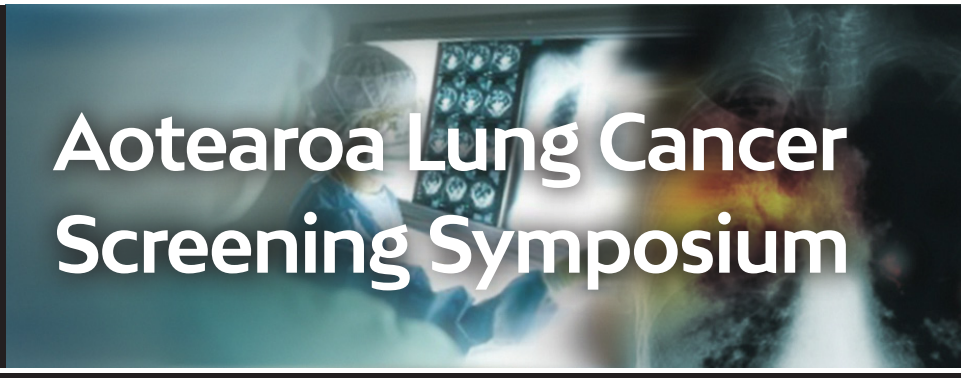
A RESEARCH REVIEW™
EXPERT FORUM

Aotearoa Lung Cancer Screening Symposium



Making Education Easy 2021

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- NLST and post hoc analyses
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Abbreviations used in this review

CT = computerised tomography
COPD = chronic obstructive pulmonary disease
COVID-19 = coronavirus disease 2019
DHB = district health board
ICER = incremental cost-effectiveness ratio
IASLC = International Association for the Study of Lung Cancer
ILST = International Lung Screening Trial
LC = lung cancer
LDCT = low-dose computerised tomography
NELSON = Dutch-Belgian Randomized Lung Cancer Screening trial
NLST = National Lung Screening Trial
PLCO = Prostate, Lung, Colorectal, and Ovarian
RCT = randomised controlled trial
USPSTF = United States Preventive Services Task Force

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Welcome

to this review of the *Aotearoa Lung Cancer Screening Symposium*, which was organised by the Thoracic Society of Australia and New Zealand (TSANZ) and held in Auckland on 30 April 2021. The symposium was well attended by clinicians representing respiratory medicine, oncology, radiology, Māori health, and public health, which reflects the multidisciplinary nature of LC care. The symposium marked an important step forward for LC screening in Aotearoa as it brought together for the first time, Māori health leaders, clinicians and researchers in LC screening and representatives of Ministry of Health (Te Aho o Te Kahu/Cancer Control Agency and National Screening Unit) for an opportunity to discuss ways to establish LC screening in Aotearoa with an equity lens.

This review presents highlights from the presentations. Broadly, the symposium could be divided into three parts. The first session sets the scene with presentations on the international landmark LC screening trials (NSLT and Nelson trials) and screening in the Indigenous population in the USA. Presentations from the second session focused on the need for a Māori led approach to LC screening and two NZ studies (Auckland/Waitemata and Midlands) with particular emphasis on the need to design an equity-focused screening programme to reduce cancer outcome inequities for Māori, where LC mortality remains disproportionately high. Other presentations include cost-effectiveness, barriers, and facilitators in LC screening programmes. Finally, the presentation on the ILST informed on the Australian experience with LC screening so far, highlighting the roles of risk prediction models and fixed screening criteria.

Dr Elaine Yap – NZ branch President TSANZ

LC SCREENING OVERVIEW IN THE US (INDIGENOUS PEOPLE)

Prof. Gerard A. Silvestri – Medical University of South Carolina, Charleston, SC

The two largest screening trials published to date are NLST and NELSON.[1,2] The selection criteria differed slightly between the two trials. NELSON included persons out to 50 instead of 55 years of age, instead of a 30 pack-year smoking history used a 20 pack-year history, and included persons who had quit in the last 10 years instead of the last 15 years. Differences in the screening intervals between the two studies suggests the need for yearly screening to prevent early-stage LC.

A significant stage shift to earlier stage LC was observed in both studies.[1,2] Picking up early-stage cancer is an important outcome of LC screening. Women did better than men in terms of LC mortality reduction in both trials. Overall survival was improved in NLST but not in NELSON, a finding at least partially attributable to NELSON not being powered to demonstrate a difference in all-cause mortality due to screening.

Expanded USPSTF screening criteria

Following publication of NLST in 2011,[1] the USPSTF 2013 LC screening guidelines[3] recommended screening of persons 55 to 80 years of age with a smoking history of 30 or more pack-years, who currently smoke or quit smoking within the past 15 years.

Since publication of the NELSON results in 2020,[2] the main differences in the expanded USPTF 2020 LC screening guidelines[4] compared with the USPSTF 2013 recommendations[3] are age range 50–80 years instead of 55–80 years and smoking history 20 or more pack-years instead of 30 or more pack-years. These proposed changes will add 6.5 million people being eligible for LC screening in the US to the 8 million people eligible for screening under the USPSTF 2013 criteria.[3]

First million screens

A comparison of the first 1 million screens in the American College of Radiology's lung cancer screening Registry (LCSR; data from 2016–2019) with the 8 million Americans eligible for LC screening according to the USPSTF 2013 criteria reveals that 88% of the first 1 million screens met the USPSFT criteria, indicating that we are good at screening the 'eligible'.[5] Of the 150,772 LCSR screens not meeting the USPSTF 2013 criteria,[3] 40,426 would be eligible under the USPSTF 2020 criteria.[4]

Some of the demographic implications of the comparison are:

- More women than men are being screened suggesting a need for focused messages to men to increase their uptake of screening.
- Older people have higher rates of screening, possibly related to Medicare insurance.
- More current smokers than former smokers are being screened.
- People with a higher level of education have greater access to screening services but are less likely to need screening due to lower smoking rates versus those with lower levels of education.
- Having better insurance is associated with higher rates of screening and uninsured people have the highest smoking rates.

Adherence

A less encouraging finding of the first 1 million screened comparison was that only 22% of eligible persons (Lung-RADS ≤2) returned for an annual screen within 11–15 months.[5] Predictors of non-adherence based on modelling are: being African American or Hispanic; having a less than high school education; self-pay or being uninsured; being a current smoker; and geographical location.

System level, physician level, and patient-level interventions are needed to increase adherence to repeat screening. In NLST, approximately half of cancers were picked up in subsequent screens.[1]

Life expectancy and LC screening?

Life expectancy has not been included in eligibility criteria for LC screening. In a re-analysis of NLST data to determine whether the benefits and potential harms of the applied screening criteria vary according to risk of LC death, screening with LDCT prevented the greatest number of deaths in participants who were at highest risk (Quintile [Q] 5 of 5-year risk of LC death) and prevented very few deaths in those at lowest risk (Q1).[6] This finding supports individualising risk for every patient.

Co-morbidities and LC screening

All participants in NLST were asymptomatic and otherwise healthy;[1] however, there is a need to balance competing causes of death from other causes with risk of death from LC. A comparison of NLST data with a Medicare insurance database found that competing causes of death (i.e., having significant comorbidities) may diminish the benefits of screening.[7]

The standard belief is that as the risk of LC increases the benefits of screening increase. However, once comorbidities take effect and there are competing causes of death the benefits of screening reach an inflexion point and start declining (**Figure 1**).[8] There may be a 'sweet spot' for screening where the risk is high enough to pick up a lot of cancers and there is a benefit from surgery.

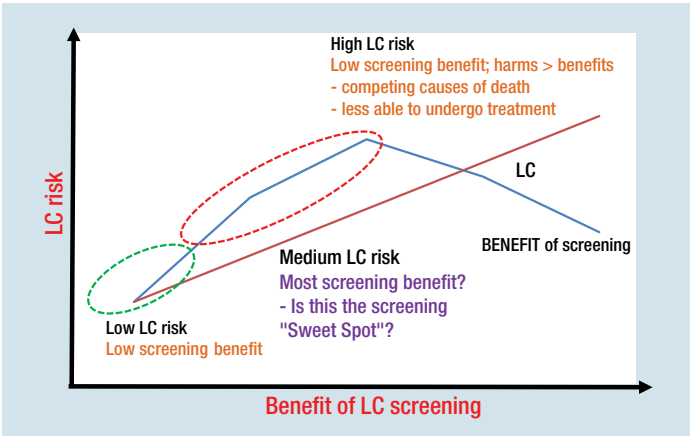

Figure 1. The 'sweet spot' for LC screening.[8]

Disparities

A secondary analysis of data from NLST found that screening with LDCT reduced LC mortality in all racial groups but more so in African Americans.[9] They were younger, less well educated, had more comorbidities, and were more likely to be current smokers compared with the whole study population. African Americans will benefit from screening but are likely to have lower access to screening services.

In terms of consideration of racial differences in smoking patterns, the 30 pack-year history inclusion criteria in the USPSTF 2013 guidelines[3] excluded a higher proportion of high-risk persons due to their lower smoking history. African Americans develop LC with a lower smoking history, which means they may not be eligible for screening. Expanding LC screening eligibility to individuals with lower smoking history would increase the proportion of screening-eligible African Americans.

Recent research indicates that you can have a viable and effective screening programme in underserved communities and that the USPSTF 2020 screening criteria[4] will capture more minority populations. Matching the distribution of screening centres to regions with a high burden of LC is also important. Approaches to expanding LC screening to under-represented groups when uptake has been so poor include:

- Increasing community engagement, e.g., outreach in community settings, local champions, and media campaigns.
- Instituting systems-level changes including improving access to insurance and making referral and eligibility confirmation easier.

TAKE-AWAY MESSAGES

- LC screening uptake is increasing slowly and the majority of those screened are eligible.
- Demographics differ in some important ways.
- Adherence is an important aspect of LC screening that has been overlooked and will negatively affect screening effectiveness and cost effectiveness.
- Disparities in LC screening exist, which will be ameliorated with changes in the USPSTF 2020 criteria but systems-level changes are needed for minorities to access screening.
- As screening rates rise, lung nodule evaluation becomes critical such that we do not miss cancers when they are present but do not cause harm for those without cancer.

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OVERVIEW OF THE NLST AND POST HOC ANALYSES

Assoc. Prof. Robert Young – University of Auckland

In 2011, NLST showed that LDCT LC screening could reduce LC mortality in high-risk patients by 20% compared with chest radiography, which equated to a number needed to screen of 320.[1] However, there was only a 6–7% reduction in all-cause mortality.

With publication of NLST results, the key question has become what proportion of people with LC in a case series would have had their cancer detected by screening. There has been a progression to widening the criteria for screening eligibility; however, while more people may be included in a screening cohort, there is a loss of screening efficiency. i.e., a lower LC detection rate.

How can risk models improve the current screening paradigm?

The most well-validated risk prediction model, the $PLCO_{m2012}$, which includes 11 variables (including age, number of cigarettes smoked per day, and duration of smoking) that refine the risk for LC, predicts COPD almost as well as it predicts LC.

When looking at the $PLCO_{m2012}$ risk of LC by quintiles [(Q1 (low risk) to Q5 (high risk)] with regard to the prevalence of COPD in a NLST sub-group, the prevalence of COPD increased from ≈20% in Q1 to ≈50% in Q5. Moreover, as LC deaths increased from Q1 to Q5 non-LC deaths increased even more. The group at the highest risk of LC (Q5), also has the highest prevalence of COPD and the highest rate of non-LC deaths. The same relationship applies depending on the severity of COPD (GOLD 1, GOLD 2, or GOLD 3–4).

The benefits of screening fall off at high levels of LC risk, which may be due to competing causes of death, reduced surgery rates, and more complications. Hence, screening may not be appropriate for people who are less able to tolerate surgery due to having high rates of comorbidity. In a simulation study that looked at life expectancy and the benefits of screening for LC, as the risk of LC increases Q1 to Q5,[2] the benefits of screening for LC fall off at about Q5, i.e. the 60% of otherwise eligible smokers in Q2 to Q4 gain the greatest benefit of screening (the so-called "20–80 rule").

In summary:

- Risk models that include a variety of risk variables can better determine the risk of LC.
- Increasing risk of LC does not correlate with increasing benefits from screening.
- Screening benefit may be attenuated for people at greatest risk for LC (Q5) due to reduced life expectancy (competing causes of death) and reduced ability to tolerate LC treatment.
- Moderate-to-heavy smokers at intermediate risk for LC (Q2–Q4) may be the optimal group to screen.

How does COPD affect outcomes in CT screening?

COPD and LC may be linked. An unpublished post hoc analysis[3] of data from over 18,000 participants in NLST demonstrated that LC screening is not comparable to screening for breast and colon cancer due to LC populations having higher rates of comorbidities, including the presence of COPD. The analysis hypothesised that COPD not only increases a person's risk of LC but also has a major effect on outcomes from screening and LC histology. LC outcomes are driven by a complex interaction between patient and LC factors.

In a preliminary analysis of those eligible for screening in NLST, participants with GOLD3–4 disease had more aggressive LC compared with those who were GOLD 1–2 as well as increased LC detection, reduced LC surgery, and increased LC deaths.[3] In addition, deaths from CV disease and respiratory disease were much higher in GOLD3–4 participants, which may have a considerable impact on outcomes in the context of screening.

In summary:

- Worsening COPD is associated with a greater risk of LC but those with GOLD 3–4 get minimal or no benefit screening.
- Worsening COPD is also associated with more aggressive forms of LC, reduced surgery overall, and less detection during screening.
- GOLD 3–4 is associated with higher non-LC deaths relative to LC deaths.
- GOLD 3–4 is not associated with stage shift with CT-based screening nor a meaningful reduction in LC mortality.

Differences in screening outcomes according to gender

Preliminary results from a post hoc analysis of the 18,000 NLST participants[3] help to inform why women have better screening outcomes than men – histology or competing causes of death?

In the NLST subgroup the reduction in LC deaths with screening was higher in women (30%) than in men (16%). Gender demographics were similar except for women smoking slightly fewer cigarettes per day and having greater COPD history. Women also reported more respiratory disease and less CV disease and diabetes. In terms of histology, men had more squamous while women had more BAC than men. Cancer stage was similar for both genders and there was no difference in surgical rates for LC. The main difference was what men and women died of: women had more LC deaths and respiratory deaths while men had more CV deaths and cancer deaths.

The overall conclusion is that women do better in LC screening possibly because LC is a leading cause of death whereas men die of many causes (competing cause of death analysis).

TAKE-AWAY MESSAGES

- LDCT was shown to reduce LC mortality by 20% in NLST.
- Risk models help to identify and target those at greatest risk; however, the increased efficiency of screening is attenuated by the poorer outcomes observed in low (Q1) and high (Q5) risk individuals.
- The following sub-populations of eligible smokers may do better with screening when the bigger picture is considered: i) those with reasonable lung function; those at intermediate risk (Q2–4); and iii) those for whom LC is the likely major cause of death.

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OVERVIEW OF THE NELSON STUDY

Dr Paul Dawkins – Middlemore Hospital

Implementation of a new cancer screening programme requires establishment of its effectiveness, that the benefits of screening outweigh the harms, and that it is cost effective for the population being screened.

NELSON

The Dutch–Belgian lung-cancer screening study (Nederlands–Leuvens Longkanker Screenings On-derzoek [NELSON]) is a population-based RCT initiated in 2000 that compared volume-based LDCT LC screening with standard care (vs a standard chest x-ray in NLST[2]) in high-risk participants at 10 years of follow-up.[1] NELSON was designed to include mainly male volunteers given the difference in smoking between men and women but more women volunteers were added later in the study.

A total of 15,792 people participated in the study, 85% of which are male. Participants in the screening group received four CT scans with increasing intervals (0, 1, 2, 2.5 years) and with the results of both groups compared 10 years after the first CT scan. LC incidence, mortality, and the performance of the four screening rounds among male participants (main analysis) and female participants (subgroup analyses) have been reported.

NELSON males

Of all participants screened, 2.1% were referred to a pulmonologist for work-up and 0.9% these had LC detected. Hence, for men referred for further diagnostics almost one in two (43.5%) had a positive LC diagnosis (9.2% had an indeterminate LC test).

LC incidence at 10 years of follow-up was 5.58 versus 4.91 cases per 1,000 person-years in the screening group versus control group (**Figure 1**). A stage shift was evident in the male participants: 60% had stage I and 80% had stage IV in the screening group (341 LCs found) compared with 13% with stage I and 46% with stage IV in the control group (304 LCs found).

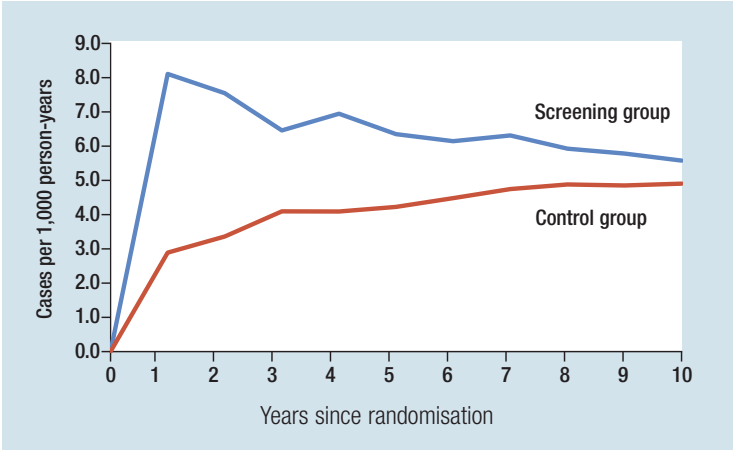

Figure 1. LC incidence with screening versus standard care at 10-years of follow-up in NELSON.[1]

LC mortality was 2.50 versus 3.30 deaths per 1000 person-years in the screening versus control groups at 10 years' follow-up (p=0.01). NELSON was not powered to show a possible favourable difference in all-cause mortality due to screening because it would have required an unrealistic minimum trial sample size (>50,000 participants). Comparison with NLST at 8 years follow-up showed a lower LC mortality rate ratio for men in NELSON (0.76) than in NLST (0.92). There was also a lower LC mortality rate ratio for females in NELSON (0.41) compared with NLST (0.73). The more favourable result in NELSON is likely due to the screening and imaging algorithm used in NELSON.

NELSON females

In NELSON, an analysis of the female participant subgroup (n=2,369) revealed a lower LC mortality ratio (0.67) than that found for men (0.76) at year 10. One explanation for the gender difference is that women have a longer duration between developing LC and displaying symptoms. Hence, women are likely to benefit more from screening because men are more likely to present with symptoms at an earlier stage of their LC.

Benefits and harms of LC screening

Based on NLST data, the main harms of LC screening are over-diagnosis (people who are diagnosed with LC but die of something else), false positive scan results (causing anxiety and additional costs), and unnecessary procedures (surgery or biopsy for benign lesions).

Compared with other cancer screening programmes in the Dutch population (based on the NELSON data), LC screening is comparable with colorectal and breast cancer screening in terms of deaths prevented, life-years gained, and cost. In terms of the cost effectiveness of LC screening, international analyses suggest a relatively high cost per life-year gained for LC screening; however, it is possible this will be lower in the NZ healthcare setting via use of more sophisticated risk selection criteria and a more realistic cost for CT scans.

Selection of individuals for LDCT LC screening programmes using the $PLCO_{m2012}$ risk ≥0.0151 criterion should improve screening efficiency compared with selection by USPSTF 2013 criteria, which only include age and smoking history and result in more low-risk individuals being included.[3]

Regarding screening intervals, current trial data and modelling favour annual screening. However, risk-stratification by CT scan result can substantially reduce the number of screens needed, which will lead to reduced harms and lower costs. In NELSON, the probability of a LC diagnosis in the two years following detection of a nodule <50 mm^3 (i.e., negative baseline CT) was 0.4% compared with 25.7% following detection of a nodule of volume ≥1,000 mm^3. These results suggest biennial rather than annual screening for participants with negative baseline CT results.

TAKE-AWAY MESSAGES

- LC is the leading cause of cancer-related mortality.
- NLST and NELSON have confirmed substantial reductions in LC mortality with LDCT screening in high-risk populations and that it is higher in women than men.
- LC screening is effective; the challenge is to develop risk selection criteria specific for NZ that will make screening cost effective and acceptable to the population.

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OVERVIEW OF THE LONDON/MANCHESTER LUNG HEALTH STUDY APPROACH

Prof. Ross Lawrenson – University of Waikato Medical Research Centre

Recommendations from the IALSC CT Screening Workshop 2011 Report that are particularly relevant to the implementation of a future national LDCT LC screening programme in NZ are the identification of the high-risk individuals and the integration of smoking cessation practices.

UK Lung Cancer Screening pilot

The UK Lung Cancer Screening (UKLS) was a pilot RCT of LDCT screening for LC versus usual care that used a population-based questionnaire to identify high-risk individuals.[1] The pilot determined optimum recruitment, screening, reading, and care pathway strategies. The psychological consequences and health economics of screening were also assessed. Individuals aged 50–75 years at high risk of LC were recruited from primary care trusts. A total of 4,061 high-risk positive responders consented to participate and 4,055 were randomised.

Key results were as follows:

- 42 screened participants were diagnosed with confirmed LC.
- 34 were detected at baseline or 3 months, giving a baseline prevalence of 1.7%.
- Overall 2.1% were diagnosed with LC.
- 36/42 (85.7%) of the screen-detected cancers were identified at stage 1 or 2.
- Of those with a confirmed cancer, 17/42 (40.5%) were from the most socioeconomically deprived quintile.
- Short-term psychosocial consequences of LC screening were modest and temporary.
- The health-economic analysis indicated that LDCT screening could be cost-effective.

Involvement with general practice was important. Although the UKLS pilot did not use GP-based recruitment of participants, it did include strategies to engage effectively with the GPs of participating patients throughout the pilot pathway, including involvement in patient follow-up.

Manchester pilot – lung health checks

Following the UKLS pilot,[1] a number of UK centres moved to actively screen for LC. The Manchester Pilot assessed mobile LDCT LC screening using a one-stop Lung Health Check (LHC) approach to access a high-risk high-needs community.[2] All attendees were offered smoking cessation advice. The pilot included ever smokers aged 55–74 years registered with participating GP practices. Those with LC risk ($PLCO_{m2012}$) ≥1.5% at 6 years were offered annual screening with LDCT for 2 years.

Key results included the following:

- LC prevalence was 3% (42/1,384) during the first round of screening.
- Over 80% of detected cancers were stage at 1 or 2.
- The same group of patients were then screened in a planned second screening round.
- A further 30/1,194 scans were positive, with one person declining further assessment.
- Of the 29 patients assessed, 19 had LC.
- Over two screening rounds, 4.4% of those screened (1,384 initial screen, 1,194 returnees) were diagnosed with LC, which is a high pick-up rate over two rounds of screening:
  - one person for each 23 people screened had LC.
  - 79% were at stage I.
  - 89% identified at screening could be offered treatment with curative intent.
- Spirometry identified a significant number of individuals with airflow obstruction who did not have a prior diagnosis of COPD.
- Having a diagnosis of COPD was associated with a significantly increased the risk of LC.

Provision of brief quit smoking advice and being directed to stop-smoking services resulted in a 10.2% quit rate at 12 months. Having a positive LDCT was not associated with likelihood of quitting.

Screening for biomarkers

Screening for biomarkers of LC is potentially less expensive and more specific than LDCT LC screening. Potential biomarkers being investigated include blood tests, breath tests, and sputum.

The Early Diagnosis of Lung Cancer Scotland (ECLS) trial was a RCT of 12,208 general practice patients at risk of developing LC. The intervention arm received an EarlyCDT-Lung test and, if test-positive, LDCT scanning 6-monthly for up to 2 years.[3] The EarlyCDT-Lung test is a high-specificity blood-based autoantibody biomarker panel. EarlyCDT-Lung test-negative and control arm participants received standard clinical care.

A total of 127 LCs (1.0%) were detected in the study population at 2 years. Of the 6,088 randomised to the EarlyCDT-Lung test, 598 (10%) had a positive blood test and of those 18 (3%) had LC. For the patients who did not have a positive blood test, 36/5,489 (0.7%) had LC. In the non-screening control group, 71/6,121 (1.15%) developed LC. Hence, the EarlyCDT-Lung test had poor sensitivity, was not overly specific, and did not make a difference to the overall number of LCs detected. However, the 18 cases of LC picked by the intervention were at an earlier stage than those in the non-screening group.

TAKE-AWAY MESSAGES

- The UKLS pilot trial showed that 80% of LC detected was at an early stage.
- The Manchester pilot demonstrated that taking LC screening into communities is effective and engages populations in deprived areas.
- The UK has generally adopted a two-stage lung health check approach, with LDCT screening used for those at risk.
- Spirometry and smoking cessation advice should also be included in the lung health check.
- LC screening should be targeted at high-needs communities.
- Use of mobile LDCT is an option.
- More research is needed on other risk factors such as spirometry and biomarkers to improve specificity.

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ABOUT EXPERT FORUMS

Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies. Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution.

CANCER CONTROL AGENCY

Prof. Diana Sarfati – Te Aho o Te Kahu, Cancer Control Agency

Cancer is the leading cause of death in NZ. Moreover, there are long-standing and persistent inequities in cancer that must be addressed. Cancer survival is improving in NZ but not at the same rate as that in comparable countries. These are the reasons that the Te Aho o Te Kahu, Cancer Control Agency was set up (in December 2019).

Role of the Te Aho o Te Kahu, Cancer Control Agency

The role of the Te Aho o Te Kahu, Cancer Control Agency is to provide national leadership for cancer control, provide sound policy advice to the Government, and to be accountable for ensuring transparency in the implementation of the NZ Cancer Action Plan 2019–2029.

The objectives of the Cancer Action Plan 2019–2029 are to ensure that New Zealanders:

1. Have a system that delivers consistent and modern cancer care.
2. Experience equitable cancer outcomes.
3. Have fewer cancers.
4. Have better cancer survival, supportive care, and end-of-life care.

The Te Aho o Te Kahu, Cancer Control Agency is a standalone departmental agency that reports directly to the Minister of Health but independent of the government. The agency is supported by the Te Aho o Te Kahu Council as well as clinical, consumer, and Hei Āhuru Mōwai leadership groups, with strong Māori representation. Four Cancer Regional Hubs (formerly the Regional Cancer Networks) provide the capacity for policy implementation and input from those working on the front-line of cancer care.

Some of the major activities and projects undertaken by the Agency's six teams include:

- The Equity Team looking at facilitation of travel and accommodation for people trying to access cancer treatment.
- The Treatment, Quality, and Standardisation Team is responsible for the Quality Improvement Work Programme, which compares performance across DHBs.
- The Data, Monitoring, and Reporting Team is responsible for improving the quality of cancer data and reporting. Workforce modelling includes future demand for radiation oncologists.
- The Person and Whānau-centred Care Team is conducting a series of community hui across the country to workshop solutions to local issues in pathways of care.
- The Privatisation, Innovation, and Research Team is doing a lot of work around strengthening the approach to molecular testing in NZ and supporting LC screening.

Opportunities to reduce the impact of LC in NZ

1. Reducing LC incidence and mortality: LC is where the biggest inequity in mortality from cancer exists, with substantially higher LC incidence and death rates in Māori compared with non-Māori. Focusing on reducing rates of smoking through Smokefree 2025 initiatives remains a top priority.

2. Improving cancer survival: LC survival is improving over time in NZ but not as quickly as other comparable countries. Earlier diagnosis of LC translates to better outcomes; however, there exist barriers to LC diagnosis.

3. Organised screening: As discussed in this symposium.

4. Better or more consistent treatment: There is a need to understand the reasons for different regional performance in terms of LC outcomes and how performance can be improved. In terms of LC survival, New Zealanders do not have access to the same range of medicines available in some other countries.

5. Research: There is an underspend on research into LC compared with many other cancer types. Also, many policy questions related to LC screening remain unanswered. The Te Aho o Te Kahu, Cancer Control Agency has submitted an RFP so that work addressing these policy issues can start.

AUCKLAND/WAITEMATA SCREENING PILOT

Prof. Sue Crengle – University of Otago (On behalf of the Te Oranga Pūkahukahu team)

This is an opportunity to develop the first LC screening programme in the world that is indigenous-focused, is indigenous-led, and is specifically focussed on ensuring equity for Māori.

LC screening differs from current cancer screening

Current cancer screening programmes have significant inequities in Māori participation and outcomes. Action across the lung health pathway is required to improve Māori LC outcomes. LC screening needs to operate within context of a national organized screening programme, especially given that opportunistic programmes have failed to deliver the required outcomes to Māori.

LC screening is a two-stage process: i) identifying people eligible for risk assessment; and ii) inviting people above a risk threshold to have a LDCT scan. Testing and understanding the invitation process is required to ensure that Māori participate. The balance of benefits and harms of screening are dependent on the risk threshold chosen and there is a need to understand this balance for Māori and non-Māori.

Te Oranga Pūkahukahu

The programme name, Te Oranga Pūkahukahu, symbolises that lung health is a journey, not only for patients but also for their whānau and loved ones so that they can be around for future generations.

The programme is a collaborative Māori-led approach involving the University of Otago, Auckland DHB, and Waitematā DHB. Ten of the 13 members of the Steering Group are Māori. Key elements of the programme approach are placing participants and whānau at the centre of the development process and identifying and systematically addressing barriers to participation.

Foundational work

Work completed to date includes initial focus groups (hui process) and a survey of those eligible for screening and their whānau. This work has informed understanding of beliefs and attitudes with respect to LC screening, what people want to know about LC screening, in what form that information should be delivered, how they want to be invited to be screened, and the integration of other aspects into screening (e.g., smoking cessation, spirometry).

The information from the focus groups and survey has also informed the design of trials, participant materials, communication approaches, and shared-decision making resources supported by Māori health literacy and communication experts.

Enablers for screening included a targeted by Māori for Māori whānau approach, accessible services, a 'non-clinical' friendly approach, and the use of Iwi/Māori providers. The opportunity to identify a cancer early was also seen as a key message to enable whānau. Barriers to screening included cost, time to access screening, and fear of the unknown.

A survey of attitudes and beliefs showed that 91% (plus 8% maybe) of the sample said they would attend a screening programme if told that they were at 'high risk' for LC and offered a free CT scan. The main barriers to screening were a belief that LC is usually not curable, stigma related to smoking, and a perception that LC treatment might be worse than the cancer itself.

LDCT screening

The pathway of LC screening will involve:

- Identifying eligible people and inviting them to risk assessment.
- Undertaking risk assessment.
- A shared-decision making process for those over the risk threshold.
- Offering a LDCT scan of the chest.
- Providing appropriate follow-up and management.

Fixed community-based lung scanning facilities will be used as high cost excludes mobile screening.

Next steps – trials overview

The screening programme will involve end-to-end LC screening. Components of the programme either underway or proposed (pending funding) are a pilot, an invitation trial, and a risk prediction trial (**Figure 1**).

An implementation science framework will also be used for the invitation trial to obtain data for important screening methodology and outcomes parameters. Integration of spirometry and smoking cessation advice are also planned components of the invitation trial. A trial of the performance of a risk prediction tool is also planned. The invitation trial is Māori only while the risk prediction tool trial involves Māori and non-Māori.

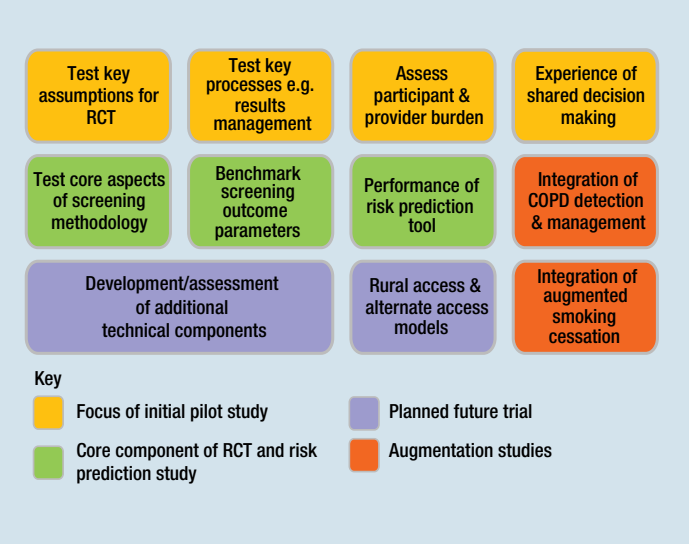

Figure 1. Overview of the Te Oranga Pūkahukahu trials programme.

Other implementation science questions, related to how screening can be designed and implemented for those most at risk, include: assessment of shared-decision making (SDM) tools; assessment of patient experience, acceptability, and participation across the whole pathway; testing of end-to-end pathways (including primary care and DHB systems and services); and optimisation of nodule management processes.

SUMMARY

- This is an opportunity to design an equity-focused screening programme that is available to everyone who is eligible and ultimately reduces LC mortality and inequities.
- Māori health, medical specialists and researchers, and whānau will work together to prepare for LC screening in Aotearoa.
- Key areas of focus are Māori leadership, participant and whānau experience of the screening process, and the readiness of secondary care.

LC SCREENING: AOTEAROA NEW ZEALAND COST EFFECTIVENESS RE-ANALYSIS

Dr Peter Sandiford – Auckland DHB and Waitemata DHB
Dr Melissa McCleod – Otago University, Wellington (on behalf of the research group led by Prof. Sue Crengle – University of Otago)

Because LC is a major cause of death and a major contributor to ethnic inequalities in life expectancy, interventions that reduce LC mortality have huge potential benefits. LC screening can save lives and can help close the life expectancy gap but for screening to be introduced it needs to be cost effective in the NZ setting.

In 2018, the conclusion of a cost-effectiveness analysis by the BODE Research Group was that LDCT screening for LC is unlikely to be cost effective for any population group in NZ.[1] However, the analysis did not consider screening parameters and assumptions from NELSON and did not explicitly model the impacts of LC screening on health equity for Māori.

An in-depth analysis of the BODE[3] CT LC model documented five errors, four of which would contribute to underestimating the cost effectiveness of screening. The authors for the BODE[3] CT lung model paper undertook further assessment, accepted four errors for correction, and updated the data. They published a corrigendum in 2020,[2] concluding that LC screening is overall unlikely to be cost effective for the target population in NZ but is likely to be cost effective for Māori, particularly Māori women.

Against this background, a re-analysis of a corrected BODE Markov model was conducted to incorporate different base assumptions and parameters from NELSON with specific consideration of the impact of screening on health equity for Māori.[3]

Key questions

The re-analysis aimed to answer two questions: i) is LC screening likely to be cost-effective in the NZ population as whole and in gender and ethnic subgroups; and ii) what is the likely impact of the LC screening programme on inequalities in health for Māori compared with non-Māori?

Objective

To model the potential lifetime health gains, equity impacts, and cost-effectiveness of a national biennial LDCT screening programme for LC in smokers aged 55–74 years with a 30 pack-year history, and for former smokers who have quit within the last 15 years.

Design

A Markov macrosimulation model estimated health benefits (health-adjusted life-years [HALYs]), costs, and cost-effectiveness of LDCT screening in the NZ setting. Biennial LDCT screening for LC was compared with usual care. A healthcare system perspective was used and 3% discount rate applied to gains and costs. Incremental cost-effectiveness ratios (ICERs) were calculated using the average difference in costs and HALYs between the screened and the unscreened populations. Equity analyses included substituting non-Māori values for Māori values of background morbidity, mortality, and stage-specific survival. Changes in inequities in LC survival and 'health-adjusted life expectancy' (HALE) were measured.

Results

LDCT screening in NZ is likely to be cost-effective for the total population at NZ$34,400 per HALY gained (using a threshold of gross domestic product per capita NZ$45,000) and relatively more cost-effective for Māori than for non-Māori and for females than males (**Table 1**). Health gains per capita for Māori females were twice that for non-Māori females and 25% greater for Māori males compared with non-Māori males.

The data also indicates that LC screening will narrow absolute inequities in HALE and LC mortality for Māori but will slightly increase relative inequities in mortality from LC compared with non-Māori due to differential stage-specific survival. Equity scenarios whereby current inequities for Māori were not assumed showed that LC screening will be even more cost effective in Māori.

CONCLUSIONS

- There are large inequities in the LC burden for the Māori population.
- LC screening is likely to be cost-effective in NZ, especially for Māori and females.
- Māori are likely to see greater health gains from screening than non-Māori.
- Absolute inequities in LC are reduced with screening.
- Inequities in local-stage LC need to be addressed.

	Total (95% UI)	Māori (95% UI)	Non-Māori (95% UI)
All 55+ year olds			
Cost of intervention (NZ$; millions)	$68 ($58 to $80)	$9.3 ($7.9 to $10.8)	$59 ($50 to $69)
Net cost NZ$; millions)	$105 ($87 to $126)	$18 ($14 to $22)	$88 ($73 to $104)
Total HALYs gained	3,230 (2,320 to 4,310)	670 (480 to 900)	2,550 (1,770 to 3,300)
ICER	$34,400 ($27,500 to $42,900)	$27,400 ($22,000 to $33,000)	$36,300 ($28,800 to $45,300)

Table 1. LDCT LC screening is cost effective in NZ for the total population and Māori separately, using a threshold of gross domestic product per capita NZ$45,000.[3]

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LUNG SCREENING EQUITY – AN INDIGENOUS RIGHT

Dr Nina Scott – Hei Āhuru Mōwai - Māori Cancer Leadership Aotearoa

LC is a major driver of the cancer death and life expectancy equity gaps between Māori and non-Māori New Zealanders. Evidence very clearly shows that a Māori-led, national LC screening programme is essential to address these long-standing inequities, which are, by definition; avoidable, unfair, and fixable. The impetus to accelerate lung screening in Aotearoa is further advanced by recent evidence revealing that LC screening for Māori is cost effective.

The right to health equity and to develop Māori models of care, funded by the Crown and delivered through Māori organisations, is mandated under the United National Declaration on the Rights of Indigenous People and te Tiriti o Waitangi.

Hei Āhuru Mōwai is a national Māori cancer network that has been entrusted by numerous Māori organisations to be māngai (entrusted speaker and leader). Hei Āhuru Mōwai has repeatedly stated that the development, testing, implementation, and monitoring of lung screening in Aotearoa must be Māori led from the outset.

Establishing and implementing an equitable LC screening programme will require considerable effort to counter the dominant racist and inequity-generating environment that exists in Aotearoa.

Māori cancer inequity

Inequities in cancer death rates between Māori and non-Māori have increased over time.[1] The Te Aho o Te Kahu, State of Cancer in NZ 2020 report highlighted substantial ethnic differences in risk of death from cancer for most cancers and for LC in particular (**Figure 1**).[2] A shocking 48% of the inequity in the overall 72% higher cancer death rate for Māori compared with non-Māori is due to LC.[3]

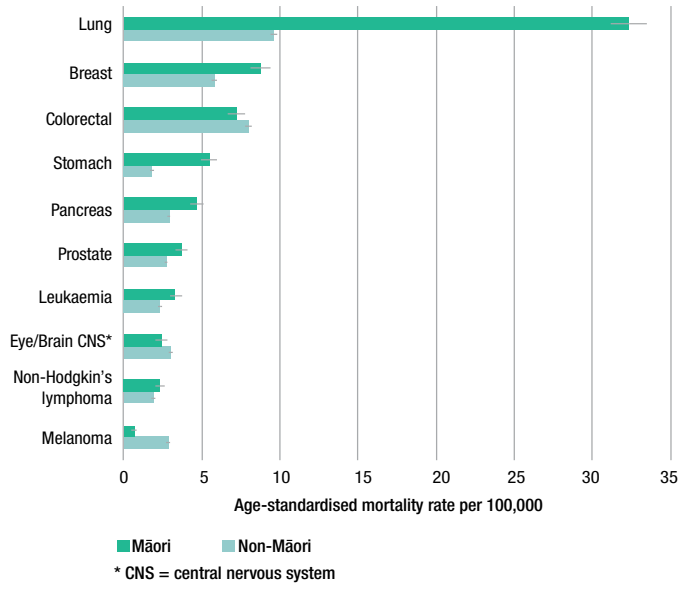

Figure 1. Mortality rates for the 10 most commonly diagnosed cancers in Aotearoa, Māori and non-Māori, age- and sex-standardised, 2007–2017.[2]

These inequities illustrate how poorly we are doing as a country and the considerable amount of work that will be required just to provide basic LC care in Aotearoa, especially for Māori. Te Aho o Te Kahu, the national Cancer Control Agency certainly has its work cut out.

Current cancer screening programmes are not Māori-led

There has never been an equitable national cancer screening programme in Aotearoa.

Cancer screening programmes in Aotearoa have been and continue to be inequitably led. They all deliver lower screening access for Māori and push whānau into services where cultural safety is not the norm. A lower Māori screening "uptake" is then framed as Māori being problematic and as having a "cultural reluctance to present for care". This reinforces the positivist Western discourse and victim blaming culture of our health system.

The Bowel Screening Programme's lack of responsiveness to equity illustrates the need to embed Māori cancer experts and leaders at decision-making levels within, and over, cancer screening programmes. Cancer experts have communicated clear evidence for lowering the age of eligibility to bowel screening by a decade for Māori and Pacific people. However, of ten bowel screening equity recommendations – made in 2019 by a panel of experts – only the recommendation to establish national Māori and Pacific bowel screening networks has been actioned. Lowering the age of eligibility by 10 years for Māori and Pacific populations remains imperative.

We must not follow the existing framework of leadership and governance used for the national breast, cervical, and bowel screening programmes in the design and development of our LC screening programme. A properly developed LC screening programme must address both the chronic lack of focus and underinvestment in Māori health, as well as inequities in power and control at health decision-making tables.

How do we achieve Māori-led LC screening?

LC screening equity for Māori can be achieved if we establish a LC screening programme that is evidence based, adequately resourced, and Māori led. This will require fundamental changes to the way that screening programmes have been established in Aotearoa.

There are many Indigenous models for working in partnership and sharing power. They include frameworks for working together respectfully and sharing power in an ethical space.

Māori have the right to develop our own models, determine our own health programmes, and administer such programmes through our own organisations. Further, as detailed in the United Nations Declaration on the Rights of Indigenous Peoples, the government has a responsibility to fund these endeavours.

Achieving an equitable Māori-led LC screening programme will require: *"free, frank, and fearless discussions in which there is zero tolerance for white fragility and racism, and in which there is an understanding that Māori and Pacific leaders' knowledge and expertise will be privileged rather than undermined"*.

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MIDLAND LUNG SCREENING PILOT

Dr Denise Aitken – Lakes DHB
Prof. Ross Lawrenson – University of Waikato Medical Research Centre

The Manchester Lung Health Study informed interest in setting up a local screening pilot in 2013, in part because targeted intervention in socially deprived communities could be a model for NZ.

Why Midland?

Midland communities' experience of LC and its outcomes drove this work. Lakes and Tairawhiti are the two DHBs included in the study of the implementation of LC screening in the NZ.

Smoking rates and age-standardised mortality rates in Lakes and Tairāwhiti exceed national averages. Tarāwhiti has the highest incidence of LC with 67.5 cases per 100,000 people and Lakes is close behind with 55.6 per 100,000. The majority (83.5%) of newly diagnosed LC patients present with stage 3 or 4 disease. Moreover, the population in these DHBs experiences significant social deprivation and LC outcomes are poor.

Furthermore, the midland LC database is an important resource. It has been collecting LC data since 2004 and contains staging and treatment data of high accuracy, which enables assessment of outcomes from LC interventions in midland and by DHBs.

Hā Ora Project

Led by Ross Lawrenson, this research project prioritised engagement with communities and co-design. It aims to identify barriers to early cancer diagnosis experienced by Māori LC patients and whānau and to co-design interventions to improve early cancer diagnosis for whanau in the localities studied.

Community hui were an important part of the design to capture the consumer voice. Early request for information at every hui included awareness of early symptoms of LC, availability of screening, and the likelihood of getting LC. The research identified patient factors (e.g., fear) and systemic factors (e.g., cost, remoteness, relational barriers with health providers) as challenges to the early diagnosis of LC.

There was a varied response from communities to the co-design component of the study. A feature of the response was a wish to focus on growing knowledge of lung health generally and not just LC screening. A wide variety of projects were supported.

Health Research Council RFP: LC screening

In February 2021, the Health Research Council released a request for proposal (RFP) specifically for LC screening. Details of the midland proposal in response to that request are as follows.

Primary objective

The primary objective is to develop and assess a Māori model of LC screening that engages those at highest risk. The first priority is co-design of the lung health check, to make it fit for our communities. A Poutiaki or stakeholder group will be established in each DHB to strengthen relationships between key stakeholders, provide leadership for a whānau-centric lung health model and identify specific cultural issues that should feature in the programme and appropriate communities to start with.

Programme outline

Components of the model include:

- Lung health check days for high-needs Māori communities. In line with Hā ora, these will include lung health advice and information to participants.
- Provision of smoking cessation advice and support and offer of a screen for COPD.
- Risk assessment for LC using the modified $PLCO_{m2012}$ risk assessment tool.
- Same criteria as the Manchester Study for invites to LDCT (i.e., risk of >1.5% over 6 years).
- Transportation and support to attend.
- The invitation process will be determined by the Poutiki group and user engagement groups.
- People aged 40–75 years with a history of or current smoking, or who are concerned about their lung health will be invited to attend.

Programme outcomes and objectives

Over 2 years it is expected that about 3,200 participants will be screened, 1,000–1,200 LDCT scans performed, and 30 new cases of LC found. The primary outcome of the proposal is evaluation of the co-design project and eventual delivery. The objectives of the programme are to:

- Understand who attended (e.g., did high-risk groups attend and accept lung health checks).
- Assess current smoking status and offer cessation advice and support.
- Determine the prevalence of undiagnosed COPD in the community by spirometry.
- Determine the proportion of attendees meeting the threshold for LDCT.

A follow-up community hui is planned to understand the community view of the appropriateness, accessibility, and acceptability of the lung health checks.

Summary

- A Hauora model offering lung health checks in an environment that is culturally safe for Māori is proposed. At its core, is a partnership approach with Māori providers, aimed at directly addressing the equity gap created by late diagnosis and poor outcomes for Māori.
- This implementation pilot will test a variety of recruitment methods for high needs and hard-to-reach patients. It will also engage a defined Māori population in which the risk assessment tool for undiagnosed cancer will be tested and will clarify the effectiveness of LDCT scanning in this population.

NATIONAL SCREENING ADVISORY COMMITTEE

Dr Jane O'Hallahan – Clinical Director, National Screening Unit, Ministry of Health

The National Screening Advisory Committee (NSAC) is an advisory group of the Ministry of Health. NSAC provides strategic governance and makes evidence-based recommendations related to new national screening programmes and major changes to current programmes. Achievement of equitable access to the screening pathway and equitable outcomes for all population groups is a key principle of national screening programmes.

Screening criteria and equity

NZ's National Health Committee document "Screening to Improve Health in New Zealand: Criteria to Assess Screening Programmes" states that screening programmes should:[1]

- Reach those who need it the most and specific approaches may be required for different population groups with priority given to Māori.
- Ensure recognition of the burden of any given condition, particularly for Māori, and the need for Māori participation.
- Involve Māori in the planning, delivery, monitoring, and evaluation of any programme using a framework responsive to Māori and underpinned by te Tiriti o Waitangi.

NSAC considerations

NSAC recently considered the NELSON study results and NZ cost effectiveness modelling. They concluded that the evidence supports LC screening effectiveness and that screening in NZ would be strongly pro-equity.

NSAC supports development of a national LC screening programme as well as proposed NZ LC screening trials and their evaluation. NSAC also noted that:

- Smoking cessation remains vitally important.
- Development of a LC screening programme is important but is at least a ten-year initiative, with adequate resourcing an absolute requirement, or it will disappoint in terms of achievement.
- The National Screening Unit must first prioritise outstanding initiatives, e.g. delivery of primary HPV cervical screening.

Central to the success of a LC screening programme will be the ability to achieve an equity-positive programme for Māori. Key areas that need to be addressed in the first instance are:

1. Planning for equity from the start and what this entails.
2. Recruitment/invitation strategy and what should be considered.
3. Co-design in terms of the rollout and how would this work.
4. Māori governance and what are the possible models.

Actioning the roll out of LC screening

Roll out of an equitable national LC screening programme will require:

- A recruitment/invitation strategy to ensure high Māori participation.
- Risk stratification to identify risk populations.
- Call-recall/register requirements.
- Screening guidelines and pathways, screening intervals, lung nodule management protocols, diagnostic and referral guidelines, and a monitoring and evaluation framework.
- Integration of smoking cessation.
- Government support via articulation of the heath system requirements and capacity and estimation of costs (e.g., equipment, IT systems, workforce, treatment).

The National Screening Unit and Te Aho o Te Kahu, the Cancer Control Agency, are working in partnership on LC screening to ensure that current diagnostic and treatment pathways are fit for purpose, assist with the local research questions, and initiate Māori governance.

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AUSTRALIAN LC SCREENING EXPERIENCE

Prof. Kwun Fong – University of Queensland Thoracic Research

The ILST is a prospective cohort study that began as collaboration between Australia (n=2,000) and Canada (n=2,000) but has since expanded more globally to include Hong Kong (n=400) and Spain (n=400). The primary aims of the ILST are to:

1. Define the optimal criteria for selecting participants for LDCT screening and specifically to compare the USPSTF 2013 recommendations against the $PLCO_{m2012}$ risk-prediction model.
2. Prospectively evaluate lung nodule management efficiency using the PanCan (Brock) nodule risk calculator to define management of abnormal CT scans.

The $PLCO_{m2012}$ risk-prediction model has been shown to be more sensitive than the NLST selection criteria for LC detection.[1] The USPSTF 2013 criteria recommend annual screening for LC with LDCT in adults **aged 55–80 years** who have a **30 pack-year smoking history** and currently smoke or have quit within the past 15 years.[2] Therefore, the hypothesis of the ILST was that the predictive accuracy of $PLCO_{m2012}$ would be greater than the USPSTF 2013 criteria for selecting at-risk individuals for screening who are subsequently diagnosed with LC. Participants who meet the ILST selection criteria will undergo baseline and 2-year LDCT screening. Baseline nodules are managed according to PanCan probability score. Participants will be followed-up annually for a minimum of 5 years.

Invitation process

Due to the number of different centres involved in the study, a variety of invitation strategies were employed depending on the recruitment site, including direct contact with primary care physicians, media advertising, and electoral roll mail-out invitations to identify potentially suitable individuals for screening. Interested participants would undergo eligibility assessment for the $PLCO_{m2012}$ criteria by phone with research nurses or web-based questionnaire. Current smokers irrespective of screening eligibility were offered smoking cessation advice and the national Quitline programme.

Eligibility

In terms of eligibility confirmation, a key inclusion criterion was satisfying either the $PLCO_{m2012}$ model for a 6-year risk score of ≥1.51% for developing LC over that time or the USPSTF 2013 screening criteria, i.e., ≥30 pack-years smoking history and quit ≤15 years ago. Exclusion criteria included clinical symptoms suggesting LC, concurrent major illness, previous LC, and other cancers not beyond 5 years of cancer-free follow-up. Those eligible were offered an interview to determine QOL assessment and pulmonary function testing.

Radiation protocol and LDCT reporting

The ILST radiology protocol was based mainly on the NLST protocol except for the use of more modern technology. The target effective radiation dose was maintained at ≤1.5 mSv effective dose.

The reporting protocol required collaboration with experienced radiologists who had read ≥300 CT chest scans in the last 3 years and use of a standardised reporting protocol for all findings. Nodules were managed according to the PanCan nodule malignancy probability calculator within an algorithm leading to calculation of the probability of a nodule being malignant. Participants will undergo baseline and 2-year LDCT screening. Participants will be followed up for a minimum of 5 years.

Interim results

In 2019, a $PLCO_{m2012}$ score ≥1.704 resulted in the same numbers screened as the USPSTF 2013 selection criteria. With 3,018 participants meeting both criteria, the $PLCO_{m2012}$ criteria detected 20 more cancers (18.2%; 95% CI: 11.5–26.7) compared with the USPSTF 2013 criteria.

At the end of 2020, all sites except Hong Kong and Barcelona have completed T0 recruitment and are currently undertaking T2 screening. Of those, 4,367 participants have been scanned in Australia, Canada, and Hong Kong. The 2020 interim results indicate that the $PLCO_{m2012}$ risk-prediction model selects statistically significantly (vs USPSTF 2013 criteria) more individuals diagnosed with LC. Despite the $PLCO_{m2012}$ model selecting individuals who were older and who had more comorbidities, the overall weighted balance of life-years potentially liveable if LC deaths were averted significantly favours using the $PLCO_{m2012}$ criteria.

ILST in 2021

The Australian experience with the ILST suggests that:

1. Use of risk prediction models to select for LC screening is feasible
2. LDCT screening can be delivered in the metropolitan centres of Australia.
3. Combined interim results suggest that risk-prediction selected screening is more effective than the USPSTF 2013 recommendations.

However, the USPSTF has subsequently reviewed and updated its guidance for LC screening. The USPSTF 2020 criteria recommend annual screening for those **aged 50–80 years** who have a **20 pack-year smoking history** or have quit in the past 15 years, i.e., compared with the USPSTF 2013 recommendations, the age range has been expanded and the pack-year threshold lowered.[4] These changes have implications for the participants who get screened. Whether the USPSTF 2020 criteria perform as well as risk-prediction selected LC screening is unclear at the present time.

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CLOSING COMMENTS

We held the inaugural meeting of the *Aotearoa Lung Cancer Screening Symposium* in April 2021 in Auckland. This one-day meeting heard from international experts, local experts, and leaders of governmental organisations with an interest in screening for LC. The meeting focussed on the recent results of international randomised trials showing LC screening successfully reduces LC mortality and how best to apply this information to address the significant disparity in LC mortality that exists for Māori. The meeting was very successful in its primary aim of bringing interested parties together to discuss how to best implement LC screening in Aotearoa New Zealand. This review provides a succinct summary of the meeting.

Assoc. Prof. Rob Young – Co-Chair of the Organising Committee for the Aotearoa Lung Cancer Screening Symposium