Study Protocol

A protocol for modelled evaluations to maximise the long-term health and economic gains of lung cancer interventions in Australia: The Lung cancer Evaluation And Policy program (LEAPp)

Pavla Vaneckova[1]^, Stephen Wade[1]^, Michael Caruana[1], Preston Ngo[1]^, Silvia Behar Harpaz[1]^, Peter Sarich[1]^, Qingwei Luo[1]^, David Eamon Goldsbury[1]^, Elvin Cheng[1], Xue Qin Yu[1]^, Christina Watts[1]^, Katherine Barron[1], Mei Ling Yap[2,3,4], Paul Bernard Grogan[1]^, Emily Banks[5]^, Kwun Meng Fong[6,7]^, Henry Marshall[6,7]^, Deme Karikios[8,9]^, Nicole Marion Rankin[10]^, Martin Carl Tammemägi[11]^, Annette McWilliams[12], Sonya Cressman[13]^, Karen Canfell[1]^*, Marianne Frances Weber[1]^*

[1]The Daffodil Centre, The University of Sydney, A Joint Venture with Cancer Council NSW, Sydney, NSW, Australia; [2]Collaboration for Cancer Outcomes, Research and Evaluation, Ingham Institute for Applied Medical Research, UNSW Sydney, Liverpool, NSW, Australia; [3]The George Institute for Global Health, Newtown, NSW, Australia; [4]Liverpool and Macarthur Cancer Therapy Centres, Western Sydney University, Campbelltown, NSW, Australia; [5]Australia National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, ACT, Australia; [6]Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, QLD, Australia; [7]University of Queensland Thoracic Research Centre at The Prince Charles Hospital, Brisbane, QLD, Australia; [8]Nepean Cancer Care Centre, Nepean Hospital, Kingswood, NSW, Australia; [9]Nepean Clinical School, the University of Sydney, Kingswood, NSW, Australia; [10]Melbourne School of Population and Global Health, University of Melbourne, Parkville, VIC, Australia; [11]Department of Health Sciences, Brock University, St Catharines, ON, Canada; [12]Fiona Stanley Hospital, Murdoch, WA, Australia; [13]Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally for the senior authorship.

Correspondence to: Dr. Pavla Vaneckova. The Daffodil Centre, PO Box 572, Kings Cross 1304, Australia.
Email: pavla.vaneckova@nswcc.org.au; apawnr@gmail.com.

Background: Tobacco control interventions in Australia have had success in recent decades, international screening trials have yielded significant mortality benefits, and therapeutic innovation in disease management is burgeoning; however, lung cancer remains the leading cause of cancer death and disease burden in Australia and the most appropriate combination of interventions to address this is unclear. Underpinned by modelling infrastructure, *The Daffodil Centre's* Lung cancer Evaluation And Policy program (LEAPp) combines large-scale linked data analysis, clinical trial data, statistical projections, evidence review, and stakeholder engagement to quantify and optimise the long-term health and economic impacts of lung cancer interventions for Australia, both alone and in combination.

Methods: A 'toolkit' of mathematical simulation models are in development to estimate which combination of interventions are likely to result in the best outcomes for the population, including in terms of morbidity, mortality, equity, health services and costs. A microsimulation model of the natural history of lung cancer,

^ ORCID: Pavla Vaneckova, 0000-0001-9213-8733; Stephen Wade, 0000-0002-2573-9683; Preston Ngo, 0000-0001-5453-0734; Silvia Behar Harpaz, 0000-0003-2287-8220; Peter Sarich, 0000-0001-9596-6825; Qingwei Luo, 0000-0002-8902-6869; David Eamon Goldsbury, 0000-0001-6247-2706; Xue Qin Yu, 0000-0001-8638-7979; Christina Watts, 0000-0002-3803-6151; Paul Bernard Grogan, 0000-0002-7680-1811; Emily Banks, 0000-0002-4617-1302; Kwun Meng Fong, 0000-0002-6507-1403; Henry Marshall, 0000-0002-9626-8014; Deme Karikios, 0000-0003-1734-9615; Nicole Marion Rankin, 0000-0002-0715-1405; Martin Carl Tammemägi, 0000-0002-4989-5058; Sonya Cressman, 0000-0003-4769-8082; Karen Canfell, 0000-0002-6443-6618; Marianne Frances Weber, 0000-0001-5731-9651.

Policy1-Lung, will simulate long-term estimates of lung cancer incidence and mortality in relation to multiple existing and hypothetical lung cancer control scenarios. Key inputs of *Policy1-Lung* will include those from a stand-alone, dynamic, Australian smoking behaviour model, and a discrete-event simulation model of systemic therapy costs and survival. In parallel with the lung cancer specific outputs of *Policy1-Lung*, a macrosimulation model of all tobacco-related diseases will be developed to capture broader health and cost impacts of tobacco interventions. Priority interventions for evaluation include integration of population-wide tobacco control strategies with low dose computed tomography (LDCT) lung cancer screening, while accounting for evolution in lung cancer therapeutics.

Discussion: LEAPp is a unique, comprehensive approach to optimising the effectiveness and cost-effectiveness of lung cancer control in Australia. The program is designed to meet evidence needs to guide policy and practice decision-making aimed at maximising the health gains of lung cancer interventions.

Trial Registration: Not applicable.

Keywords: Lung cancer; prevention; early detection; screening; modelling

Received: 16 October 2022; Accepted: 24 February 2023; Published online: 09 March 2023.
doi: 10.21037/ace-22-11
View this article at: https://dx.doi.org/10.21037/ace-22-11

Introduction

Lung cancer is the leading cause of cancer death in Australia and worldwide (1,2). In 2020, it was the second most common cancer globally, with ~2.2 million new cases and 1.8 million deaths, constituting 18% of all cancers (3). In Australia, lung cancer is one of the most diagnosed cancers (4th in men and 5th in women in 2021) (4), and remains the most common cause of cancer-related death (17.7%), with 8,693 deaths (4,998 men and 3,695 women) in 2021 (5). As a leading cause of cancer burden (3) the disease has a significant impact on Australian individuals and communities, and imposes substantial economic costs to the health care system (6). Although age-standardised lung cancer rates have been decreasing in Australia and are expected to fall over the next several decades, the number of deaths from lung cancer is expected to increase, mainly due to population growth and ageing (7). As such, investment in lung cancer control remains a key priority in Australia, and evidence-based interventions are required across all components of lung cancer development and progression. A central challenge is knowing which investments, and combinations of investments, are likely to result in the best outcomes for the population, including in terms of morbidity, mortality, equity, health services and costs.

It is in this context that *The Daffodil Centre* has developed a research framework aimed at identifying 'best buys' in lung cancer control by using a suite of methodological approaches to systematically evaluate the effectiveness and cost-effectiveness of lung cancer interventions both alone and in combination. Where data providing a specific answer to a policy question are lacking—a common situation especially when comparing and considering synergies of different population-level and regulatory strategies—predictive modelling is a frequently used surrogate for informing policy decisions and can be used to optimise key implementation parameters (8,9). Leveraging *The Daffodil Centre's* existing program of work in bowel (10) and cervical cancer (11), the Lung cancer Evaluation And Policy program (LEAPp) will be underpinned by mathematical modelling infrastructure. Although the natural history of disease is unique to each specific cancer, the modelling methodologies share design principles, health and economic perspectives, time horizons, implementation of costs and other technical details. Integrating multiple data sources, these sophisticated models make reliable projections of cancer outcomes in relation to multiple 'what if' scenarios, comparing the impact of new and existing cancer interventions. Furthermore, by modelling interventions in combination, the short- *vs.* long-term impact of these interventions can be optimised—for example the long-term lung cancer incidence reductions in relation to investment in primary prevention can be balanced against the short-term mortality reductions in relation to screening.

Since its inception in 2016, LEAPp has involved the development of program model components using evidence review, large scale epidemiologic analyses, and statistical projections. Each model component and/or data input has

Figure 1 A schematic of the LEAPp models and analytic approach. LEAPp, Lung cancer Evaluation And Policy program; DALY, disability-adjusted life year; QALY, quality-adjusted life year.

also served as a unique contribution to the national and international evidence base on lung cancer causes, care, and outcomes. Currently, four independent models are in development to meet LEAPp objectives (*Figure 1*): (I) a microsimulation model of the natural history of lung cancer, *Policy1-Lung*; (II) a microsimulation model of lung cancer treatment and survival, *txSim*; (III) a microsimulation model of Australian tobacco smoking patterns; and (IV) a macrosimulation model of smoking-related chronic diseases. The four models are complemented by statistical projections which provide independent, rapid insights into policy-relevant issues and can also be used for validation purposes. These population-wide models can be used separately and in combination to quantify the potential impact of existing and emerging lung cancer control interventions on long term health gains and costs. Under the guidance of a scientific advisory group (SAG), key lung cancer control components to be addressed initially by LEAPp include population-wide tobacco control strategies and policy-relevant smoking prevalence benchmarks, lung cancer screening with low dose computed tomography (LDCT), and evolving treatment patterns.

Primary prevention: tobacco smoking in Australia

Tobacco smoking is the predominant modifiable risk factor for lung cancer. In Australia, up to 84% of men and 71% of women diagnosed with lung cancer have a history of smoking (12) and as such, tobacco control remains the most important and effective primary prevention strategy for

lung cancer and is also key to preventing at least 30 other diseases, including heart disease, respiratory disease, and other cancer types (13). Australia has a strong history of tobacco control and was one of the first countries to ratify the World Health Organization Framework Convention on Tobacco in 2004 (14). Since the early 1990s, Australia has implemented a wide range of population-based interventions to prevent tobacco use. These include the Tobacco Advertising Prohibition Act and first National Tobacco campaign in the 1990s; point of display bans, labelling with graphic health warnings on tobacco products, and designating smoke-free areas in the 2000s; and the Tobacco Plain Packaging Act and the second National Tobacco Campaign in the early 2010s; all underpinned with staged excise tax increases on all tobacco products (15). These interventions have been associated with significant declines in daily smoking, from 24.3% in 1991 to 11.0% among people aged ≥14 years in 2019 (16).

However, Australia's tobacco control efforts have recently decelerated (17), and Australia's National Tobacco Strategy lapsed in 2018 (18). A new National Tobacco Strategy is currently in draft (19), and while the 2021 National Preventive Health Strategy set a target of national daily smoking prevalence of 5% or less for adults (≥18 years) by 2030 (20), there are no clear strategies outlined to achieve this target. There is also a risk of increased smoking uptake among non-smoking young people in relation to e-cigarettes (21-23), and the uncertainty of the impact on rates of smoking from large social disruptions, such as the coronavirus disease 2019 (COVID-19) pandemic (24). Thus, there is an ongoing need for contemporary evidence to support government investment in tobacco control programs and commitment to policy change that will minimise smoking and its associated health, social, and economic costs.

To evaluate the impact of tobacco control measures on smoking patterns, and in turn, the impact of smoking patterns on lung cancer and other tobacco-related chronic diseases, LEAPp is developing a simulation model of population-wide Australian smoking behaviours. Simulated estimates of smoking prevalence and intensity will be key inputs for two distinct models of disease: the lung cancer natural history microsimulation model, *Policy1-Lung*, and the macrosimulation model of tobacco-related diseases (*Figure 1*). Scenario modelling can compare the effectiveness and cost effectiveness of existing and renewed tobacco control measures on contemporary and future smoking prevalence and the downstream impact on reductions in lung cancer and other tobacco related diseases. LEAPp will also generate new evidence relating to emerging tobacco control priority areas in Australia, including tobacco retail supply, the uptake of e-cigarettes among young people, and tobacco industry interference strategies, to support policymakers to mitigate the long-term health impacts of tobacco smoking and e-cigarettes in Australia.

Early detection: lung cancer screening

Lung cancer mortality can be reduced if the disease is detected and treated early; however, early diagnosis can be difficult because symptoms are common, non-specific, or altogether absent (25). Consequently, most lung cancer patients are diagnosed clinically with symptoms of advanced lung cancer when prognosis is poor [in Australia the 5-year relative survival rate is 68% for stage I, and 3% for stage IV (26)]. Early detection strategies, such as population-based screening of asymptomatic individuals, could be important for improving lung cancer outcomes. Lung cancer screening has been demonstrated as clinically effective in two large randomised controlled trials which showed that LDCT chest scans of asymptomatic individuals with a history of heavy smoking reduced lung cancer mortality by 20–24% (27,28). However, selection criteria for these trials differed and although it is generally agreed that lung cancer screening is only likely to be of net benefit for individuals at high risk of lung cancer, there is no consensus across jurisdictions as to the optimal definition of 'high risk'. The use of individualised risk calculators that incorporate demographic and clinical factors in addition to smoking history [such as $PLCO_{m2012}$ (29)] have been shown to have better predictive performance than the broad age and categorical smoking criteria used in the trials (30). Further, implementation of risk-targeted screening at a population level remains a challenge with many issues, such as integration of smoking cessation and optimising participation, not captured in effectiveness trials (31,32).

To date, a few countries have implemented national lung cancer screening programs, and pilot programs are underway in a number of jurisdictions (33). In 2020, the Australian government conducted an enquiry into the prospects, process, and delivery of a national lung cancer screening program, which was reviewed favourably by the Medical Services Advisory Committee in 2022 (34). The enquiry concluded that a risk-targeted national lung cancer screening program in Australia would be feasible however federal funding decisions remain ongoing. A key

priority for LEAPp is to inform effective and cost-effective implementation of a national lung cancer screening program, similar to *The Daffodil Centre's* parallel work in cervical (35) and bowel cancer screening (36), which have supported policy reform in Australia.

Treatment and survival

The management of treatment for people with lung cancer is complex and depends on histology, stage, molecular profile, and location of the cancer, as well as the wellbeing of the individual and their preferences. Treatments consist of various combinations of surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, as well as supportive and palliative care (37). In the past, favourable outcomes were mainly observed in people diagnosed with early-stage disease at diagnosis. However, many targeted and immunotherapeutic agents have emerged in the last decade, improving survival for people diagnosed with locally advanced and metastatic lung cancer (38-40). The survival and economic impacts of new treatments and an evolving standard of care are highly relevant to health policy. Immunotherapies improve survival for many patients, however the costs of these drugs present funding challenges, including for the future. Further, suboptimal care in the form of delays to treatment, underutilisation of treatment, or unwarranted variations in care must be minimised to ensure that the promise of new health technologies are optimally translated from trials to the clinic. LEAPp is developing a discrete event microsimulation model of systemic therapy utilisation, costs and survival for people diagnosed with advanced lung cancer that can incorporate new therapies and indications over time. The model (*txSim*) will be used to inform cost-effectiveness analyses of strategies for lung-cancer control and provide contemporary estimates of lung cancer treatment costs and benefits, and up-to-date estimates of budget impact.

Program objectives

Bringing together a 'toolkit' of mathematical models supported by a multidisciplinary team of experts, the primary objective of LEAPp is to provide policymakers with an evidence base for decision making in lung cancer control. Planned evaluations are focused on optimising the effectiveness and cost-effectiveness of tobacco control strategies and LDCT screening, both alone and in combination, while accounting for the evolution of lung cancer care as treatments advance. By design, LEAPp can be rapidly mobilised to address contemporary, priority issues in lung cancer control over time. To this end, a secondary objective of LEAPp is to conduct high quality epidemiological research on local risk factors for lung cancer, patterns of care studies and health services research. Where applicable, we present the protocol in accordance with the SPIRIT reporting checklist (available at https://ace.amegroups.com/article/view/10.21037/ace-22-11/rc).

Methods

LEAPp components

SAG

A SAG with representatives from all states and territories of Australia was convened to guide the initial research strategy of LEAPp. Its members were appointed from a wide spectrum of medical and scientific fields across the lung cancer control continuum, including research academics, clinical specialists, general practitioners, and policy experts, through an invitation to a prioritisation workshop. The group also included public representatives, such as lung cancer survivors and their spokespersons. The objective of the workshop was to prioritise lung cancer interventions and research questions for evaluation. The workshop was structured into sessions covering intervention touch points from primary prevention through to palliative care. Prior to the meeting, issues that were considered in and out of scope were articulated, and extensive scoping reviews were conducted to identify existing and emerging lung cancer interventions including: national and international smoking prevalence policy benchmarks, smoking cessation, screening, early diagnosis, treatments for both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), interventions for side effects and complications of treatment, and psychosocial interventions. SAG members identified lines of enquiry likely to have the greatest impact on lung cancer outcomes in Australia and agreed to ongoing engagement in self-identified areas of interest and expertise. As LEAPp has evolved and intersected with these areas, SAG members have provided expert guidance on research design and outcomes. SAG members have also been invaluable as mentors to post-graduate students and early career researchers, and as partners on funding applications.

The involvement of clinicians, patient representatives, and policy experts ensures relevance of outcomes to the real-world setting. The next step is to capture clinical,

policy, and community input to guide parameterisation of the health economic models and to establish prior distributions for Bayesian analyses where existing data are scarce. The SAG will also be key to dissemination of findings through community and professional networks.

Evidence review

Evidence reviews underpin the work of LEAPp and include both systematic and scoping reviews. Scoping reviews aimed at understanding the landscape of lung cancer control in Australia were conducted prior to, and presented at, the inaugural SAG meeting in 2017 for consultation on the initial research strategy. Scoping reviews are also conducted with the purpose of horizon scanning, especially in the context of new treatments and diagnostic technologies, contemporary evidence on lung cancer risk factors, and emerging issues such as the global COVID-19 pandemic. Systematic reviews and meta-analyses are registered on PROSPERO and conducted to inform model inputs where local data are scarce or unavailable, and to advance LEAPp methodologies.

To date, LEAPp has published systematic reviews of lung cancer statistical projection methods (41), residential radon exposure and risk of lung cancer among individuals without a history of tobacco smoking (42), and smoking behaviour changes during the pre-vaccination phase of the COVID-19 pandemic (24). Scoping reviews have included an overview of environmental and genetic risk factors for lung cancer (43), a validation study of published lung cancer projections (44), and a review of methods used to apply lung cancer utility values in cost-effectiveness analyses of LDCT screening (45). Ongoing horizon-scanning reviews include: emerging lung cancer therapies, indications, and integration of therapies into routine care; the potential carcinogenic harms of vaping products, the prevalence of their use in Australia and potential impacts on future tobacco smoking rates; risk prediction tools for identifying individuals without a smoking history at high risk of lung cancer; and potential impact of the COVID-19 pandemic on health system disruptions and risk factors in Australia.

Large-scale epidemiology

Epidemiological analyses of large, population-based datasets and observational studies with linked health records will be conducted to establish the distribution, trends, and determinants of lung cancer causes, care and outcomes in the Australian population (*Figure 1*). These data are used to quantify local risk estimates for lung cancer, patterns of lung cancer care, and prognostic factors that can be used to parameterise simulation models, as well as adding to the global evidence base on lung cancer epidemiology. LEAPp utilises the Sax Institute's '45 and Up Study', a large prospective Australian study that has followed ~250,000 individuals from the state of New South Wales over the past ~15 years with linked health and death records (46). LEAPp will also access the Enduring Cancer Data Linkage (CanDLe) program (47), which is a complete capture of cancers diagnosed in New South Wales from 1972 onward linked to state hospitalisation and death records. CanDLe will be used to quantify trends in lung cancer incidence, mortality, and survival, and will serve as calibration targets for *Policy1-Lung*.

Many LEAPp model inputs have been developed using the 45 and Up Study to date, including validation of the $PLCO_{m2012}$ risk prediction tool in the Australian context (30). The cohort was used to generate contemporary relative risk estimates of smoking related cancer risk (48), which are key to estimating the number of lung cancer diagnoses and deaths that occur among Australians with a smoking history, given that smoking history is not systematically captured at a population level. Estimates of utility values by different disease states (49) and among Australians potentially eligible for lung cancer screening (50) will be used to estimate quality-adjusted life years (QALYs) in cost-effectiveness analyses. Similarly, comprehensive estimates of the total healthcare costs for lung cancer by stage, phase of care, and histological sub-type (6) will be key to cost-effectiveness estimates and budget impact studies. Analyses of patterns of lung cancer care and prognostic factors (51-54) will inform evaluations aimed at assessing the costs and impact of suboptimal care in the form of delays to treatment, underutilisation of treatment, or unwarranted variations in care.

Australian Smoking History Simulator and statistical projections

Modelling tobacco smoking behaviours is key to LEAPp, firstly because historical smoking patterns are predictive of current disease rates (due to the significant lag between population level tobacco exposure and its effect on cancer rates—up to 30 years for lung cancer) (55) and secondly because forecasting smoking behaviour is key to modelling tobacco control interventions.

LEAPp initially used a statistical projection approach to

estimate the impact of historical smoking trends on future rates of lung and other smoking-related cancers (7,56-58). Using age-period-cohort modelling that accounted for smoking trends within each period, this work estimated that ~78,000 lives were saved between 1956 and 2015 due to current and past tobacco control initiatives for lung cancer alone, and that if these measures continue to have the expected effect, they will avert a further 1.9 million lung cancer deaths in the next 85 years (58). These analyses generated predictions of future tobacco-related cancer rates at an aggregate level, and are useful for providing policymakers with rapid insights to enable priority setting. The next step is to develop a dynamic microsimulation model of life-course smoking behaviours for the Australian population (59). This type of model can account for differences in smoking behaviours at an individual level, such as duration and intensity, and can output detailed smoking histories by age, sex and birth cohort. Similar to the U.S. Smoking History Generator developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) (60,61), our Australian Smoking History Simulator will be used to underpin projections of lung cancer and other smoking-related diseases given changes in smoking initiation, cessation, and/or intensity.

Our Australian Smoking History Simulator uses a Bayesian calibration method to synthesise mortality data for the Australian population, Australian data on smoking status and age at stopping smoking, and hazard ratios of death by smoking status estimated from the 45 and Up Study. Foundational work for the model involved harmonising distinct measures of smoking behaviour across multiple survey series (62). The first iteration of the model outputs historical and future smoking prevalence trends by estimating initiation and quit rates by age, sex, and birth cohort, and will eventually incorporate patterns of smoking intensity. The model is currently being used to predict 50-year estimates of smoking prevalence given a number of hypothetical scenarios of smoking cessation and initiation, including zero uptake for Australians born after 2010. Scenario estimates such as these will constitute key data inputs for *Policy1-Lung* and the macrosimulation model of smoking related diseases (*Figure 1*) so that the health and cost impacts of smoking patterns and tobacco control interventions can be quantified.

Lung cancer projections: *Policy1-Lung*

A flexible microsimulation platform, *Policy1-Lung*, is being developed to model the natural history of lung cancer for the Australian population. Integrating multiple data sources, this mathematical model will be able to make reliable projections of cancer outcomes in relation to multiple 'what if' scenarios, comparing the impact of new and existing lung cancer interventions. *Policy1-Lung* will be calibrated using outputs from our Australian Smoking History Simulator, national cancer statistics and CanDLe, screening trial data, and epidemiologic data on smoking generated by LEAPp, evidence reviews, along with guidance from SAG and stakeholder consultation. It will simulate individuals' events relating to the 'natural history' of lung cancer including preclinical and clinical lung cancer, and deaths due to lung cancer or other causes (*Figure 2*). The structure of the pre-clinical 'states' for an individual in *Policy1-Lung* resembles that of MISCAN-Lung (63), which has been utilised by the CISNET Lung working group to investigate the benefits and harms of hundreds of different lung cancer screening strategies (9). The two-stage clonal expansion carcinogenesis and pre-clinical stage-progression model was chosen because it was most similar to our other in-house models of bowel (10) and cervical cancer (11). Parameterisation of the event rates and estimation of the parameter-values will be performed by a Bayesian calibration (or evidence synthesis) procedure. This includes SAG and expert input to determine a suite of possible models with distinct parameterisations and prior beliefs about the parameter values; then parameter-values that are most compatible with the data listed above (smoking behaviour, cancer incidence and survival, screening test characteristics and stage outcomes, and all-cause mortality by smoking status) are found using Markov Chain Monte Carlo methods, and finally a model selection process is applied guided by goodness-of-fit statistics. Once calibrated, the model will be validated using independent data sources, such as the PLCO trial data. The model will be used to evaluate the impact of population lung cancer control measures, including the number of lives saved and health system costs, and will initially be used to evaluate lung cancer screening, comparing the effects of participation and screening adherence rates on effectiveness and cost-effectiveness. Ultimately, the model can be tailored to address the interplay between tobacco control, screening, and therapeutic innovation, by assessing the relative benefits of a combination of interventions across lung cancer development and progression.

Lung cancer treatment and survival modelling: *txSim*

The cost-effectiveness of upstream interventions that impact the incidence (e.g., tobacco control) and stage

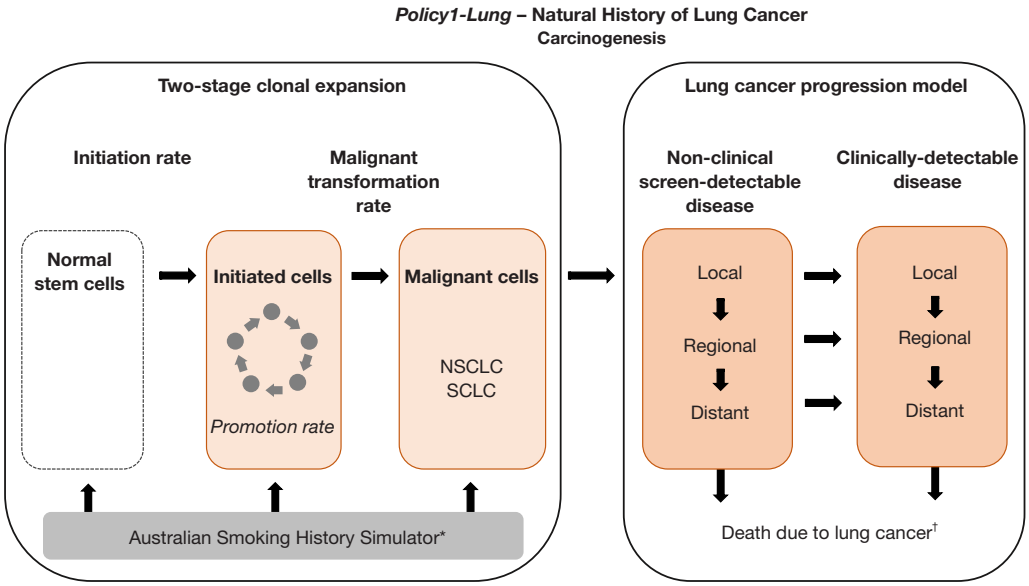

Figure 2 A schematic of *Policy1-Lung*, a microsimulation model of lung cancer carcinogenesis as a process of two-stage clonal expansion. *, rates depend on smoking intensity; †, death can also occur from causes other than lung cancer at any stage and may also be related to smoking status. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

distribution (e.g., lung cancer screening) of lung cancer will depend partly on the survival and cost expectations of lung cancer treatments for advanced disease. Because therapeutic innovation in the era of immunotherapy and targeted therapy is changing rapidly, direct measurement or estimates of contemporary per-patient lung cancer treatment costs and survival are not available. There is therefore a need for reliable and contemporary data on lung cancer treatment in Australia that can incorporate new therapies and indications over time. To this end, LEAPp is developing a discrete event microsimulation model (*txSim*) to estimate costs and survival expectations under contemporary treatment for advanced lung cancer. Initially simulating patients with advanced lung cancer, the model incorporates progression-free survival data from clinical trials, biomarker prevalence rates from epidemiologic analyses, expert-derived treatment algorithms, and Australian health system costs to simulate patient treatment histories and their accompanying costs. Model outputs from *txSim* can then be applied to lung cancer incidence rates generated from *Policy1-Lung* to estimate contemporary costs of treatment, without the need for data from large-scale, observational studies of patient populations which are resource intensive, costly and become obsolete relatively quickly. The model can be expanded over time to incorporate innovations in treatments for earlier stage disease, including radiotherapy, immunotherapy and targeted therapy.

Projections of smoking related diseases: macro-simulation model

To estimate the health economic impact of tobacco control interventions on lung cancer and other tobacco-related diseases simultaneously, allowing for comorbidity, LEAPp is developing a macrosimulation model (i.e., models the whole population rather than individuals). To do this, a proportional multi-state life table (pMSLT) approach is being used, similar to previous methodologies (64,65). Key inputs for pMSLT are smoking factors generated by the Australian Smoking History Simulator, national data on the incidence and mortality of diseases established as having a causal link with tobacco smoking (e.g., cancers of the larynx, oesophagus, liver, head-and-neck, liver, bladder, pancreas and colorectum, and cardiovascular and respiratory disease), data on disability weights and quality of life, as well as costs. The model can compare years of life lost (YLLs), disability adjusted life years (DALYs), quality-adjusted-life years (QALYs), and costs in a population with and without an intervention. Evaluations will be conducted from a societal and health services perspective over the remaining lifetime of selected Australian cohorts (e.g., everyone alive in Australia in 2016).

Table 1 Priority LEAPp evaluations. The impact of evaluations will be assessed in terms of health outcomes, resource use and costs

Evaluation	Focus area	Status (anticipated completion date)
Renewed national mass media anti-smoking campaign	Reduction in smoking-related disease	Planning (2025/2026)
Restrictions on the number of tobacco retail outlets	Reduction in smoking-related disease	Potential
Best-practice smoking cessation treatment in cancer clinics	Reduction in smoking-related cancers	Planning (2026/2027)
Smoking initiation and cessation scenario modelling—impact on 50-year predictions of smoking prevalence	Reduction in smoking prevalence	Complete (under review)
Smoking initiation and cessation scenario modelling—impact on the number of Australians potentially eligible for lung cancer screening	Healthcare resource utilisation	Ongoing (2023/2024)
Achieving ≤5% daily adult smoking prevalence by 2030	Reduction in smoking-related disease	Ongoing (2023/2024)
A National Lung Cancer Screening Program as recommended by Cancer Australia (34), including the impact of participation and screening adherence	Reduction in lung cancer mortality	Planning (2025/2026)
A National Lung Cancer Screening Program that incorporates smoking cessation treatment	Reduction in lung cancer mortality	Planning (2026/2027)
Optimising risk criteria to define eligibility for a National Lung Cancer Screening Program	Reduction in lung cancer mortality	Planning (2027/2028)
5-year lung cancer patient population by stage, histology, and molecular status to inform health-system resource needs	Lung cancer prevalence estimates	Ongoing (2023/2024)
Optimising investment in tobacco control and lung cancer screening in combination	Reduction in lung cancer mortality	Potential
Optimal implementation of lung cancer care guidelines versus current practice	Reduction in lung cancer mortality	Potential
Potential disruptions of lung cancer diagnosis and care during COVID-19 pandemic	All lung cancer outcomes	Potential

LEAPp, Lung cancer Evaluation And Policy program; COVID-19, coronavirus disease 2019.

Health economic framework

LEAPp uses a common health economic framework so that best-value investment, or 'best buys', can be compared within and between analyses (10). For each evaluation, several primary outcomes are considered, including health benefits (e.g., reduction in lung cancer incidence/mortality), harms (e.g., adverse consequences of screening), resource use (e.g., treatment, diagnosis, and screening-related healthcare costs), and health economic outcomes (e.g., discounted lifetime cost, life years, QALYs, and cost-effectiveness). For each intervention, the primary outcomes listed may be expanded or tailored. The comparator for analyses is the general population (or specific subgroup of interest) without the influence of the intervention being assessed. A health services perspective is applied, and efforts are being made to expand to the societal perspective, including characterisation of out-of-pocket expenses. From a health services perspective, costs incurred by governments and the health system over a person's lifetime are incorporated. For each evaluation, multiple time horizons may be chosen as appropriate to the specific intervention. A 5% annual discount rate and the indicative willingness-to-pay (WTP) threshold of AUS$30,000–$50,000 per life year saved will be used, with alternative WTP thresholds included for comparability. One-way and probabilistic sensitivity analyses and uncertainty analyses will be conducted as required to assess the impact of model parameter uncertainties on the key model findings (10).

Priority analyses and evaluations

A list of priority modelled analyses and evaluations are listed in *Table 1*. Broadly, these cover epidemiological forecasts for lung cancer patient populations and evaluations of

interventions to reduce lung cancer incidence and mortality, as well as other chronic diseases caused by smoking. Forecasts of patient or screening-eligible populations will be used to estimate future demand for health resources, particularly systemic therapies and lung cancer screening, and will inform budget impact analyses in health technology assessments. The long-term health and economic benefits of renewed investment in mass media anti-smoking campaigns will be forecast using the macrosimulation platform, with a potential extension to analyses of restrictions on tobacco retail outlets. Modelling assumptions would be underpinned by data from prior campaigns [e.g., (66-68)] and experiences from other jurisdictions [e.g., (69,70)].

Priority evaluations of the National Lung Cancer Screening Program as recommended by Cancer Australia and the Medical Services Advisory Committee (34) will include analysis of the impact of participation and screening adherence, and will combine estimates of the eligible population using the Australian Smoking History Simulator, estimates of the numbers of lung cancers detected from the *Policy1-Lung* natural history model, and estimates of lung cancer costs and survival from *txSim*. Resource utilisation data, nodule detection rates, and follow-up procedures, will be obtained from the International Lung Screening Trial (71). Other planned program-related evaluations include analyses of potential alterations to the program, such as changes to eligibility, screening intervals, and the incorporation of smoking cessation interventions; driven by data including from the international experience in implementation, expert input, and *Policy1-Lung's* scenario-modelling capability. The impact of these interventions will be assessed in terms of health outcomes, resource use, costs, and cost-effectiveness. Lastly, potential analyses could consider investment strategies for combinations of tobacco control and lung cancer screening interventions, or improvements in the adherence or updates to lung cancer care guidelines (37).

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). As human subjects were not involved in the LEAPp protocol, approval by a Human Research Ethics Committee was not required. Ethics approval for the use of deidentified data from 45 and Up Study was provided by the NSW Population and Health Services Research Ethics Committee (2019/ETH01746). Findings will be published as governmental reports or publications in peer-reviewed journals, and presented at scientific meetings, conferences, and media outlets.

Discussion

LEAPp is a multi-component, dynamic research program that aims to improve lung cancer control in Australia. The program is underpinned by modelling approaches that synthesise data from multiple sources and allow systematic identification of lung cancer control strategies that are efficient, effective and cost-effective. LEAPp has been leveraged from existing programs in bowel and cervical cancer, which have transformed cancer control both in Australia and worldwide (72). Components of each LEAPp model and data generated to parameterise each model, are disseminated as independent research outputs and enhance the international evidence base on lung cancer causes, care, and outcomes, as well as tobacco control and other smoking-related chronic diseases. Further, many of the LEAPp research outputs to date have been conducted and published by post-graduate students and early-career researchers, which demonstrates the program's potential for capacity building. Initial planned evaluations are focused on providing policy- and practice-relevant evidence for renewed investment in tobacco control, optimised implementation of lung cancer screening, and reducing inequities in lung cancer patterns of care.

LEAPp is designed to be able to respond rapidly to emerging health and policy issues. Several emerging areas of interest are already in consultation, and a particular issue highlighted by consumer representatives on the SAG is lung cancer among individuals without a history of smoking. Current evidence shows that lung cancer patients without a history of smoking are more likely to be women, to be diagnosed with adenocarcinoma, and/or to be diagnosed at an earlier age (43). LEAPp analyses found that Asian-born Australians who never smoked are about three times as likely to be diagnosed with lung cancer than those born elsewhere (73). Scoping reviews have identified many environmental and occupational exposures for lung cancer, however apart from individuals in certain occupations, to date, there is no known targeted strategy to identify lung cancer early for individuals without a smoking history. Work in this area is ongoing, and as evidence emerges, *Policy1-Lung* can be mobilised to evaluate the effectiveness and cost-effectiveness of potential strategies for prevention and early detection.

Another key issue in lung cancer control for Australia is the relatively high rates of smoking and smoking-related

chronic diseases in Aboriginal and Torres Strait Islander communities, those living in rural and remote areas, and those with low socioeconomic indicators (15,34,74-76). While the LEAPp modelling infrastructure is initially being developed to capture whole of population exposure and outcomes, over time it can be parameterised and calibrated to priority populations. By capturing their unique smoking history, LEAPp can quantify the long-term gains of smoking prevention strategies and will be a powerful tool for demonstrating progress in tobacco control. Model outputs can be used to quantify long-term health gains and assess the potential impact of screening [similar to models conducted for bowel screening in Australia (77)].

Population-wide data on the impact of the COVID-19 pandemic on lung cancer outcomes will be an important factor to account for in all planned evaluations. In 2020 the COVID-19 pandemic triggered unprecedented public health interventions that affected all aspects of public life. Various waves of measures such as social/physical distancing and 'lockdowns' have resulted in changes in risk behaviour (e.g., tobacco use), and delays and changes in healthcare delivery (78). The long-term consequences of widespread health system disruptions on cancer outcomes are largely unknown. Given the lack of empirical evidence, modelling provides a unique opportunity to generate policy-relevant information to balance health system disruptions against prioritisation strategies for reducing long-term harms. The COVID-19 and Cancer Global Modelling Consortium (CCGMC, www.ccgmc.org) brought together the global cancer modelling community with the purpose of supporting decision-making in cancer control in response to pandemic disruptions. As LEAPp develops over time, it can also be harnessed to contribute to the global modelling efforts aimed at quantifying the long-term impacts of the COVID-19 pandemic on cancer outcomes world-wide.

The successes of LEAPp to date have largely come from access to high quality, population-based health datasets, a multidisciplinary team of experts, and the integration of modelling with stakeholder engagement. Rigorous epidemiologic analyses of patterns of disease from large-scale datasets, such as routinely collected, administrative health databases, are critical for informing robust model parameters and modelling assumptions. We leveraged in-house expertise from existing, more advanced simulation models for bowel and cervical cancer and have gained critical input from shared experiences in other jurisdictions, such as Canada. Collaboration with national and international experts will also provide opportunities for comparative analyses and access to additional data that could be used to validate our models. Combining program components has required careful planning to balance the time-consuming process of model building with the more immediate need for research outputs. Overall, modelling and large-scale health data are most powerful when harnessed within a broader framework of lived experience, including patient and clinician perspectives and the constraints and needs of public policy. The SAG and ongoing involvement with advocacy organisations in the not-for-profit sector have been integral to identifying community-relevant issues, evidence gaps, and stakeholders. The direct involvement of the SAG in research design, and meaningful engagement with community networks will also lead to more equitable and impactful research outputs; we expect that this framework will result in knowledge gains that will maximise improvements in lung cancer control in Australia.

Lung cancer is Australia's leading cause of cancer death and opportunities to reduce the lung cancer burden are substantial. Bringing together a comprehensive toolkit of mathematical simulation models that integrate large-scale epidemiology, evidence synthesis, and public policy, with expert input from a SAG, LEAPp will lead to long-term reductions in lung cancer incidence, morbidity, mortality, and inequity by continually optimising evidence-based interventions in lung cancer control.

Acknowledgments

We are grateful to the members of the Scientific Advisory Group who kindly continue to provide feedback to the LEAPp. We would also like to thank the Sax Institute, the Australian Institute of Health and Welfare, the Australian Bureau of Statistics, for providing us with data for many of the studies in our program. Scientific Advisory Group members: A/Prof. Cleola Anderiesz, Cancer Australia (previous appointment); Prof. David Ball, Peter MacCallum Cancer Centre; Prof. Emily Banks, Australian National University National Centre for Epidemiology and Population Health; Dr. Allison Black, Royal Hobart Hospital; Dr. Jeff Bowden, Flinders Medical Centre Southern Adelaide Local Health Network/Flinders University; Dr. Lauren Bradbury, Orange Hospital; Ms Clare Brown, Chris O'Brien Lifehouse; A/Prof. Wendy Cooper, Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital; Mary Duffy, Peter MacCallum Cancer Centre; Dr. Sally Dunlop,

Consultant; Prof. Jon Emery, University of Melbourne; Prof. Kwun Fong, The Prince Charles Hospital, University of Queensland (chair); Dr. Becky Freeman, University of Sydney; Dr. Catherine Granger, Austin Hospital; Dr. Laura Kirsten, The Nepean Cancer Care Centre; A/Prof. Nicole Kiss, Peter MacCallum Cancer Centre; Dr. Renee Manser, Peter MacCallum Cancer Centre Royal Melbourne Hospital; A/Prof. Henry Marshall, Holy Spirit Northside Private Hospital; Dr. Nikki McCaffrey, Deakin University; Dr. Sam McCormack, RPAH Medical Centre, Quality and Clinical Training across Alfred Imaging sites; Dr. Annette McWilliams, Institute for Respiratory Health, Fiona Stanley Hospital; Prof. Christine Paul, University of Newcastle; A/Prof. Nick Pavlakis, Royal North Shore Hospital University of Sydney; Dr. Chris Pene, Sacred Heart, St Vincent's Hospital; Prof. Jennifer Philip, St. Vincent's Hospital; Carolyn Riordan (In memoriam); Gill Stannard, consumer representative; A/Prof. Emily Stone, Department of Thoracic Medicine, St Vincent's Hospital; Prof. Shalini Vinod, Liverpool Hospital, University of NSW; Dr. Thanuja Thachil, Alan Walker Cancer Care Centre; Dr. Mei Ling Yap, Liverpool and Macarthur Cancer Therapy Centres, Western Sydney University, Campbelltown, New South Wales, Australia.

Funding: This program has received funding from a Medical Research Future Fund (MRFF) Preventive and Public Health Research Initiative: 2019 Target Health System and Community Organisation Research Grant Opportunity (No. MRF1200535).

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://ace.amegroups.com/article/view/10.21037/ace-22-11/rc

Peer Review File: Available at https://ace.amegroups.com/article/view/10.21037/ace-22-11/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://ace.amegroups.com/article/view/10.21037/ace-22-11/coif). XQY serves as an unpaid editorial board member of *Annals of Cancer Epidemiology*. SW declares that he received funding from Australian Department of Health (as part of a sub-contract with the Australian National University) for a report on trends in smoking prevalence in Australia (paid to institution), which is featured in this protocol. SW also received grant funding from the Australian National Health and Medical Research Council (paid to his institution) for a project to predict trends in cancer in Australia on which he is an associate investigator. MC is an investigator on an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass') (ACTRN12613001207707 and NCT02328872), which is conducted and funded by the Australian Centre for the Prevention of Cervical Cancer (ACPCC), a government-funded health promotion charity. The ACPCC has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc. USA. However neither MC nor his institution on his behalf (The Daffodil Centre, a joint venture between Cancer Council NSW and The University of Sydney) received direct or indirect funding from industry for Compass Australia or any other project. PN was supported by an Australian Research Training Program PhD scholarship funded by the Australian Government. EC was supported by a Cancer Council NSW PhD scholarship program. CW has received payment to her institution for research relating to e-cigarettes from the Australian Federal Department of Health and Aged Care, Cancer Council NSW, Cancer Institute NSW, NSW Minister of Health, and the Minderoo Foundation. CW also has received consultancy payment from the Australian Federal Department of Health and Aged Care and Cancer Council NSW for research services relating to the National Tobacco Campaign (paid to individual). EB is supported by a Principal Research Fellowship from the National Health and Medical Research Council of Australia (reference 1136128), paid to her institution. KMF's work has been supported by multiple National Health and Medical Research Council (NHMRC) and Medical Research Future Fund (MRFF) grants (paid to institution). KMF has also received royalties from UpToDateReviewer and the Cochrane Clinical Answers Reviewer (both paid to self). KMF also received travel support from WCLC 2022 and ATS 2022, and previously, held a role of President of the Asia Pacific Society of Respirology (unpaid). KMF received support by Olympus with loan bronchoscope for the purpose of a research study (no financial funding) and he received software licensing for Computer Aided Diagnosis research in the International Lung Screen Trial (ILST) by Mevis Veolity. HM has been supported by NHMRC and MRFF grants related to lung cancer screening trials (paid to institution). HM has received honoraria from Astra Zeneca for lectures on lung cancer and smoking cessation and held an advisory role on DSM for VANISH trial

ACTRN12618001792213 (unpaid). HM has also held a (leadership) role of Convenor of Tobacco Control SIG at the Thoracic Society of Australia & New Zealand (unpaid) and has been an education committee member of the Asian Pacific Society of Respirology (APSR) (unpaid) as well as unpaid advisory roles for Lung Foundation Australia/2023 Australian Lung Cancer Conference. DK received honorarium by MSD and Amgen for educational event (presentation) in 2021. This honorarium was unrelated to the current manuscript. KC declares the following conflicts of interest [1-4]: 1. Commonwealth Department of Health, Australia - Contract funding to KC's institution (The Daffodil Centre, a joint venture between Cancer Council NSW and The University of Sydney) for work to monitor the safety of the National Cervical Screening Program. 2. KC is co-PI of an investigator-initiated trial of cervical screening, "Compass", run by the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity. Compass receives infrastructure support from the Australian government and the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics, USA. KC is also co-PI on a major implementation program Elimination of Cervical Cancer in the Western Pacific which has received support from the Minderoo Foundation and the Frazer Family Foundation and equipment donations from Cepheid Inc. 3. KC also receives support for a range of other Australian and international government projects including support from philanthropic organizations, WHO, and government agencies related to cervical cancer control. 4. Chair or member of a number of government or meetings convened by the World Health Organization (WHO), or philanthropic organizations such as Bill and Melinda Gates Foundation (BMGF). Also, Australian Government - Chair, Expert Advisory Group to the Elimination Response (EAGER); Cancer Council Australia (CCA) - Chair, Cancer Screening and Immunization Committee (CSI). MFW received contract funding from Cancer Australia for a report on Prevalence and impact of lung cancer exposures on lung cancer risk in Australia to inform a governmental inquiry on the feasibility of lung cancer screening in Australia (paid to her institution). MFW's work has also been supported by the Australian Department of Health (paid to her institution) as part of a sub-contract with the Australian National University for a report on trends in smoking prevalence in Australia. MFW is a chief investigator on a National Health and Medical Research Council grant for a project unrelated to this manuscript. MFW also received an honorarium for a presentation on work unrelated to the current manuscript at the virtual JCA 2021 congress in lieu of travel expenses by the Japanese Cancer Association. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). As human subjects were not involved in the LEAPp protocol, approval by a Human Research Ethics Committee was not required. Ethics approval for the use of deidentified data from 45 and Up Study was provided by the NSW Population and Health Services Research Ethics Committee (2019/ETH01746).

References

1. World Health Organization. Cancer. 2022. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Australian Institute of Health and Welfare. Cancer in Australia 2021. Cancer series no. 133. Cat. no. CAN 144. Canberra: AIHW. 2021. Available online: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2021/data
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
4. Australian Bureau of Statistics. Causes of Death, Australia. Statistics on the number of deaths, by sex, selected age groups, and cause of death classified to the International Classification of Diseases (ICD). 2021. Available online: https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/latest-release#content
5. Australian Institute of Health and Welfare. Cancer Australia. Lung cancer in Australia statistics.

2021. Available online: https://www.aihw.gov.au/getmedia/0ea708eb-dd6e-4499-9080-1cc7b5990e64/aihw-can-144.pdf.aspx?inline=true
6. Goldsbury DE, Weber MF, Yap S, et al. Health services costs for lung cancer care in Australia: Estimates from the 45 and Up Study. PLoS One 2020;15:e0238018.
7. Luo Q, O'Connell DL, Yu XQ, et al. Cancer incidence and mortality in Australia from 2020 to 2044 and an exploratory analysis of the potential effect of treatment delays during the COVID-19 pandemic: a statistical modelling study. Lancet Public Health 2022;7:e537-48.
8. Ten Haaf K, Bastani M, Cao P, et al. A Comparative Modeling Analysis of Risk-Based Lung Cancer Screening Strategies. J Natl Cancer Inst 2020;112:466-79.
9. Meza R, Jeon J, Toumazis I, et al. Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: Modeling Study for the US Preventive Services Task Force. JAMA 2021;325:988-97.
10. Feletto E, Lew JB, Worthington J, et al. Pathways to a cancer-free future: a protocol for modelled evaluations to minimise the future burden of colorectal cancer in Australia. BMJ Open 2020;10:e036475.
11. Velentzis LS, Smith MA, Simms KT, et al. Pathways to a cancer-free future: A protocol for modelled evaluations to maximize the future impact of interventions on cervical cancer in Australia. Gynecol Oncol 2019;152:465-71.
12. Laaksonen MA, Canfell K, MacInnis R, et al. The future burden of lung cancer attributable to current modifiable behaviours: a pooled study of seven Australian cohorts. Int J Epidemiol 2018;47:1772-83.
13. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 2021;397:2337-60.
14. United Nations. Treaty Collection. Multilateral Treaties Deposited with the Secretary-General. Chapter IX: Health. WHO Framework Convention on Tobacco Control. Geneva, 21 May, 2003. Available online: https://treaties.un.org/pages/ViewDetails.aspx?src=TREATY&mtdsg_no=IX-4&chapter=9&clang=_en
15. Greenhalgh EM, Scollo MM, Winstanley, MH. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2023. Available online: www.TobaccoInAustralia.org.au
16. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia. Tobacco. 2022. Available online: https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/about
17. Grogan P, Banks E. Far from 'mission accomplished': time to re-energise tobacco control in Australia. Public Health Res Pract 2020;30:3032016.
18. Australian Government Department of Health and Aged Care. National Tobacco Strategy 2012–2018. Available online: https://www.health.gov.au/resources/publications/national-tobacco-strategy-2012-2018
19. Australian Government Department of Health. Consultation Draft National Tobacco Strategy 2022–2030. Publication number: 12710. 2022. Available online: https://consultations.health.gov.au/atodb/national-tobacco-strategy-2022-2030/
20. Australian Government Department of Health. National Preventive Health Strategy 2021–2030. 2021. Available online: https://www.health.gov.au/sites/default/files/documents/2021/12/national-preventive-health-strategy-2021-2030.pdf
21. Khouja JN, Suddell SF, Peters SE, et al. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. Tob Control 2020;30:8-15.
22. Baenziger ON, Ford L, Yazidjoglou A, et al. E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis. BMJ Open 2021;11:e045603.
23. Pierce JP, Zhang J, Crotty Alexander LE, et al. Daily E-cigarette Use and the Surge in JUUL Sales: 2017-2019. Pediatrics 2022;149:e2021055379.
24. Sarich P, Cabasag CJ, Liebermann E, et al. Tobacco smoking changes during the first pre-vaccination phases of the COVID-19 pandemic: A systematic review and meta-analysis. EClinicalMedicine 2022;47:101375.
25. Peake MD, Navani N, Baldwin DR. The continuum of screening and early detection, awareness and faster diagnosis of lung cancer. Thorax 2018;73:1097-8.
26. Australian Government Cancer Australia. National Cancer Control Indicators. Cancer Control Continuum. Outcomes. Relative Survival Rate. Relative survival by stage at diagnosis (lung cancer). 2019. Available online: https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-lung-cancer
27. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382:503-13.
28. The National Lung Screening Trial Research Team;

Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
29. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368:728-36.
30. Weber M, Yap S, Goldsbury D, et al. Identifying high risk individuals for targeted lung cancer screening: Independent validation of the PLCOm2012 risk prediction tool. Int J Cancer 2017;141:242-53.
31. Rankin NM, McWilliams A, Marshall HM. Lung cancer screening implementation: Complexities and priorities. Respirology 2020;25 Suppl 2:5-23.
32. Moldovanu D, de Koning HJ, van der Aalst CM. Lung cancer screening and smoking cessation efforts. Transl Lung Cancer Res 2021;10:1099-109.
33. Poon C, Haderi A, Roediger A, et al. Should we screen for lung cancer? A 10-country analysis identifying key decision-making factors. Health Policy 2022;126:879-88.
34. Australian Government Cancer Australia. Report on the Lung Cancer Screening Enquiry, Cancer Australia, Surry Hills, NSW. 2020. Available online: https://www.canceraustralia.gov.au/publications-and-resources/cancer-australia-publications/report-lung-cancer-screening-enquiry
35. Lew JB, Simms KT, Smith MA, et al. Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program. Lancet Public Health 2017;2:e96-e107.
36. Lew JB, St John DJB, Xu XM, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. Lancet Public Health 2017;2:e331-40.
37. Cancer Council Australia. Clinical Guidelines. Clinical practice guidelines for the treatment of lung cancer. Sydney: Cancer Council Australia. Available online: https://wiki.cancer.org.au/australia/Guidelines:Lung_cancer
38. Eisenstein M. New lung-cancer drugs extend survival times. Nature 2020;587:S10-2.
39. Takano N, Ariyasu R, Koyama J, et al. Improvement in the survival of patients with stage IV non-small-cell lung cancer: Experience in a single institutional 1995-2017. Lung Cancer 2019;131:69-77.
40. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
41. Yu XQ, Luo Q, Hughes S, et al. Statistical projection methods for lung cancer incidence and mortality: a systematic review. BMJ Open 2019;9:e028497.
42. Cheng ES, Egger S, Hughes S, et al. Systematic review and meta-analysis of residential radon and lung cancer in never-smokers. Eur Respir Rev 2021;30:200230.
43. Cheng ES, Weber M, Steinberg J, et al. Lung cancer risk in never-smokers: An overview of environmental and genetic factors. Chin J Cancer Res 2021;33:548-62.
44. Luo Q, Steinberg J, Yu XQ, et al. How Well Have Projected Lung Cancer Rates Predicted the Actual Observed Rates? Asian Pac J Cancer Prev 2021;22:437-45.
45. Ngo PJ, Cressman S, Behar-Harpaz S, et al. Applying utility values in cost-effectiveness analyses of lung cancer screening: A review of methods. Lung Cancer 2022;166:122-31.
46. Bleicher K, Summerhayes R, Baynes S, et al. Cohort Profile Update: The 45 and Up Study. Int J Epidemiol 2023;52:e92-e101.
47. Cancer Institute NSW. CanDLe program. The Enduring Cancer Data Linkage (CanDLe). 2022. Available online: https://www.cancer.nsw.gov.au/research-and-data/cancer-data-and-statistics/candle-program
48. Weber MF, Sarich PEA, Vaneckova P, et al. Cancer incidence and cancer death in relation to tobacco smoking in a population-based Australian cohort study. Int J Cancer 2021;149:1076-88.
49. Ngo PJ, Wade S, Banks E, et al. Large-Scale Population-Based Surveys Linked to Administrative Health Databases as a Source of Data on Health Utilities in Australia. Value Health 2022;25:1634-43.
50. Ngo PJ, Wade S, Vaneckova P, et al. Health utilities for participants in a population-based sample who meet eligibility criteria for lung cancer screening. Lung Cancer 2022;169:47-54.
51. Yap S, Goldsbury D, Yap ML, et al. Patterns of care and emergency presentations for people with non-small cell lung cancer in New South Wales, Australia: A population-based study. Lung Cancer 2018;122:171-9.
52. Ngo P, Goldsbury DE, Karikios D, et al. Lung cancer treatment patterns and factors relating to systemic therapy use in Australia. Asia Pac J Clin Oncol 2022;18:e235-46.
53. Yu XQ, Yap ML, Cheng ES, et al. Evaluating Prognostic Factors for Sex Differences in Lung Cancer Survival: Findings From a Large Australian Cohort. J Thorac Oncol 2022;17:688-99.
54. Yap ML, O'Connell DL, Goldsbury DE, et al. Actual

Versus Optimal Radiotherapy Utilisation for Metastatic Cancer Patients in the 45 and Up Study Cohort, New South Wales. Clin Oncol (R Coll Radiol) 2021;33:650-60.
55. Adair T, Hoy D, Dettrick Z, et al. Reconstruction of long-term tobacco consumption trends in Australia and their relationship to lung cancer mortality. Cancer Causes Control 2011;22:1047-53.
56. Luo Q, Yu XQ, Wade S, et al. Lung cancer mortality in Australia: Projected outcomes to 2040. Lung Cancer 2018;125:68-76.
57. Luo Q, Steinberg J, Yu XQ, et al. Projections of smoking-related cancer mortality in Australia to 2044. J Epidemiol Community Health 2022;76:792-9.
58. Luo Q, Steinberg J, O'Connell DL, et al. Lung cancer mortality in Australia in the twenty-first century: How many lives can be saved with effective tobacco control? Lung Cancer 2019;130:208-15.
59. Wade S, Weber MF, Sarich P, et al. Bayesian calibration of simulation models: A tutorial and an Australian smoking behaviour model. 2022 [cited 2022 Jul 19]; Available online: https://arxiv.org/abs/2202.02923
60. Holford TR, Levy DT, McKay LA, et al. Patterns of birth cohort-specific smoking histories, 1965-2009. Am J Prev Med 2014;46:e31-e37.
61. Jeon J, Meza R, Krapcho M, et al. Chapter 5: Actual and counterfactual smoking prevalence rates in the U.S. population via microsimulation. Risk Anal 2012;32 Suppl 1:S51-68.
62. Vaneckova P, Wade S, Weber M, et al. Birth-cohort estimates of smoking initiation and prevalence in 20th century Australia: Synthesis of data from 33 surveys and 385,810 participants. PLoS One 2021;16:e0250824.
63. Schultz FW, Boer R, de Koning HJ. Chapter 7: Description of MISCAN-lung, the Erasmus MC Lung Cancer microsimulation model for evaluating cancer control interventions. Risk Anal 2012;32 Suppl 1:S85-98.
64. Barendregt JJ, Van Oortmarssen GJ, Van Hout BA, et al. Coping with multiple morbidity in a life table. Math Popul Stud 1998;7:29-49, 109.
65. Blakely T, Moss R, Collins J, et al. Proportional multistate lifetable modelling of preventive interventions: concepts, code and worked examples. Int J Epidemiol 2020;49:1624-36.
66. Wakefield M, Freeman J, Donovan R. Recall and response of smokers and recent quitters to the Australian National Tobacco Campaign. Tob Control 2003;12 Suppl 2:ii15-22.
67. Wakefield MA, Durkin S, Spittal MJ, et al. Impact of tobacco control policies and mass media campaigns on monthly adult smoking prevalence. Am J Public Health 2008;98:1443-50.
68. Wakefield M, Freeman J, Boulter J. Changes associated with the national tobacco campaign. Pre and post campaign surveys compared. In: Hassard K, ed. Australia's national tobacco campaign. Evaluation report volume one. Canberra: Commonwealth Department of Health and Aged Care, 1999:24-82. Available online: https://webarchive.nla.gov.au/awa/20140801095025/http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-publicat-document-metadata-tobccamp.htm
69. Petrović-van der Deen FS, Blakely T, Kvizhinadze G, et al. Restricting tobacco sales to only pharmacies combined with cessation advice: a modelling study of the future smoking prevalence, health and cost impacts. Tob Control 2019;28:643-50.
70. Pearson AL, Cleghorn CL, van der Deen FS, et al. Tobacco retail outlet restrictions: health and cost impacts from multistate life-table modelling in a national population. Tob Control 2016;tobaccocontrol-2015-052846.
71. Lim KP, Marshall H, Tammemägi M, et al. Protocol and Rationale for the International Lung Screening Trial. Ann Am Thorac Soc 2020;17:503-12.
72. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020;395:591-603.
73. Cheng ES, Weber MF, Steinberg J, et al. Evaluating risk factors for lung cancer among never-smoking individuals using two Australian studies. J Cancer Res Clin Oncol 2022;148;2827-40.
74. Australian Bureau of Statistics. 4715.0 - National Aboriginal and Torres Strait Islander Health Survey, 2018-19: Smoking. 2019. Available online: https://www.abs.gov.au/AUSSTATS/abs@.nsf/Latestproducts/4715.0Main%20Features152018-19?opendocument&tabname=Summary&prodno=4715.0&issue=2018-19&num=&view=
75. Australian Institute of Health and Welfare. Australia's health 2018. Australia's health series no. 16. AUS 221. Canberra: AIHW. 2018. Available online: https://www.aihw.gov.au/getmedia/0c0bc98b-5e4d-4826-af7f-b300731fb447/aihw-aus-221-chapter-5-2.pdf.aspx
76. Alcohol and Other Drugs Knowledge Centre. Tobacco. Tobacco and Aboriginal and Torres Strait Islander people. 2022. Available online: https://aodknowledgecentre.ecu.edu.au/learn/specific-drugs/tobacco/
77. Lew JB, Feletto E, Worthington J, et al. The potential for

tailored screening to reduce bowel cancer mortality for Aboriginal and Torres Strait Islander peoples in Australia: Modelling study. J Cancer Policy 2022;32:100325.

78. Moynihan R, Sanders S, Michaleff ZA, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open 2021;11:e045343.

doi: 10.21037/ace-22-11

Cite this article as: Vaneckova P, Wade S, Caruana M, Ngo P, Behar Harpaz S, Sarich P, Luo Q, Goldsbury DE, Cheng E, Yu XQ, Watts C, Barron K, Yap ML, Grogan PB, Banks E, Fong KM, Marshall H, Karikios D, Rankin NM, Tammemägi MC, McWilliams A, Cressman S, Canfell K, Weber MF. A protocol for modelled evaluations to maximise the long-term health and economic gains of lung cancer interventions in Australia: The Lung cancer Evaluation And Policy program (LEAPp). Ann Cancer Epidemiol 2023;7:1.

