal and Torres Strait Islander people, given their higher prevalence of smoking and their lower age for lung cancer diagnosis and mortality, an age range of 50 to 74 years is proposed. Indigenous Australians compared to non-Indigenous Australians have higher rates of lung cancer incidence and mortality rates and diagnosis at an earlier age. The age-specific lung cancer rates for Indigenous Australians compared to non-Indigenous Australians are higher: • for the 50-54yr age group the lung cancer incidence rate for Indigenous Australians is 77 per 100,000 compared with 33 per 100,000 for non-Indigenous Australians	No	Yes (Table 54 in economic evaluation report)

[1] 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.

[2] 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.

[3] Ten Haaf K, Bastani M, Cao P, Jeon J, Toumazis I, Han SS, et al. A comparative modeling analysis of risk-based lung cancer screening strategies. J Natl Cancer Inst. 2019.

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

[5] 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.

[6] Ten Haaf K, Tammemagi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. PLoS Medicine / Public Library of Science. 2017;14(2):e1002225.

[7] Wade S, Weber M, Caruana M, Kang YJ, Marshall H, Manser R, et al. Estimating the Cost-Effectiveness of Lung Cancer Screening with Low-Dose Computed Tomography for High-Risk Smokers in Australia. Journal of Thoracic Oncology. 2018;13(8):1094-105.

[8] Kumar V, Cohen JT, van Klaveren D, Soeteman DI, Wong JB, Neumann PJ, et al. Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis. Ann Intern Med. 2018;168(3):161-9.

[9] Yang W, Qian F, Teng J, Wang H, Manegold C, Pilz LR, et al. Community-based lung cancer screening with low-dose CT in China: Results of the baseline screening. Lung Cancer. 2018;117:20-6.

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				• for the 55-59yr age group the lung cancer incidence rate for Indigenous Australian is 134 per 100,000 compared with 59 per 100,000 for non-Indigenous Australians • the lung cancer incidence rate for Indigenous Australians aged 50-54yrs (77 per 100,000) is higher than the incidence rate for non-Indigenous Australians aged 55-59yrs (59 per 100,000). The lower age rate was supported by consultation including with Indigenous health professionals who advised it is not only acceptable to target a younger Aboriginal and Torres Strait Islander population but considered necessary.		
Age threshold for stopping screening	74 years	NLST[1] NELSON[10] Weber et al (2017)[2] Wade et al (2018)[7] Ten Haaf et al (2019)[3]	80 years No cessation age	The two main RCTs, the NLST and the NELSON trial, used an eligible age range of 55-74 years and 50-75 years respectively. Criss et al (2019)[11] compared the cost-effectiveness of different stopping ages for different screening strategies and showed that increasing the age at which to stop screening resulted in a greater reduction in mortality but also led to higher costs and higher overdiagnosis rates. The age range eligibility criterion for the NLST was 55-74 years, and this age range has been used in many of the cost-effectiveness studies, including that in Australia by Wade et al (2018)[7], in the US by Kumar et al 2018[8], and in Taiwan (Yang et al 2018)[9], all of which have shown cost-effectiveness using this screening age range in a variety of models. The United States Preventive Services Taskforce (USPSTF) made a recommendation in 2013 to extend the previously recommended age inclusion criterion from 55-74 years as used in the NLST, to 55-80 years (USPSTF 2013). The Centers for Medicare & Medicaid Services (CMS 2015) later indicated that there was inadequate evidence to cover LDCT screening for individuals outside of the range of 55-77 years of age. Ten Haaf et al (2019)[3] compared selected risk-based for stopping ages of 77 and 75 years and found similar comparative effectiveness to the USPSTF stopping age of 80 years. It was noted that the risk thresholds corresponding to selected outcomes differed slightly by stopping ages, however no further detail was provided. Ten Haaf et al also considered risk-based strategies screening between ages 55 and 80 years and accounting for limited life expectancy (i.e., excluding individuals with life expectancies <5years), which showed greater selection efficiency than USPSTF criteria (2019). Based on these findings, life-expectancy information could augment risk estimates to personalise screening stopping ages and may allow for personalised overdiagnosis risk assessments. In the National Health Service (NHS) protocol in the UK, participants 'exit the program at 75 or 76 years of age, depending on whether the timing of the final LDCT is 12 or 24 months from baseline'[12].	No	Yes (Table 54 in economic evaluation report)
Risk prediction tool for initial referral or not to LDCT	PLCOm2012	Weber M, et al 2017[2] Tammemagi MC, et al 2014[13]	PLCOm2014 LCDRAT/LCRAT Bach Liverpool Lung Project LLP2008, LLPv2 Spitz models	*See Attachment 4 below.* Risk prediction tools, which use algorithms to calculate an individual's risk of lung cancer based on a combination of a variety of established sociodemographic and health-related factors, perform better in the identification of individuals for targeted lung cancer screening than eligibility criteria of age and smoking alone. The PLCOm2012 model has consistently performed well in validation studies and is referenced in international screening guidelines and program protocols, is currently the only risk prediction model to be tested in an Australian population, and has shown positive interim results in the International Lung Screening Trial (ILST). At present, it is the most feasible model for a national LDCT-based screening program in Australia.	No	No

[10] 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.

[11] Criss SD, Cao P, Bastani M, ten Haaf K, Chen Y, Sheehan DF, et al. Cost-effectiveness analysis of lung cancer screening in the United States. Annals of Internal Medicine. 2019;171(11):796-804.

[12] 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/.

[13] 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.

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			USPSTF eligibility criteria	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. Tammemagi (2019)[14] demonstrated that, compared with NLST-like criteria, accurate lung cancer risk prediction models are more sensitive in selecting individuals who develop lung cancer, have higher positive predictive values, have a lower number needed to screen to avert 1 lung cancer death, and are more cost effective. PLCOm2012 is the model showing best concordance between numbers of lung cancer cases predicted and reported in registries[15]. The importance of validating risk prediction models in specific countries was highlighted in a recent publication by Robbins et al (2021[16]). In this analysis, LCDRAT/LCRAT was determined to be best for the UK, very good for PLCOm2012, and lowest for LLPv2. A similarly recent publication examining 9 of the risk prediction models currently available indicated that any of four models – Bach, PLCOm2012, LCRAT, LCDRAT – could be used to select smokers in the US population at greatest risk of lung cancer incidence or lung cancer deaths[17]. PLCOm2012 is the only model to have been validated in the Australian population[2]. The PLCOm2012 model has been demonstrated to provide superior performance compared to the NLST eligibility criteria (age, smoking), with improved sensitivity and PPV, and no loss of specificity. Tammemagi (2019)[14] noted that the PLCOm2012 has been validated by research teams in several countries. The PLCOm2012 model (Tammemagi 2013)[18], 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. To date, the PLCOm2012 is the most frequently cited risk-model in screening guidelines and protocols[19,12]. The PLCOm2014 model is a version of the PLCOm2012 model for never smokers, however no individual in the 65,711 never smokers in the dataset examined by Tammemagi et al (2014) were found to have a lung cancer risk of ≥1.51[13].		
Risk prediction threshold for initial referral or not to LDCT	PLCOm2012 ≥0.0151 (1.51%)	Tammemagi et al (2014)[13] Weber M, et al 2017[2]	Absolute increments of 0.1% between 0.9% and 3.6%	The PLCOm2012 risk threshold of ≥0.0151 over 6 years was the threshold for which a lung cancer mortality benefit of LDCT screening versus CXR was observed in the PLCO and NLST datasets[13]. In this study, 8.8% fewer individuals were selected for screening and 12.4% more lung cancers were detected compared to the USPSTF criteria. While Tammemagi 2014[13] has indicated that it is unclear at what threshold of risk screening should be recommended, the PLCOm2012 ≥1.5% has been proposed as an appropriate threshold for screening when using this model. Tammemagi indicated that other thresholds may be suitable for different models and in different settings. In preparation for the HR_LCSP, Cancer Care Ontario (CCO) prepared a health technology assessment which included a MISCAN microsimulation modelling-based cost effectiveness analysis (CEA). As part of the CEA, 576 different NLST-like and NELSON-like selection criteria were evaluated[6]. Ten models were identified which were on the efficiency frontier, that is, saved the most life-years per a given cost. A preferred	No	Yes (Table 50 in economic evaluation report)

[14] Tammemagi MC, ten Haff K, et al. Development and Validation of a Multivariable Lung Cancer Risk Prediction Model That Includes Low-Dose Computed Tomography Screening Results A Secondary Analysis of Data From the National Lung Screening Trial JAMA Network Open. 2019;2(3):e190204.

[15] Hűsing A, Kaaks R. Risk prediction models versus simplified selection criteria to determine eligibility for lung cancer screening: an analysis of German federal-wide survey and incidence data.

[16] Robbins, H.A., Alcala, K., Swerdlow, A.J. et al. Comparative performance of lung cancer risk models to define lung screening eligibility in the United Kingdom. Br J Cancer 124, 2026–2034 (2021). https://doi.org/10.1038/s41416-021-01278-0

[17] Katki HA, Kovalchik SA, Petito LC, et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Ann Intern Med. 2018;169(1):10-9. doi:10.7326/M17-2701

[18] 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.

[19] 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.

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				model was chosen which was believed to be acceptable to government budgets. The preferred model had an incremental cost effectiveness ratio of just under $50,000 Canadian. The PLCOm2012 model was compared to the MISCAN preferred model and at a ≥2% risk threshold it would lead to the same number of individuals being screened but had significantly higher sensitivity and PPV when evaluated in PLCO control smokers. Thus, the CCO's HR_LCSP selects individuals for screening using PLCOm2012 ≥2% risk as this approach was considered to be most efficient while being affordable to the health care system. The PLCOm2012 is currently the only lung cancer risk prediction model to have been validated in the Australian population[2]. In this retrospective evaluation in a subset of the 45 and Up study, a threshold of ≥1.51% risk was confirmed as appropriate for identifying those at high-risk of lung cancer within 6 years, achieving high PPV and sensitivity, with only minimal loss in specificity at this threshold, in comparison with the NLST eligibility criteria[2]. The NCCN guidelines (Version 3.2018) suggest a threshold of ≥1.3% risk over 6 years[19], while the recently released NHS screening protocol suggests a threshold of ≥1.51% risk over the same period[12]. The PLCOm2012 model with a risk threshold of ≥1.51% over 6 years is being applied in current screening trials – the ILST – and in program implementation elsewhere – e.g., the Manchester Lung Health Check[20]. Concerned that retrospective analyses may not translate well when applied in implemented screening programs[21], Ten Haaf et al evaluated the long-term effects of risk-based strategies with different risk-models and risk thresholds in the general population using natural history modelling[3]. Evaluating Bach, PLCOm2012 and LCDRAT models at varying thresholds (absolute increments of 0.1%, between 0.9% and 3.6%), a total of 363 screening strategies were used to determine optimal thresholds that result in a net balance of long-term benefits (such as life-years gained and mortality reduction) and harms (such as overdiagnosis). Results indicated that strategies requiring similar screens among individuals aged 55–80 years as the USPSTF criteria (corresponding risk thresholds: Bach 2.8%; PLCOm2012 1.7%; LCDRAT 1.7%) averted considerably more lung cancer deaths, however life-years gained were only modestly higher, and overdiagnosed cases were greater for risk-based strategies. The threshold of ≥1.51 for the PLCOm2012 model is supported by published cost-effectiveness analyses. For example, Hinde et al[22] assessed the cost-effectiveness of the Manchester Lung Health Check program which used this threshold for the PLCOm2012 to define the screening population and indicated positive findings in support of LDCT screening.		
Confirm the repeat use (or not) of risk prediction tool if previously assessed but not referred to LDCT	Yes	N/A		Participants who are assessed by the risk prediction to be ineligible, i.e., do not meet the risk prediction threshold could have another risk assessment at a future date to determine eligibility.	No	No
Confirm the time interval to (frequency of) repeat use of risk prediction tool if previously assessed, but not referred to LDCT	No defined time interval or frequency	N/A		Time interval or frequency for ineligible participants to be re-assessed has not been defined.	No	No
LDCT as the screening technology	LDCT with volumetric analysis	NELSON[10] NLST[1]		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 CXR in the diagnosis of lung cancer.	No	Yes (Table 50 in economic evaluation report)

[20] 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.

[21] 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.

[22] Hinde S, Crilly T, Balata H, Bartlett R, Crilly J, Barber P, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. Lung Cancer. 2018;126:119-24.

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				LDCT is the screening intervention used across almost all of the lung cancer screening trials with the comparator being no screening or CXR. CXR was the comparator condition in the NLST and in clinical trials from the 2000s that predate the NLST. Of note 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. In relation to rationale for volumetric analysis, volumetric assessment of nodules in the NELSON trial appear to have contributed to a very small rate of false positives (1.2%).		
Nodule management protocol for assessment of baseline LDCT scan	PanCan (most recent version)	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. Van Riel SJ, Ciompi F, Jacobs C, Winkler Wille MM, Scholten ET, Naqibullah M, et al. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines. European Radiology. 2017;27(10):4019-29. 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. Tremblay A, Taghizadeh N, MacGregor JH, Armstrong G, Bristow MS, Guo LLQ, et al. Application of Lung-Screening Reporting and Data System Versus PanCanadian 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.	Lung-RADS	*See Attachment 5 below.* Nodule management protocols enable accurate assessment and classification of lung nodules and improve LDCT screening sensitivity and specificity. 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. PanCan protocol has the highest sensitivity for baseline scans. The PanCan (or Brock University) nodule malignancy probability calculator[23] was developed from trial data in which individual nodules were longitudinally evaluated. It pertains to nodules detected on baseline scans that accounted for 75% of the lung cancers found in the first 5 years[24]. Cancer Australia's Lung Cancer Advisory Group indicated support of using the combination of the PanCan risk-prediction model for baseline nodule assessment and Lung-RADS 1.1 for assessment of all new nodules found after baseline screening, with the adaptation of two-yearly screening for people who had a negative LDCT scan.	No	No
Nodule management protocol assessment of new nodules identified by subsequent (incident or interval screening) LDCT scans	Lung-RADS1.1 (or most recent version)	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.	PanCan	*See Attachment 6 below.* Nodule management protocols enable accurate assessment and classification of lung nodules and improve LDCT screening sensitivity and specificity. 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. PanCan is only validated for baseline scans. The American College of Radiology developed the Lung-RADS classification system[25]. Cancer Australia's Lung Cancer Advisory Group indicated support of using the combination of the PanCan risk-prediction model for baseline nodule assessment and Lung-RADS1.1 for assessment of all new nodules found	No	No

[23] McWilliams A, Tammemägi 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;369:910–919.

[24] Tammemägi MC, Schmidt H, Martel S, McWilliams A, Goffin JR, Johnston MR, et al. PanCan Study Team. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncol.* 2017;18:1523–1531.

[25] American College of Radiology. Lung CT screening reporting & data system (Lung-RADS V1.1). Reston, VA: ACR; 2019 [accessed 2019 July 31] Available from https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads.

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				after baseline screening, with the adaptation of two-yearly screening for people who had a negative LDCT scan.		
Time interval to (frequency of) repeat LDCT-based screening if not referred for further investigation	24 months	NELSON trial (Horeweg, 2013a; Yousaf-Khan, 2017) MILD trial (Pastorino 2012)	1 year 2.5 years	There is no consensus about the optimal screening interval, however either a 1- or 2-year interval appear to be more favourable than a 2.5-year interval, with the latter being identified as too long based on evidence from the NELSON trial. In the NELSON trial, the intervention (screening) group received LDCT screening at baseline (round 1), after 1 year (round 2), after 3 years (round 3) and 5.5 years (round 4) after baseline. Findings from the first three rounds were published in 2013, and indicated that a 'two-year interval between the second and the third screening rounds did not lead to a significantly higher proportion of advanced stage lung cancers compared with the one-year screening interval between the first and second rounds'. The authors reported the lung cancer detection rate was relatively stable across the first three rounds[26,27,28]. The analyses also indicated that, despite the 2-year interval between the second and third rounds, specificity and sensitivity of the first three rounds were higher compared with other screening trials, which suggests that lung cancer screening using biennial screening regimens after an initial screening round would be effective. In the MILD trial, when comparing results between the annual and biennial screening groups, it was evident that the biennial group reduced the number of required LDCT scans by approximately one-third whilst maintaining similar mortality rates, the proportion of stage II-IV cancers, and interval cancers[29]. Biennial screening was shown to reduce exposure to potential harms[30].	No	Yes (Table 50 in economic evaluation report)
Repeat use of risk prediction tool if previously referred to LDCT but not referred for further investigation	No	Consultation with Cancer Australia's Lung Cancer Advisory Group		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 PLCOm2012 risk prediction tool.	No	No
Other time intervals to (frequency of) repeat LDCT-based screening if referred for different types of further investigation	Low malignancy risk: 12 months Moderate malignancy risk: 3 months	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. Lim KP, Marshall H, Tammemägi M et al. Protocol and Rationale for the International Lung Screening Trial (ILST). Ann Am Thorac Soc 2020; Feb 3: doi: 10.1513/AnnalsATS.201902-102OC		Based on the guidance of nodule management protocol.	No	No
Management of incidental findings	Managed according to relevant clinical guidelines	Consultation with stakeholders including Cancer Australia's Lung Cancer Advisory Group.		Incidental findings range from benign or insignificant findings through to clinically significant pulmonary, cardiovascular, or gastrointestinal co-morbidities. Incidental findings would be managed outside the proposed Program according to relevant clinical guidelines.	No	Yes (Table 51 in economic evaluation report)
Use of mobile LDCT facilities, incorporating referral to LDCT using the	Mobile screening van	Cancer Australia 2020. Report on the Lung Cancer Screening enquiry Surry Hills, NSW 2020.		The most appropriate pathway to LDCT would vary across Australia and within implementation sites. In most cases, private sector radiology services would be the provider. State radiology services can also provide	No	No

[26] Horeweg N, van der Aalst CM, Thunnissen E, Nackaerts K, Weenink C, Groen HJ, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. Am J Respir Crit Care Med. 2013;187(8):848-54.

[27] Horeweg N, Nackaerts K, Oudkerk M, de Koning HJ. Low-dose computed tomography screening for lung cancer: results of the first screening round. J Comp Eff Res. 2013;2(5):433-6.

[28] Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J. 2013;42(6):1659-67.

[29] Sverzellati N, Silva M, Calareso G, Galeone C, Marchianò A, Sestini S, et al. Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen. Eur Radiol. 2016;26(11):3821-9.

[30] Pastorino U, Sverzellati N, Sestini S, Silva M, Sabia F, Boeri M, et al. Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening. European Journal of Cancer. 2019;118:142-8.

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risk prediction tool and including centralised support via the "virtual diagnostic hub"				access to LDCT and in other locations, particularly in remote and very remote locations, access to LDCT would be by means of mobile vans as part of a broader access strategy. With some exceptions, the existing infrastructure of LDCTs in each State/Territory is likely to meet the demand generated by the roll out of the proposed Program. Assessment so far indicates shortfalls of infrastructure in Tasmania and in remote locations on the mainland.		
Confirm definition of geographical areas using fixed and mobile facilities (the latter being for remote/rural Australia)	ASGS remoteness areas: major cities; inner regional Australia; outer regional Australia; remote Australia; very remote Australia; other	Cancer Australia 2020. Report on the Lung Cancer Screening enquiry Surry Hills, NSW 2012.		To ensure equitable access to CT scans across Australia, mobile scanning facilities would be required for the remote and very remote areas of Australia.	No	No
Including prison populations in the Program	Mobile vans	Cancer Australia 2020. Report on the Lung Cancer Screening enquiry Surry Hills, NSW 2012.		Access to LDCT for eligible individuals in correctional facilities will be discussed with states and territories as part of the broader access strategy.	No	No
Health care professionals to undertake risk prediction to refer to LDCT in fixed facilities	Risk prediction is undertaken by an authorised health professional	Cancer Australia 2020. Report on the Lung Cancer Screening enquiry Surry Hills, NSW 2012.		Risk prediction is undertaken by an authorised health professional who is able to refer eligible participants for LDCT.	No	No
Register	Register	Cancer Australia 2020. Report on the Lung Cancer Screening enquiry Surry Hills, NSW 2012.		A register would be a core component of the proposed Program and essential to ensuring that national quality assurance standards would be maintained. The register would have a central role in the effective functioning of the Program. Its three core capabilities would be: • Data collection and storage • Data sharing and analytics to support governance, reporting, research, and evaluation • Correspondence and management of participants. Further, a number of register requirements would be essential for the initial rollout of the Program. These include: • issuing participant communication and reminders • managing rescreening cadence • capturing, consolidating, managing, and presenting data • allowing for scalability and future-proofing of the Program.	No	No

Attachment 2: Tables of randomised controlled trials of LDCT-based lung cancer screening programs

Table 1: Characteristics of randomised controlled trials of LDCT-based lung cancer screening programs

Trial ID	Characteristics						Country/ counties participating in the trial	Trial completed or ongoing	Median duration of follow-up for results presented (years)	Population basis of the analysis (ITT or specific other population)
	No of participants	Screening tests	Eligible age range (years)	Eligible smoking history (pack-years)	Eligible smoking cessation (years since quit)	Other inclusion/exclusion criteria				
AME[9] 2013	6657 (3114 males, 3543 females)	LDCT vs no screening (LDCT every two years for three rounds)	45-70	Smoking optional risk factor; ≥20 pack-years	≤15	**Inclusion:** At least one of: family history of any type of cancer; previous history of cancer; occupational exposure to carcinogenic agents; passive smoker (>2 hours per day in homes/indoor workplace for >10 years); exposure to cooking oil fumes (>50 dish-years)	China	Completed	2	Gender
DANTE[31] 2001	2450 (male participants only)	Baseline CXR, sputum cytology & LDCT vs usual care (five annual LDCT scans: one baseline and four incidence scans)	60-74	≥20 pack-years	<10	**Exclusion:** Severe comorbidity; life expectancy <5 years; previous malignancy (except non-melanoma skin cancer); early squamous cancer of the larynx/oral cavity <5 years	Italy	Completed	8.35	No intention-to-treat or population analysis
DLCST[32] 2004	4104 (2267 males, 1837 females)	LDCT vs no screening (five annual LDCT scans: one baseline and four incidence scans)	50-70	≥20 pack-years	<10	**Exclusion:** History of lung cancer, breast cancer, melanoma, or hypernephroma; other malignant disease <5 years; tuberculosis <2 years; life expectancy <10 years; chest CT screening <12 months	Denmark	Completed	10	Gender
ITALUNG [33] 2004	3206 (2074 males, 1132 females)	LDCT vs no screening (annual invitation to LDCT scans for four years)	55-69	≥20 pack-years	≤8	**Exclusion:** History of previous cancer other than non-melanoma skin cancer	Italy	Completed	9	No intention-to-treat or population analysis
LUSI[34] 2007	4052 (2622 males, 1430 females)	LDCT vs no screening (five annual LDCT scans: one baseline and four incidence scans)	50-69	36 pack-years (≥15 cigs/day for ≥25 years or ≥10 cigs/day for ≥30 years)	<10	**Exclusion:** History of lung cancer or other malignancy (except basal cell carcinoma); history of a disease that would preclude surgical and medical treatment of lung cancer; other serious illnesses	Germany	Completed	8.89	Gender
MILD[35] 2005	4099 (2716 males, 1383 females)	LDCT vs no screening (LDCT scans further randomised to annual or biennial for four scans)	49-75	≥20 pack-years	<10	**Exclusion:** History of malignant disease	Italy	Completed	10	No intention-to-treat or population analysis
NELSON [10,36] 2003	15,822 (13,195 males, 2594 females)	LDCT vs no screening (LDCT scans at baseline, Year 1, Year 3, and Year 5.5)	50-75	42 pack-years (≥15 cigs/day for ≥25 years or ≥10 cigs/day for ≥30 years)	≤10	**Exclusion:** Moderate/bad self-reported health; Inability to climb two flights of stairs; weight ≥140 kg; lung cancer <5 years ago or still under treatment; current or past melanoma; renal or breast cancer; chest CT <1 year	Netherlands & Belgium	Completed	10	Gender
NLST[1] 2002	53,454 (31,532 males, 21,922 females)	LDCT vs CXR (three annual scans)	55-74	≥30 pack-years	≤15	**Inclusion:** Ability to lie on the back with arms raised over the head **Exclusion:** Previous diagnosis of LC; CXR within 18 months; haemoptysis; weight loss > 6.8 kg in preceding year	USA	Completed	7.4	Intention-to-screen
UKLS[37,38] 2011	4055 (3036 males, 1019 females)	LDCT vs no screening (baseline LDCT scan only)	50-75	LLPv2 risk prediction model applied at 5% risk of lung cancer risk over 5 years.		**Exclusion:** Comorbidity which would unequivocally contraindicate either screening or treatment if lung cancer were detected; thoracic CT performed within 1 year preceding the invitation to be screened	UK	Completed	7.3	Intention-to-treat

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Table 2: Comparative safety outcomes of randomised controlled trials of LDCT-based lung cancer screening programs

Trial ID	Overdiagnosis (95% CI)	False positive rates (95% CI)	False negative rates (95% CI)	Psychological consequences of LDCT and subsequent findings	Study conclusions
AME[9] 2013		21.8% (753/3460)			In this study, at baseline, non-calcified nodules ≥4 mm were detected in 804/3512 (22.9%) participants on baseline low-dose CT, and 6.3% (51 of 804) of these were malignant.
DANTE[31] 2001					No information was provided on comparative safety outcomes.
DLCST[32] 2004	67.2% (in Heleno et al 2018)	3% (in Saghir et al 2012)		Reduced psychological consequences (anxiety, behaviour, dejection, and negative impact on sleep, respectively) for LDCT: Prevalence round (Year 1). p-values: 0.07, 0.05, 0.03, and 0.20 Incidence round (Year 2): p-values: 0.03, 0.01, 0.01, and 0.10 Less worsening of psychological consequences in LDCT vs. control	Overdiagnosis could be a substantial problem associated with lung cancer screening in a population with these characteristics. There were both relatively few false-positive screens and few interval cancers in the DLCST.
ITALUNG[33] 2004	Nil				Together with the high false positive rate, overdiagnosis is the major potentially harmful effect of LDCT screening. Although further studies are necessary to confirm our results, the comparison of the number of lung cancer cases diagnosed in the two groups in the ITALUNG study does not suggest overdiagnosis after an adequate follow-up period.
LUSI[34] 2007					Also, more precise estimates are needed for potential lung cancer overdiagnosis—a major potential adverse effect of LDCT screening.
MILD[35] 2005					No information was provided on comparative safety outcomes.
NELSON[10,36] 2003	8.9% (−18.2% to 32.4%) over extended follow-up (11 years, 5.5 years after final screening round)	1.2%	0.1% (0.1% to 0.1%)	No statistically significant differences were found in in any HRQoL scores or psychological consequence over time between the screen and control groups	Volume CT screening enabled a significant reduction of harms (e.g., false positive tests and unnecessary workup procedures), without jeopardizing favourable outcomes.
NLST[1] 2002	18.5% (5.4% to 30.6%)	23.3% (22.79% to 23.81%)		No statistically significant differences between LDCT and CXR for any of the outcomes	In addition to the high rate of false positive results, two other potentially harmful effects of low-dose CT screening must be mentioned. Overdiagnosis, a major source of controversy surrounding low-dose CT lung-cancer screening, results from the detection of cancers that never would have become symptomatic. Although additional follow-up would be necessary to measure the magnitude of overdiagnosis in the NLST, a comparison of the number of cancers diagnosed in the two trial groups suggests that the magnitude of overdiagnosis with low-dose CT as compared with radiographic screening is not large.
UKLS[37,38] 2011		3.6%	6.7%		No other information was provided on comparative safety outcomes.

Table 3: Comparative effectiveness outcomes of randomised controlled trials of LDCT-based lung cancer screening programs

Trial ID	Lung cancer deaths	Overall deaths	Lung cancers detected	Stage at diagnosis						Study conclusions
				Cohort	I	II	III	IV	Unknown	
AME[9] 2013			LDCT: 1.5% (51/3512) Control: 0.3% (10/3145)	LDCT	48 (94%)	1 (2%)	1(2%)	0	1(2%)	The detection at an earlier stage represents a stage shift and subsequently a probable mortality rate reduction in the future. Compared to standard care, LDCT led to a 74.1% increase in detecting early-stage lung cancer.
				Control	2 (20%)	3 (30%)	1 (10%)	4 (40%)	0	
DANTE[31] 2001	LDCT: 4.7% (59/1264) Control: 4.6% (55/1186) HR: 0.99 95% CI: 0.69 to 1.43	LDCT: 14.2% (180/1264) Control: 14.8% (176/1186) HR: 0.95 95% CI: 0.77 to 1.16	LDCT: 8.23% (104/1264) Control: 6.07% (72/1186) p = 0.0418	LDCT	47 (45%)					In the DANTE study, patients with both early and advanced disease were increasingly detected in the LDCT arm after a drop after the baseline screen, and in the end no stage shift could be observed. Lung cancer-specific and all-cause mortality were unfortunately similar in the screening and in the control arm. Given the limited statistical power of the DANTE trial, our data do not allow making a definitive statement about whether or not LDCT screening is effective in reducing lung cancer mortality.
				Control	16 (22.2%) RR: 2.03 95% CI: 1.26 to 3.29					
DLCST[32] 2004	LDCT: 1.9% (39/2052) Control: 1.9% (38/2052) HR: 1.03 95% CI: 0.66 to 1.60	LDCT: 8.0% (165/2052) Control: 7.9% (163/2052) HR: 1.02 95% CI: 0.82 to 1.27		LDCT	50 (50%)					No statistically significant effects of CT screening on lung cancer mortality were found.
				Control	8 (15.1%) RR: 3.31 95% CI: 1.70 to 6.46					
ITALUNG [33] 2004	LDCT: 43 (29.3 per 10,000 person-years) Control: 60 (42.1 per 10,000 person-years) RR: 0.70 95% CI: 0.47 to 1.03	LDCT: 154 (105.1 per 10,000 person-years) Control: 181 (127.0 per 10,000 person-years) RR: 0.83 95% CI: 0.67 to 1.03	LDCT: 7 (49.9 per 10,000 person-years) No screening: 1 (53.7 per 10,000 person-years) RR: 0.93 95% CI: 0.67 to 1.30	LDCT	24 (36%)	5 (7%)	9 (13%)	24 (36%)	5 (7%)	Despite the lack of statistical significance, the ITALUNG trial outcomes suggest that LDCT screening could reduce lung cancer and overall mortality. The ITALUNG study has confirmed that LDCT screening, in conjunction with improvement of treatment strategies in early stage lung cancer cases and effective national policies for smoking cessation, is an important tool for the reduction of deaths from lung cancer.
				Control	8 (11%)	5 (7%)	8 (11%)	35 (49%)	15 (21%)	
LUSI[34] 2007	LDCT: 1.4% (29/2029) Control: 2.0% (40/2023) RR: 0.72 95% CI: 0.45 to 1.16	LDCT: 7.3% (148/2029) Control: 7.4% (150/2023) RR: 0.98 95% CI: 0.79 to 1.22	LDCT: 4.2% (85/2029) Control: 3.3% (67/2023) p = 0.16	LDCT	48 (56.5%)					Findings from LUSI are in line with those from other trials, including the NLST, that suggest a stronger reduction of lung cancer mortality after LDCT screening among women as compared to men. This heterogeneity could be the result of different relative counts of lung tumour subtypes occurring in men and women.
				Control	6 (9.0%) RR: 6.31 95% CI: 2.87 to 13.84					
MILD[35] 2005	LDCT: 2.3% (40/1723) Control: 1.7% (40/2376) p = 0.14	LDCT: 6.2% (106/1723) Control: 5.8% (137/2376) p = 0.61	LDCT: 3.5% (60/1723) Control: 4.1% (98/2376) p = 0.29	LDCT	49 (50%)	4 (4.1%)	16 (16.3%)	29 (29.6%)		The MILD trial provides additional evidence that prolonged screening beyond 5 years can enhance the benefit of early detection and achieve a greater overall and lung cancer mortality reduction compared with the NLST.
				Control	13 (21.7%) p < 0.0004	5 (8.3%)	10 (16.7%)	32 (53.3%)		
NELSON1 [10,36] 2003	LDCT: 156 (2.5 per 1000 person-years) Control: 206 (3.3 per 1000 person-years) Absolute risk difference: 0.8 deaths per 1000 person-years RR: 0.76 95% CI: 0.61 to 0.94		5.2% (341 of 6583*) *NELSON male cohort	LDCT	673 (39.6%)	145 (8.5%)	298 (17.5%)	468 (27.5%)	112 (6.6%)	The NELSON trial showed that volume CT lung-cancer screening, with low rates of follow-up procedures for test results suggestive of lung cancer, resulted in substantially lower lung-cancer mortality than no screening among high-risk persons. The minimum 10-year follow-up for the NELSON trial has been realized, and full data on incidence, mortality and cause of death are equally available for both arms. A (non- significant) 41.8% lung cancer mortality reduction has been achieved in the small subset of 2,382 Dutch women. Post-hoc analysis shows a 51.4% (p = 0.04) lung cancer mortality reduction at 8 years of FU. Data for the full cohort will be presented on behalf of the NELSON investigators.
				Control	462 (27.5%)	153 (9.1%)	321 (19.1%)	597 (35.5%)	143 (8.5%)	
NLST[1] 2002	LDCT: 247 deaths per 100,000 person-years CXR: 309 deaths per 100,000 person-years RRR: 20.0% 95% CI: 6.8% to 26.7%	LDCT: 1877 CXR: 2000 RRR: 6.7% 95% CI: 1.2% to 13.6%	LDCT: 645 lung cancers per 100,000 person-years CXR: 572 lung cancers per 100,000 person-years RR: 1.13 95% CI: 1.03 to 1.23	LDCT	119 (58.9%)	19 (9.4%)	33 (16.3%)	19 (9.4%)	13 (6.4%)	Screening with the use of low-dose CT reduces mortality from lung cancer.
				Control	20 (14.1%)	10 (7%)	28 (19.9%)	73 (51.8%)	10 (7.1%)	
UKLS[37,38] 2011	LDCT: 1.5% (30/1987) Control: 2.3% (46/1981) RR: 0.65 95% CI: 0.41 to 1.02	LDCT: 12.4% (246/1987) Control: 13.4% (266/1981) RR: 0.91 95% CI: 0.77 to 1.09	LDCT: 4.3% (86/1987) Control: 3.8% (75/1981) RR: 1.15 95% CI: 0.84 to 1.57	LDCT	45 (64.3%)	9 (12.9%)	9 (12.9%)	7 (10.0%)	16	The UKLS trial of single LDCT indicates a reduction of lung cancer death of similar magnitude to the NELSON and NLST trials and was included in a meta-analysis of nine randomised trials which provides unequivocal support for lung cancer screening in identified risk groups.
				Control	12 (21.8%)	6 (10.9%)	10 (18.2%)	27 (49.1%)	20	

Attachment 3: Meta-analysed results of randomised controlled trials of LDCT-based lung cancer screening programs

Meta-analysis (Author, Year, ID)	Study characteristics					Results							Limitations (risk of bias/authors identified)	Author conclusions
	No of participants	RCTs included*	RCTs excluded	Search period	Eligibility criteria	Lung cancers detected	Stage of diagnosis	Lung cancer mortality	All-cause mortality	Overdiagnosis	False positive rate	False negative rate		
Field et al. 2021[38]	94,384	UKLS NELSON NLST LUSI LSS ITALUNG DLCST DANTE	AME: less than 3 years median follow up	1946 – 2 November 2020	**Inclusion** Studies with all the following: -RCTs of LDCT screening for lung cancer -Non-LDCT control arm -High-risk population of adults aged >49 years -Measure lung cancer mortality with at least 3 years median follow up			LDCT vs control RR: 0.84 95% CI: 0.76 to 0.92 I^2 = 14.2% p = 0.312	LDCT vs control RR: 0.97 95% CI: 0.794 to 1.00 I^2 = 0% p = 0.611					In conclusion the meta-analysis incorporating the results from nine RCTs provides further support for lung cancer screening by low-dose chest CT.
Hoffman et al. 2020[39] ID not registered/ provided	96,559	LSS DANTE NLST NELSON DLCST ITALUNG MILD LUSI AME		January 2017 – April 2020	**Inclusion:** RCTs of CT that reported lung cancer and/or overall mortality data		LDCT vs control Stage 1 cancers detected RR: 2.73 95% CI: 1.90 to 3.91 I^2 = 79% 95% CI: 58% to 89%	LDCT vs control RR: 0.84 95% CI: 0.75 to 0.93 I^2 = 0% 95% CI: 0% to 64%	LDCT vs control RR: 0.96 95% CI: 0.91 to 1.01 I^2 = 0% 95% CI: 0% to 66%	33%	8% 95% CI: 4% to 15%		Risk of bias low. Population generalisability. One study included second-hand smoke. Translatability from trial to practice.	Our meta-analysis, utilizing the most recently published RCT data, demonstrated that LDCT screening is associated with a significant reduction of lung cancer mortality though not overall mortality. Women appeared more likely to benefit from screening than men, but data were inconclusive. The estimated risks for false positive results, screening complications, overdiagnosis, and incidental findings were low.
Ebell et al. 2020[40] CRD 42020171213	90,475	LSS MILD NSLT DANTE LUSI ITALUNG DLCST NELSON	AME - large imbalance between the number of patients in the screening and control groups (3,512 vs 3,145) and provided no details regarding randomization procedures or concealment of allocation	Up to 26 February 2020	**Inclusion**: required RCTs and a low risk of bias, and compared LDCT with chest radiography or usual care in adults at elevated risk for lung cancer	LDCT vs control RR: 1.25 95% CI: 1.02 to 1.55 I^2 = 66.8% p = 0.017		LDCT vs control RR: 0.81 95% CI: 0.74 to 0.89 I^2 = 0% p = 0.465	LDCT vs control RR: 0.96 95% CI: 0.92 to 1.01 I^2 = 0% p = 0.465	20%			Risk of bias low. Visual inspection of the forest plots revealed some heterogeneity. All-cause mortality power low. Lack of blinding.	This meta-analysis showing a significant reduction in lung cancer-specific mortality, albeit with a trade-off of likely overdiagnosis, supports recommendations to screen individuals at elevated risk for lung cancer with LDCT.
Passiglia et al. 2021[41] CRD 42018105409	88,497	LSS DANTE NLST NELSON DLCST ITALUNG MILD LUSI DEPISCAN		Inception – February 2020	**Inclusion:** RCTs comparing LDCT with either no screening or CXR in a high-risk population with a cigarette smoking history of ≥15 pack-years, including former smokers who had quit within the previous 15 years		Lung cancer screening associated with increase of early-stage diagnosis RR: 2.84 95% CI: 1.76 to 4.58	LDCT vs control RR: 0.87 95% CI: 0.78 to 0.98 I^2 = 24%	LDCT vs control RR: 0.99 95% CI: 0.94 to 1.05 I^2 = 27%	30%			Lack of blinding for the majority of included studies, which may have increased the risk of potential detection bias. Heterogeneity of included trials and population.	Despite there still being uncertainty about overdiagnosis estimate, this meta-analysis suggested that the LDCT benefits outweigh harms, in subjects with cigarette smoking history, ultimately supporting the systematic

[39] 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 (2020). https://doi.org/10.1007/s11606-020-05951-7

[40] Ebell MH., Bentivegna M., HulmeC. 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.

[41] 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.

							No screening RR: 3.33 95% CI: 2.27 to 4.89 Chest X-ray RR: 1.52 95% CI: 1.04 to 2.23 Decrease in late-stage diagnosis RR: 0.75 95% CI: 0.68 to 0.83 No screening RR: 0.67 95% CI: 0.56 to 0.80						Lack of extended follow-up data regarding yearly screening and overdiagnosis rate among the majority of included studies.	implementation of lung cancer screening worldwide.
Huang et al. 2019[42] CRD 42018111630	97,244	DANTE DLCST ITALUNG LSS LUSI MILD NELSON NLST Yang 2018		Inception – June 2019	**Inclusion:** Studies that met all of the following criteria: • Only RCTs • LDCT vs. any other type of lung cancer screening • Adult 18 years or older asymptomatic with risk factor for lung cancer • Benefits of interest included: lung cancer mortality, all-cause mortality, early detection • Harms of interest included: death and major complications after invasive procedures.		Early-stage cancer (Stage 1), LDCT vs control RR: 2.08 95% CI: 1.43 to 3.03	LDCT vs control RR: 0.83 95% CI: 0.76 to 0.90 I^2 = 1%	LDCT vs control RR: 0.95 95% CI: 0.90 to 1.00 I^2 = 0%				DANTE, MILD judged to be of low quality due to high risk of bias for mortality outcomes. Variation in trial quality and sample size may be a potential source of heterogeneity. Several biases arise in the evaluation of screening studies, including lead-time, length-time and overdiagnosis, which should be taken into account when interpreting these data.	In a meta-analysis based on sufficient evidence demonstrated by TSA suggests that LDCT screening is superior over usual care in lung cancer survival. The benefit of LDCT is expected to be heavily influenced by the risk of lung cancer in the different target group (smoking status, Asian) being screened. Due to the tenuous balance of benefits and harms, medical decision making is recommended for individuals who are considering LDCT screening.
Sadate et al. 2020[43] CRD 42018091720	84,558	DANTE NLST NELSON DLCST ITALUNG MILD LUSI		Inception – February 2018	**Inclusion:** topics about lung cancer screening, RCT study design, LDCT compared with any other intervention, population who reported an average smoking history over 15 pack-years (corresponding to the lowest criteria of the European RCTs on lung cancer screening) and the report of data on all-cause mortality or lung cancer-specific mortality.			LDCT vs control RR: 0.83 95% CI: 0.76 to 0.91 I^2 = 0%	LDCT vs control RR: 0.96 95% CI: 0.92 to 1.00 I^2 = 0%				Partial heterogeneity of the protocols studied, in particular the interventions in the control arm. Heterogeneity among studies concerned the smoking history of patients included, much higher in the NLST than in other RCTs included.	Our meta-analysis is the first systematic review to include all recent RCTs including the recent NELSON study. Our results confirm that of the NELSON study, showing an impact of lung cancer screening on lung cancer-specific mortality reduced in the LDCT group. No impact of such screening on all-cause mortality was reported.

[42] 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).

[43] Sadate A, Occean BV, Beregi JP, Hamard A, Addala T, de Forges H, Fabbro-Peray P, Frandon J. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. Eur J Cancer. 2020 Jul;134:107-14.

Brodersen et al. 2020[44] ID not registered/ provided	28,656	DLCST LUSI MILD ITLUNG NELSON			**Inclusion:** RCTs if: ● they did not provide long-term cumulative lung cancer incidence during follow-up, i.e. after the active phase of trials; or ● the control group was offered any type of lung cancer screening after or during the RCT		LDCT vs usual care RR: 1.22 95% CI: 1.02 to 1.47 I^2 = 55%			49% screen-detected cancers			This meta-analysis is based on a rapid review. High heterogeneity and low precision.	In low-dose computed tomography (LDCT) screening for lung cancer, all three main conditions for overdiagnosis in cancer screening are present: 1) a reservoir of slowly or nongrowing lung cancer exists; 2) LDCT is a high-resolution imaging technology with the potential to identify this reservoir; and 3) eligible screening participants have a high risk of dying from causes other than lung cancer. The degree of overdiagnosis in cancer screening is most validly estimated in high-quality RCTs, with enough follow-up time after the end of screening to avoid lead-time bias and without contamination of the control group.

[44] Brodersen J., Voss T., Martiny F., et al. Overdiagnosis of lung cancer with low-dose computed tomography screening: meta-analysis of the randomised clinical trials. Breathe 2020 16: 200013.

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

Risk prediction tool proposed for Program	Key published source describing option	Rationale for selection	RCTs of LDCT-based lung cancer screening programs using tools	Nominated threshold for referral or not to LDCTT	Rationale for the nominated threshold
PLCOm2012	Weber et al (2017)	PLCOm2012 is the only model to have been validated in the Australian population[2]. 'The PLCOm2012 model has been demonstrated to provide superior performance compared to the NLST eligibility criteria (age, smoking), with improved sensitivity and PPV, and no loss of specificity.	None of the RCTs included in the evidence review, nor in the meta-analyses, used risk prediction models. All RCTs were based on eligibility criteria of age and smoking history. The exception is the UKLS pilot study (RCT) of a single LDCT screening in a high-risk population, as described in the very recent publication by Field et al (Sept 2021)[40]. This pilot RCT involving only 4055 participants, applied the Liverpool Ling Project risk model (LLPv2) to identify the screening population. This trial has reported a significant reduction in lung cancer screening mortality (RR: 0.84; 95% CI: 0.76 to 0.92).	≥1.51	Weber et al (2017): The PLCOm2012 is currently the only lung cancer risk prediction model to have been validated in the Australian population[2]. In this retrospective evaluation in a subset of the 45 and Up study, a threshold of ≥1.51% risk was confirmed as appropriate for identifying those at high-risk of lung cancer within 6 years, achieving high PPV and sensitivity, with only minimal loss in specificity at this threshold, in comparison with the NLST eligibility criteria[2]. Lebrett et al (2021)

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

Proposed baseline nodule management protocol	Key published source describing option	Rationale for selection	RCTs of LDCT-based lung cancer screening programs using tool (list)
PanCan	McWilliams, 2013, 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.	Nodule management protocols enable accurate assessment and classification of lung nodules and improve LDCT screening sensitivity and specificity. 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. This rapidly changing aspect of targeted LDCT screening requires further study results to be published before selecting an optimal protocol for implementation. PanCan is a predictive tool based on patient and nodule characteristics used to estimate the probability that lung nodules detected on baseline screening LDCT scans are malignant[23]. The PanCan protocol is the only protocol that recommends a biennial screen instead of an annual screen for individuals with very low risk of lung cancer for the next 24 months based on the findings of the baseline LDCT. PanCan has only been validated at baseline, so a different nodule management guidance is required to be used at T2 and beyond. PanCan was selected as the baseline nodule management protocol based on clinical evidence and clinical consultation.	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. Van Riel SJ, Ciompi F, Jacobs C, Winkler Wille MM, Scholten ET, Naqibullah M, et al. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines. European Radiology. 2017;27(10):4019-29. 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. 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.

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

Subsequent nodule management protocol proposed for Program	Key published source describing option	Rationale for selection	RCTs of LDCT-based lung cancer screening programs using tool
Lung-RADS 1.1	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	Nodule management protocols enable accurate assessment and classification of lung nodules and improve LDCT screening sensitivity and specificity. 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. This rapidly changing aspect of targeted LDCT screening requires further study results to be published before selecting an optimal protocol for implementation. Lung CT Screening Reporting and Data System (Lung-RADS 1.1 developed by the American College of Radiology (ACR),) is a quality assurance tool designed to standardise lung cancer screening CT reporting and management recommendations, reduce confusion in lung cancer screening CT interpretations, and facilitate outcome monitoring. Lung-RADS 1.1 was selected as the nodule management protocol for subsequent scans based on clinical evidence and clinical consultation.	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.

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