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Article *in* PharmacoEconomics - Open · October 2024

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PROTOCOL

Integrating Multi-Cancer Early Detection (MCED) Tests with Standard Cancer Screening: System Dynamics Model Development and Feasibility Testing

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Accepted: 25 September 2024

Abstract

Background Cancer screening plays a critical role in early disease detection and improving outcomes. In Australia, established screening protocols for colorectal, breast and cervical cancer have significantly contributed to timely cancer detection. However, the recent introduction of multi-cancer early detection (MCED) tests arguably can disrupt current screening, yet the extent to which these tests provide additional benefits remains uncertain. We present the development and initial validation of a system dynamics (SD) model that estimates the additional cancer detections and costs associated with MCED tests.

Aim This article describes the development of a simulation model built to evaluate the additional patient diagnoses and the economic impact of incorporating MCED testing alongside Australia's well-established standard of care (SOC) screening programs for colorectal, breast, cervical and lung cancers. The model was designed to estimate the additional number of patients diagnosed at each cancer stage (stage I, II, III, IV, or unknown) and the associated costs. This simulation model allows for the analysis of multiple scenarios under a plausible set of assumptions regarding population-level participation rates.

Methods An SD model was developed to represent the existing SOC national cancer screening pathways and to integrate potential clinical pathways that could be introduced by MCED tests. The SD model was built to investigate three scenarios for the use of MCED testing: firstly, to explore the viability of MCED testing as a substitute among individuals who are not opting for SOC screening for any reason; secondly, to implement MCED testing exclusively for individuals ineligible for SOC screening, yet have high-risk characteristics; and thirdly, to employ MCED testing after SOC screening to serve as a triaging/confirmatory tool for individuals receiving inconclusive test results. The three primary scenarios were constructed by varying diagnostic accuracy and uptake rates of MCED tests.

Discussion The clinical utility and outcomes of MCED testing for screening and early detection still lack comprehensive evidence. Nonetheless, this simulation model facilitates a thorough analysis of MCED tests within the Australian healthcare context, providing insights into potential additional detections and costs to the healthcare system, which may help prioritise future evidence development. The adaptable yet novel SD model presented herein is anticipated to be of considerable interest to industry, policymakers, consumers and clinicians involved in informing clinical and economic decisions regarding integrating MCED tests as cancer screening and early detection tools. The expected results of applying this SD model will determine whether using MCED testing in conjunction with SOC screening offers any potential benefits, possibly guiding policy decisions and clinical practices towards the adoption of MCED tests.

Abbreviations

ABM	Agent-based modelling
AIHW	Australian Institute of Health and Welfare
BC	Breast cancer
CC	Cervical cancer
CRC	Colorectal cancer
CT	Computed tomography
DES	Discrete event simulation
GP	General practitioner
HTA	Health technology assessment
HPV	Human papillomavirus
iFOBT	Immunochemical Faecal Occult Blood Test
LB	Liquid biopsy
LBC	Liquid-based cytology
LC	Lung cancer
LDCT	Low-dose computed tomography
MBS	Medicare benefits schedule

Extended author information available on the last page of the article

Published online: 18 October 2024

MCED	Multi-cancer early detection
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NBCSP	National Bowel Cancer Screening Program
NHMRC	National Health and Medical Research Council
PBS	Pharmaceutical benefits scheme
PET	Positron emission tomography
PM	Precision medicine
PSA	Prostate-specific antigen
QALY	Quality-adjusted life-year
SD	System dynamics
SOC	Standard of care
TAGC	The Advanced Genomic Collaboration
TOO	Tissue-of-origin

1 Background

Cancer is a substantial contributor to global mortality, accounting for approximately 10 million fatalities in 2020, representing nearly one-sixth of the total deaths recorded during that period [1]. A significant number of cancer cases are identified at a late progressive stage, limiting the curative options for these cases. Approximately 45% of cancer-related fatalities within a 5-year timeframe are attributed to cancers diagnosed at a late stage and to post-distant metastasis despite constituting only 18% of the initially diagnosed cases [2]. Screening, as defined by the World Health Organization (WHO), plays a pivotal role in the early detection of indolent disease, contributing to the overall goal of reducing the burden of diseases within populations. Screening primarily focusses on individuals without evident symptoms, targeting specific populations to identify pre-disease abnormalities, early stage diseases or disease risk markers. The ultimate objective is to intervene early, either by reducing individual disease risk or detecting diseases before they would typically be identified without screening, thereby improving overall health outcomes. While screening holds the potential to mitigate the impact of diseases, including cancer, at both individual and population levels, it is essential to weigh the benefits and associated costs against the potential harms. The allocation of healthcare resources to screening modalities requires a consensus on the justification of associated costs versus conferred benefits [3]. To this end, many countries have implemented population-level or routine screening programs for high-prevalent cancers such as breast cancer (mammography), colorectal cancer [immunochemical faecal occult blood test (iFOBT)], cervical cancer [Papanicolaou (Pap) smears or human papillomavirus (HPV) tests] and potentially also lung cancer [low-dose computed tomography (LDCT) scans] and prostate cancer [prostate-specific antigen (PSA) test]. However, routine screening is not recommended for any other cancer types for the average population other than these four cancers (lung, breast, cervical, and colorectal), resulting in the cancer being detected at a more advanced stage [4]. In addition, adherence to the existing standard of care (SOC) screening modalities is not optimal, with low uptake rates varying widely between different screening modalities such as iFOBT, mammography, LDCT and Pap smears [5, 6].

Currently, in Australia, publicly funded screening programs are available for a select number of cancers, namely breast, colorectal, and cervical. In July 2022, the Medical Services Advisory Committee (MSAC) supported the introduction of a National Lung Cancer Screening Program to be implemented in July 2025 through the reimbursement of LDCT scans for early detection of lung cancer among asymptomatic high-risk individuals [7, 8]. However, the rationale for adopting population-wide screening for the other cancer types remains unsupported. It is also not advised due to the low prevalence rates or the lack of treatment options at a preventable stage for certain cancers, which render cost-effective interventions unfeasible with a single-organ screening approach [9].

Over recent years, there has been a significant development in cancer screening and detection due to the introduction of multi-cancer early detection (MCED) tests. These innovative and potentially ground-breaking tests have shown promise in reducing cancer-related morbidity and mortality [10, 11]. Predominantly, MCED tests identify circulating or cell-free tumour DNA (cfDNA) in blood samples. They employ diverse methodologies, including the detection of cancer-specific mutations and analysis of DNA methylation patterns, and they may also incorporate additional biomarkers such as protein biomarkers [12]. A notable feature of many MCED tests is their capacity to detect a generic cancer signal and ascertain the tissue-of-origin (TOO) of the detected cancer, as well as identify the specific cancer type [13]. Here, MCED tests may offer a logistical advantage by enabling a single blood test to screen for a broad spectrum of cancers. However, the clinical utility of MCEDs in cancer screening remains unsupported, specifically in correctly identifying additional patients while improving overall health outcomes for persons screened. Furthermore, the ratio of benefits to harms, such as anxiety caused by false-positive results, unnecessary biopsies and overdiagnosis of indolent diseases, versus benefits such as lives saved, associated with MCEDs has not yet been clearly established [14].

Recently published data provided some initial support for the potential benefits of a screening program using MCED testing in addition to usual care (e.g. SOC screening, symptomatic workup or incidental detection). Hubbell et al. [15] suggest that MCEDs can substantially reduce overall cancer mortality in a representative population aged between 50 and 79 years. Furthermore, another study by Lennon et al. [4] demonstrates that a minimally invasive MCED blood test in

combination with positron emission tomography–computed tomography (PET–CT) can be potentially incorporated into routine clinical care, as it can detect several types of cancers in individuals not previously known to have cancer. However, this study ascertains that further assessment of the clinical utility, risk–benefit ratio and cost-effectiveness of such tests is needed [4]. Finally, the SYMPLIFY and the NHS-Galleri trials, currently being conducted in the UK, are the first large-scale clinical trials of MCED tests, with promising early results for wide-scale implementation and dissemination in the community [16, 17]. With some assays testing for more than 50 cancers (e.g. GRAIL's Galleri test) simultaneously, the use of MCED testing is both promising while also concerning due to false positive and false negative results that may result in anxiety, unnecessary biopsy, overdiagnosis and overtreatment if these tests are implemented [18]. Therefore, many questions are posed, including the extent of the use of MCEDs, including who needs to be screened, how often, when and whether testing can be performed safely without harm, exceeding the benefits such as unnecessary invasive follow-up tests. However, the space of MCED testing is a rapidly growing research field where policy guidance is urgently needed because of the potentially detrimental effects such as overdiagnosis and the lack of sensitivity to detect low-incidence cancers. Such guidance must be informed by compelling clinical evidence, typically obtained from well-designed, large-scale controlled trials among healthy individuals before implementation in clinical practice [19]. However, randomised trials cannot efficiently be conducted in such a context given the fact that they are based mainly on a standardised comparison of two or more interventions among a well-defined population [20]. Given MCED testing's ability to detect several cancers concurrently, it might be challenging to establish such evidence with high statistical power for such a broad population.

While clinical evidence is yet to be developed, early stage health economic modelling could be helpful in determining how and when to best use MCEDs, in estimating the potential value proposition and in performing a risk assessment. Therefore, this might help with prioritising clinical evidence development as well as determining the value of additional research [20]. However, undertaking an early stage health economic analysis within the framework of MCED proves challenging, especially when employing widely used modelling approaches such as decision trees and Markov models. These traditional models are of limited value in accurately modelling different and heterogeneous populations, a necessity for the application of MCED testing [20, 21]. Furthermore, Markov state-transition models may not be well suited as they do not address time-dependent behaviour, such as changes in response rates over time [20]. An alternative approach to inform the implementation of MCEDs is the use of system dynamics (SD), which assesses the potential impact of interventions over time and helps identify any potential leverage points to improve public health outcomes [22–24]. In their recent systematic review, Kenzie et al. [24] examined the use of SD modelling within the realm of cancer prevention and control, identifying 32 studies that employed SD modelling across the continuum of cancer control in the literature. This approach is particularly relevant in the context of cancer screening and MCED, where SD modelling offers the ability to account for the time delays as well as feedback loops associated with intricate health problems and to capture changes in the system over time [24–28]. Moreover, SD models can capture the entire system structure, including the various elements and interconnections that affect the system's performance and behaviour. These models are usually less data-intensive given their ability to simulate the system at the aggregate level, while they allow for the inclusion of a broader set of boundaries, which are typically excluded in models dependent on established empirical data sources or in situations where data are limited [24, 28–30].

2 Study Aim

While there is an increase in early cancer detection modelling studies, not many studies, particularly no broad-boundary SD models, are yet available to study the health economic impact of MCED tests [31]. In this study, we propose a dynamic simulation modelling study using the SD approach to investigate the health–economic impact of MCED testing alongside the current SOC screening programs in the Australian setting. The overall aim of this study is to describe the development of a simulation model built to assess the potential additional value of using MCED testing alongside the well-established single screening programs for colorectal, breast, cervical and lung cancer in Australia. A SD model is therefore developed to investigate the population-level health economic outcomes associated with MCED testing in terms of the total number of patients diagnosed at different cancer stages versus the associated costs. This will be achieved by performing scenario analyses of various implementation scenarios under a plausible set of assumptions regarding the population-level uptake and participation rates. Three main scenarios have been identified for using MCED testing alongside current SOC screening, comparing it directly with SOC screening alone:

1. MCED testing is exclusively for patients eligible for SOC screening who have chosen not to undergo SOC screening for any reason. This approach is hypothesised

to augment the pool of screened individuals, thereby enhancing overall cancer detection rates.

2. MCED testing is exclusively for high-risk groups ineligible for SOC screening due to factors such as age (particularly < 50 years in most cancers), specific risk characteristics or other specified criteria.
3. MCED testing following SOC screening: in this approach, MCED testing serves as a triage tool for individuals who receive inconclusive results from SOC screening, such as those classified as low-to-medium risk or those with subthreshold readings, as this necessitates a waiting period (typically between 3 months and 1 year) and repeat testing under the current guidelines.

3 Methods

3.1 Foundation and Rationale of System Dynamics Modelling

SD simulation was chosen as the primary analysis method due to its systematic approach to analysing causes and effects relationships within feedback structures and its capacity to model the system at the aggregate level over extended time horizons. Although there are several dynamic simulation methodologies, such as discrete event simulation (DES) and agent-based modelling (ABM), which offer distinct benefits, SD may be better suited for modelling the broad-boundary effects of complex and intricate interventions such as MCED testing. This suitability also arises from its reduced data intensity, capability to take advantage of processing both qualitative and quantitative data, and comparatively lower computational demands [24, 29, 30, 32, 33]. Additionally, SD facilitates the analysis of policy implications, making it an advantageous choice in such a context [30]. Moreover, SD has the capacity to capture system intricacies and characterise structures of complex systems, as well as understand their behaviour over time and address any potential modelling challenges such as patient-level processes, test and treatment combinations, diagnostic efficacy, harms and benefit evaluations, the evolution of clinical practice guidelines and preferences of both patients and clinicians faced by the conventional modelling approaches [21, 23, 30, 34, 35]. Moreover, an essential aspect of SD is non-linearity, which is closely linked to the presence of feedback processes, in other words, an effect is rarely only proportional to the cause, while the cause also can be impacted by the effect directly or indirectly [36].

In the literature, SD modelling has been leveraged for cancer screening research, notably in the Karanfil and Sterman (2020) study [32]. Their model illustrates how decision-makers evaluate the trade-offs between harms and benefits, impacting screening protocols, thresholds and efficiency across different demographics.

Given its capabilities, SD modelling has been selected as the ideal method to represent four distinct populations within cancer streams, including both those eligible and ineligible for SOC screening. This approach meticulously addresses overlaps among these groups, where individuals might qualify for multiple SOC screening modalities. Additionally, this modelling simplifies the management of complex interdependencies and facilitates comprehensive scenario analysis, enabling the exploration of diverse policy outcomes and intervention strategies.

The core elements of SD are stocks, feedback, flows and time delays [36–38]. Stocks are defined as accruals or critical accumulations in the system, such as people, hospital beds or healthcare trusts. Flows are also known as rates, which feed in and out of their respective 'stocks' and have the same units of stocks per time unit. Figure 1 presents a basic stock and flow structure, illustrating inflow and outflow in an SD model through the effect of births and deaths on population dynamics as an example.

3.2 Model Description

A representation of our conceptual model structure is depicted in Fig. 2. The cancer screening SD model was built using Vensim™ software (Ventana Systems Inc., Harvard, TA, USA), employing a time step of one-fourth of a year, meaning the model progresses in 3-month intervals. Within the model, the screening population is kept tracked using stocks and flows, moving through the relevant modelled clinical pathway and followed until they are either diagnosed or undiagnosed with cancer. The stock and flow structure was also designed to further differentiate patients on the basis of cancer stage and whether the diagnoses and staging were because of screening initiated by SOC modalities or MECD testing.

The SD model mirrors Australia's established population-based cancer screening pathways for colorectal, breast and cervical cancers. While there is no current national SOC screening for lung cancer yet, the modelled pathways were

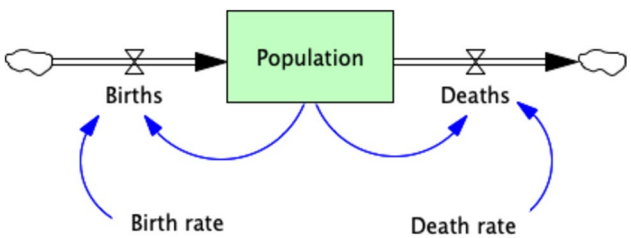

Fig. 1 A system dynamics stock and flow structure with an inflow and outflow

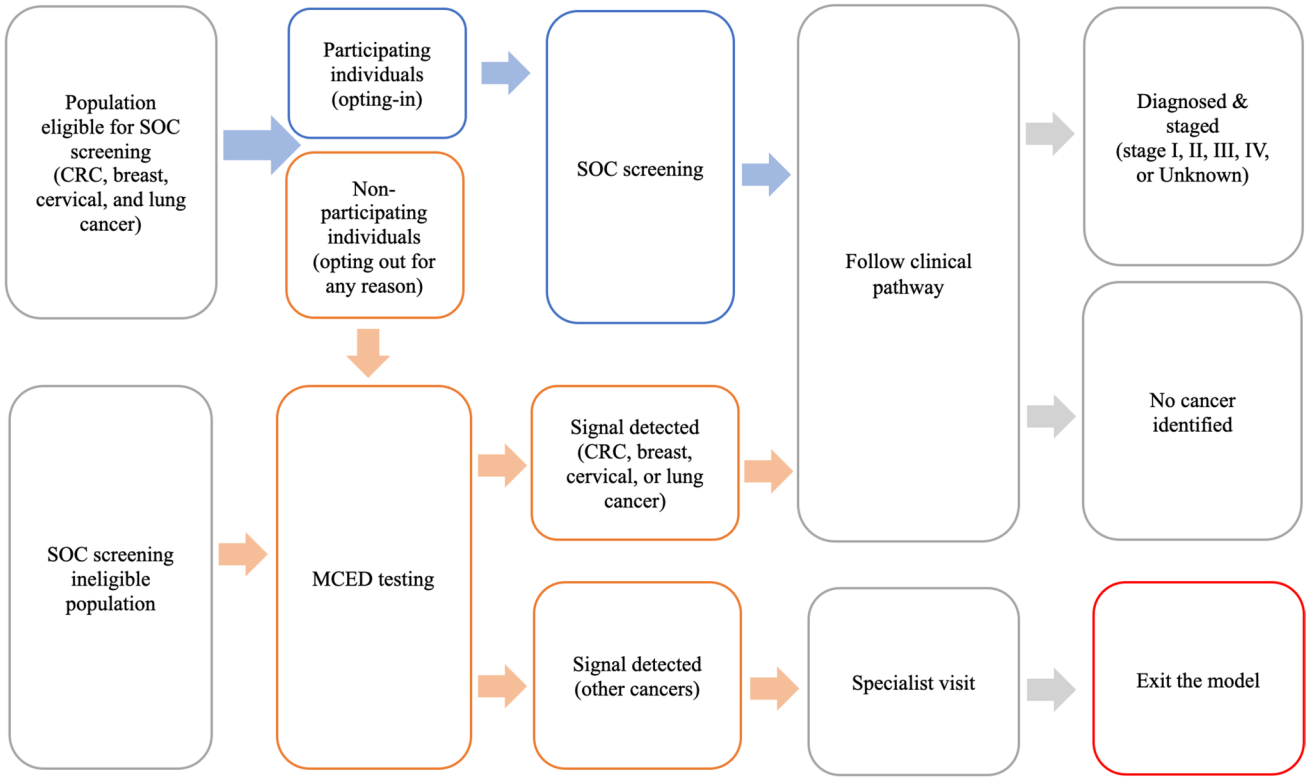

Fig. 2 System dynamics conceptual model structure. CRC, colorectal cancer; MCED, multi-cancer early detection; SOC, standard of care

based on the proposed framework presented in the Cancer Australia 2020 report "Report on the Lung Cancer Screening Enquiry" [39]. The model's boundary commences with the population (either eligible or ineligible for SOC screening) and terminates with the stage at diagnosis (categorised as stage I, II, III, IV or unknown). The fundamental building blocks of our model are stocks and flows (also known as 'stock and flow structure'), which represent the flow of patients through the modelled screening and clinical pathways for each cancer type. The detailed screening pathways for each cancer stream were further described in the subsections below (3.2.1–3.2.5). The comprehensive stock–flow model structure, encompassing pathways for the four cancers under investigation (colorectal, breast, cervical and lung), and a modelled pathway for individuals ineligible for the SOC screening, is shown in Fig. S1 of the Supplementary Appendix.

3.2.1 Colorectal Cancer

Approximately 15,400 cases are projected for colorectal cancer, making it the fourth most frequently diagnosed cancer in Australia in 2023. In the early 2000s, it held the position of being the most diagnosed cancer in the country [40]. The National Health and Medical Research Council (NHRMC) establishes standards and recommendations for the prevention, early detection and management of colorectal cancer, and the National Bowel Cancer Screening Program (NBCSP) was introduced in 2006 [41]. According to updated NHMRC guidelines in 2017, the recommended screening commences with an iFOBT test every 2 years in asymptomatic individuals, starting from age 50 years to age 74 years [41]. Recently, a change has been made to the age criteria for CRC screening; starting from 1 July 2024, individuals aged 45–49 years will also be eligible to participate in the national screening program [42]. CRC is a considerable health burden in Australia and mortality reduction is crucial, while participation rates in the national screening program remain low [41, 43].

Our simulation model structure for colorectal cancer emulates the current clinical screening pathway, sourced from relevant Australian literature (e.g. AIHW data). Patients presenting with positive results consult a specialist for a subsequent colonoscopy referral. Suspicious findings from the colonoscopy will lead to a histological examination for colorectal cancer. Patients with confirmed malignancies (histologically positive) are further assessed for cancer staging, typically through modalities such as magnetic resonance imaging (MRI), CT or PET scans. Subsequently, patients are categorised across the designated cancer stages. The modelled clinical pathways for colorectal cancer using SOC and MCED testing are presented in Fig. 3A and B, respectively.

3.2.2 Breast Cancer

Breast cancer stands as the predominant cancer diagnosis among women in Australia. Projections indicate approximately 20,500 new cases of breast cancer in female patients for the year 2023, constituting roughly 28% of the anticipated female cancer diagnoses. Furthermore, it ranks as the second most frequently diagnosed cancer among individuals aged 20–39 years and 60–79 years while holding the primary position among those aged 40–59 years in Australia [40]. Under the SOC screening programme for breast cancer (BreastScreen Australia Program), eligible women over 40 can have a free mammogram every 2 years, and women 50–74 years are actively invited to undergo mammography [44]. Positive mammographic findings necessitate a referral to a breast cancer specialist for biopsy and histological assessment. Post-diagnosis patients are categorised on the basis of the cancer's stage. The modelled clinical pathways for breast cancer using SOC screening and MCED testing are presented in Fig. 4A and B, respectively.

3.2.3 Cervical Cancer

The inception of the National Cervical Cancer Screening Program in 1991 resulted in declines in both cervical cancer incidence and mortality. This can be attributed to the program's capacity to identify pre-cancerous abnormalities, which, if untreated, could develop into cancer [40]. In this program, women and people with a cervix 25–74 years of age are invited to have a cervical screening test every 5 years [45]. In Australia, cervical cancer screening commences with HPV testing featuring partial genotyping, which can be self-collected or acquired through a general practitioner (GP) visit. Individuals yielding positive HPV outcomes are subsequently referred to a specialist for a colposcopy. If these HPV results remain inconclusive, a retest is advised within a span of 6–12 weeks (requiring a fresh sample). A positive colposcopy result then leads to a histological examination. Upon a cervical cancer diagnosis, patients are stratified and classified according to the cancer's progression stage. The modelled clinical pathways for cervical cancer

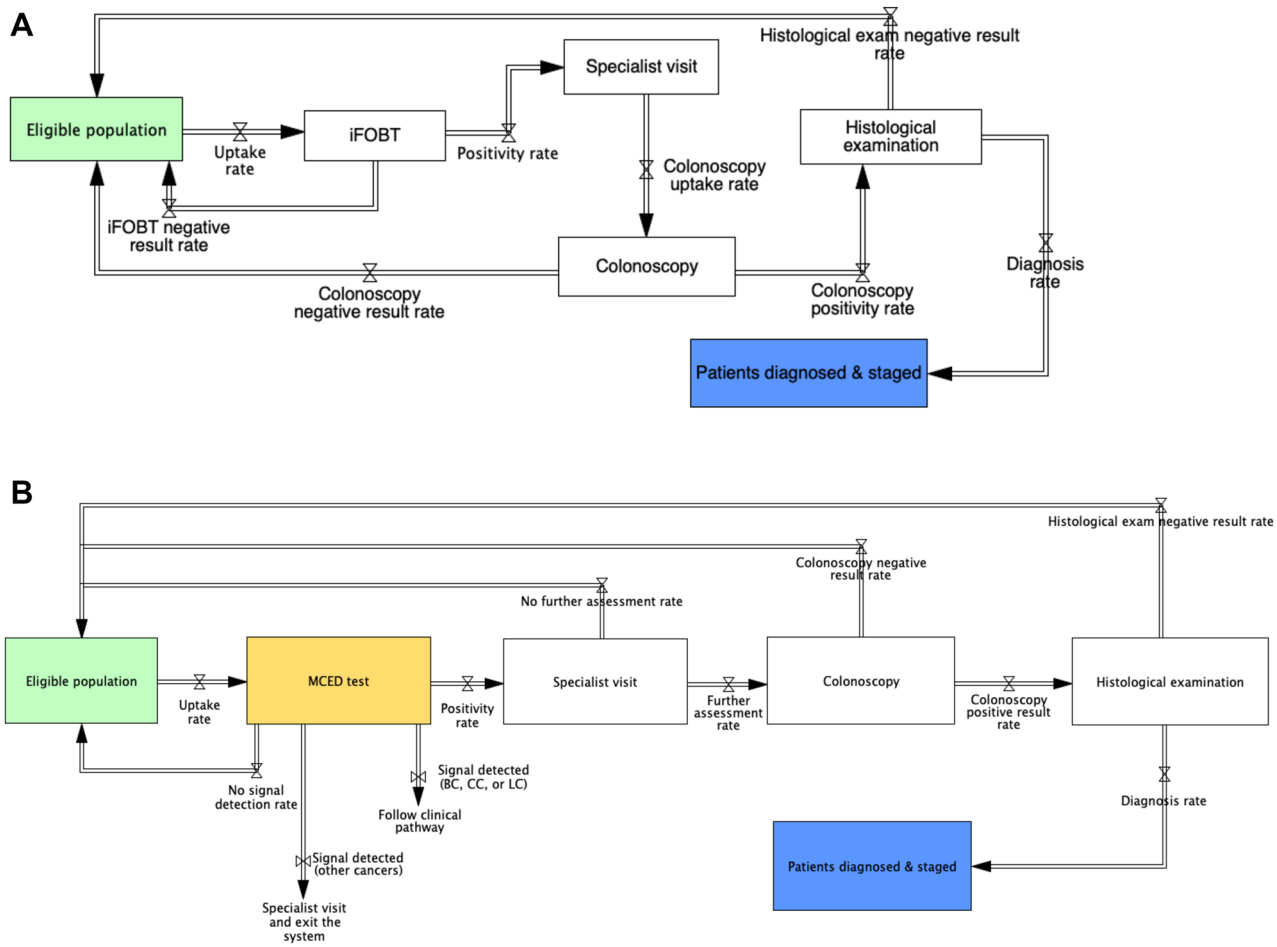

Fig. 3 **A** Clinical pathway for colorectal cancer (SOC screening). **B** Clinical pathway for colorectal cancer (MCED testing). BC, breast cancer; CC, cervical cancer; LC, lung cancer; MCED, multi-cancer early detection

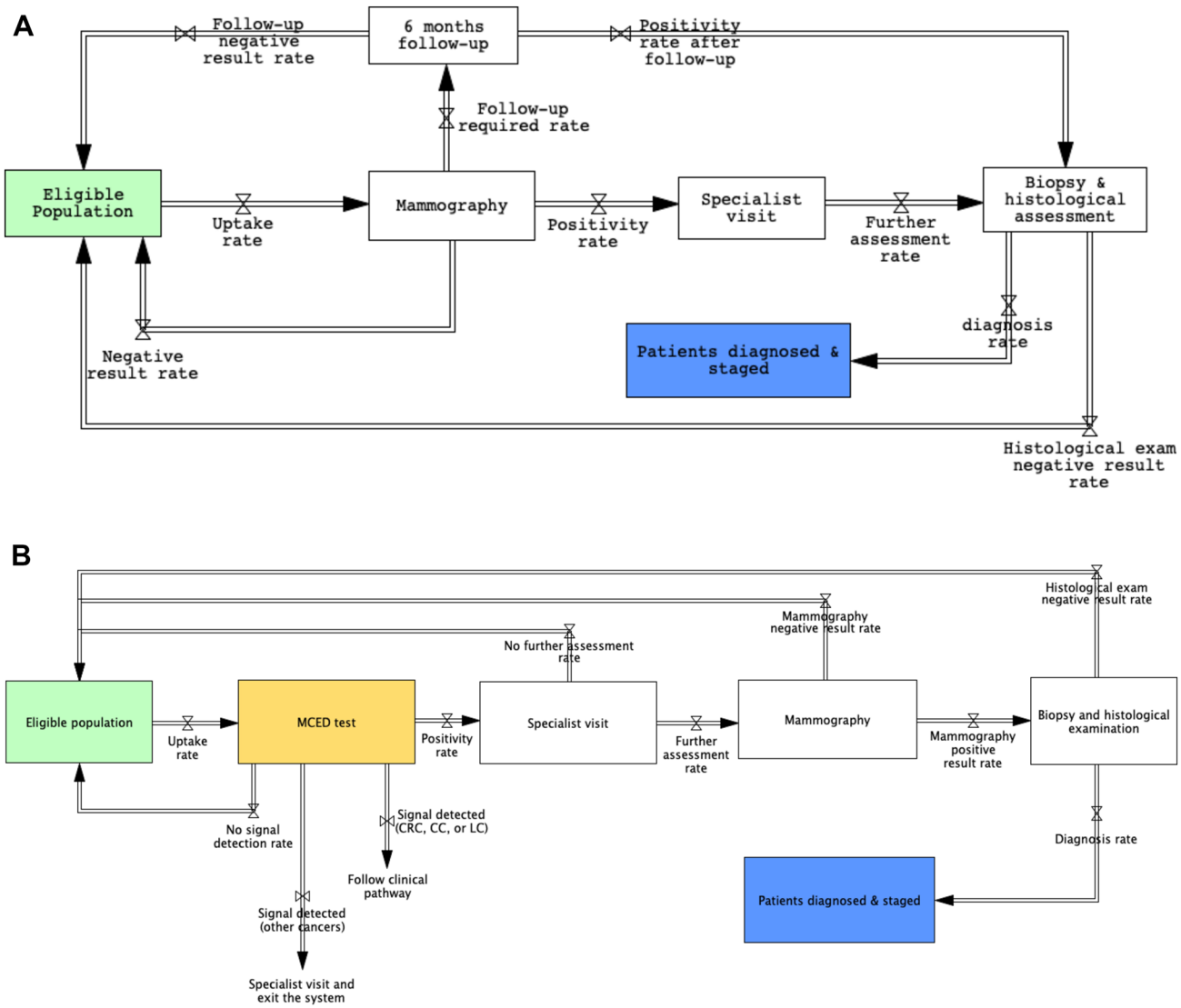

Fig. 4 **A** Clinical pathway for breast cancer (SOC screening). **B** Clinical pathway for breast cancer (MCED testing). CC, cervical cancer; CRC, colorectal cancer; LC, lung cancer; MCED, multi-cancer early detection

using SOC and MCED testing are shown in Fig. 5A and B, respectively.

3.2.4 Lung Cancer

Australia's lung cancer screening program is scheduled for initiation in July 2025, with a government investment of $263.8 million from 2023 to 2024 to implement a National Lung Cancer Screening Program on the basis of the feasibility assessment conducted by Cancer Australia and recommendation by the Medical Services Advisory Committee (MSAC) [7, 46]. This program is anticipated to avert more than 500 annual fatalities attributed to lung cancer [46]. At present, there is not an established SOC screening programme for lung cancer in the country.

The proposed clinical pathway for lung cancer was delineated on the basis of Australian guidelines presented in the MSAC consideration [7] and after consultation with medical experts. Accordingly, eligible patients will undergo biennial (every 2 years) low-dose CT scans. Those identified with low and moderate risk will be advised to repeat the low-dose CT scan at intervals of 3 months and 6 months, respectively. In contrast, high-risk patients will be immediately referred to a specialist. The consulting specialist will then determine the need for further evaluations, such as tissue diagnosis. For lung cancer, possible diagnostic approaches could involve bronchoscopy or transthoracic needle biopsy (reference). Upon diagnosis, further staging assessments, such as CT, PET–CT or tissue diagnoses, are conducted. Patients are then classified across four stages of cancer (from stages 1 to

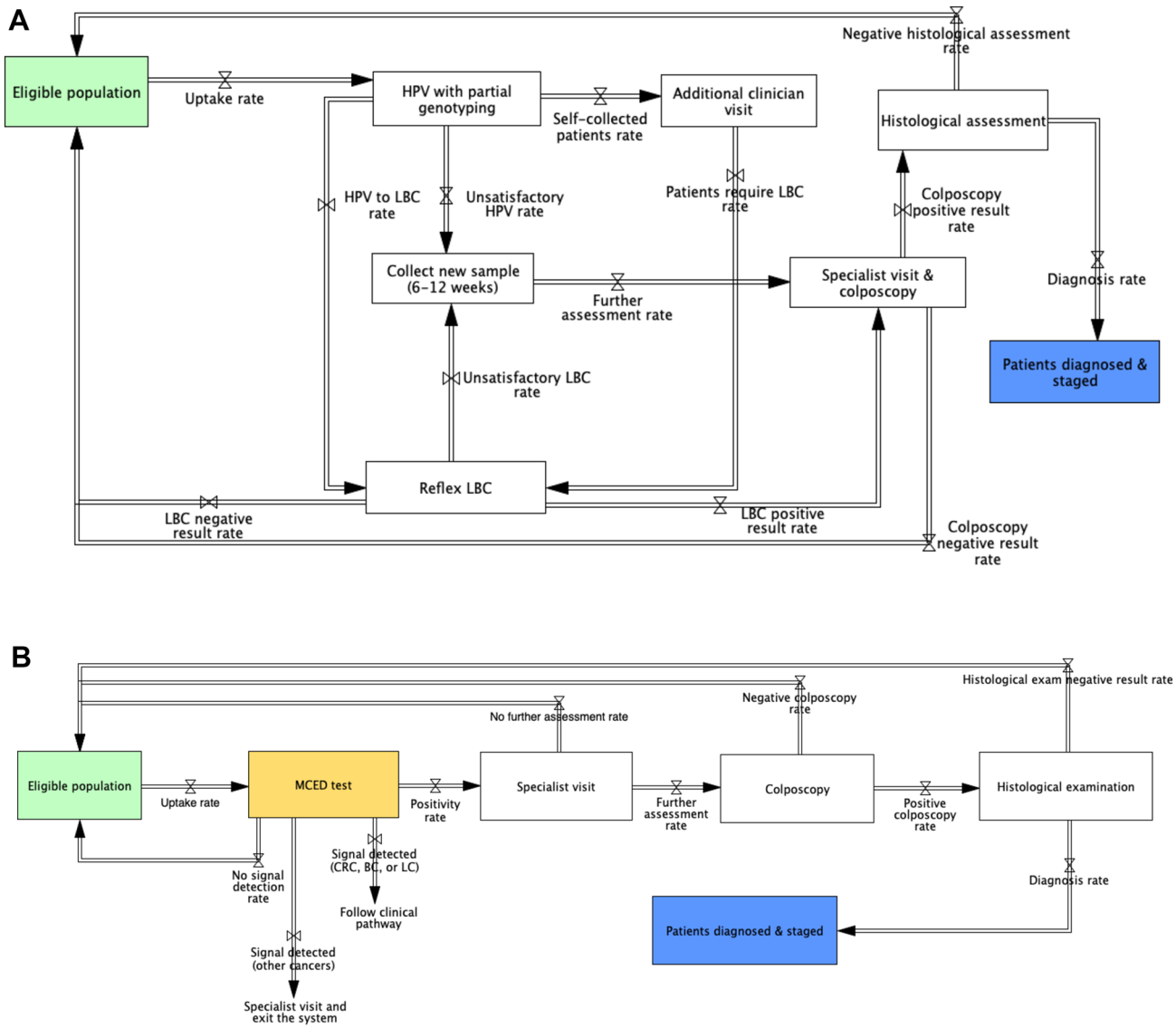

Fig. 5 **A** Clinical pathway for cervical cancer (SOC screening). HPV, human papillomavirus; LBC, liquid-based cytology. **B** Clinical pathway for cervical cancer (MCED testing). BC, breast cancer; CRC, colorectal cancer; LC, lung cancer; MCED, multi-cancer early detection

4) or categorised as 'stage unknown'. The modelled clinical pathways for lung cancer using SOC and MCED testing are shown in Fig. 6A and B, respectively.

3.2.5 Population Ineligible for the SOC Screening

It is assumed that individuals not qualifying for SOC screening, however, may choose to undergo MCED testing. Should a signal indicating one of the four cancers screened by SOC be identified (CRC, breast, cervical or lung), patients will transition into the corresponding clinical pathway. Conversely, if a signal for a cancer type not covered by SOC screening is detected, these individuals are assumed to consult a specialist before exiting the system. Owing to the complexities in modelling cancers not encompassed by SOC, no clinical pathways have been developed for these other cancer types. The modelled clinical pathway for the population ineligible for SOC screening is shown in Fig. 7.

3.2.6 MCED Testing as a Confirmatory Diagnostic Tool

To investigate the clinical and economic impact of utilising MCED testing as a confirmatory diagnostic following standard of care (SOC) screening, a model extension is proposed. This addition will incorporate a subsequent MCED testing phase 'as an additional stock' to the above-described SOC-modelled pathways; however, it will be applicable only for

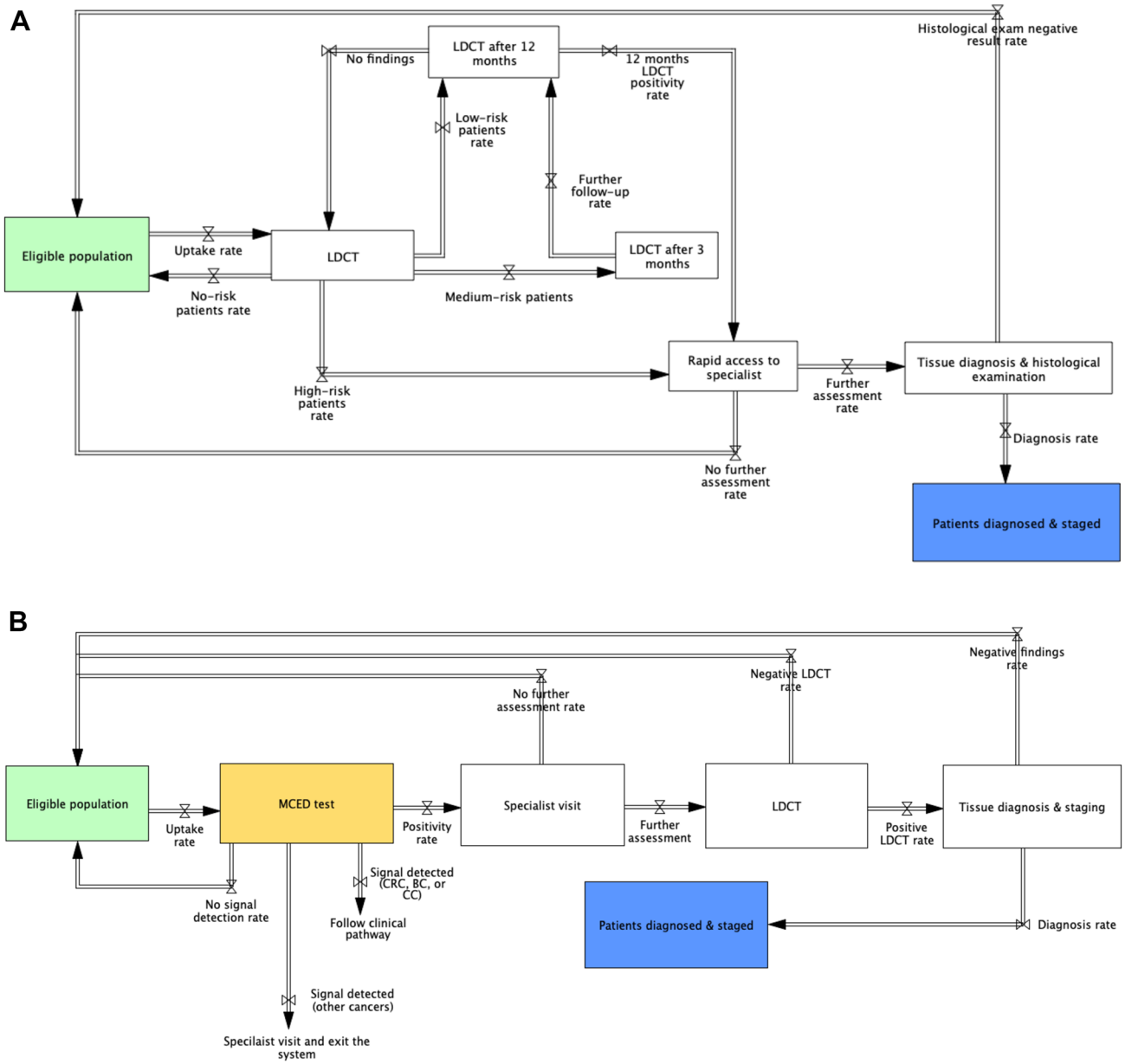

Fig. 6 **A** Clinical pathway for lung cancer (SOC screening). **B** Clinical pathway for lung cancer (MCED testing). BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; LDCT, low-dose computed tomography; MCED, multi-cancer early detection

patients whose initial SOC screenings (for colorectal, breast, cervical and lung cancers) yield inconclusive results or readings below the threshold for a positive diagnosis, according to current practice. The conceptual framework outlining this modified diagnostic pathway is depicted in Fig. 8.

3.3 Key Model Assumptions

The model is predicated on several critical assumptions outlined as follows:

- Patients are modelled to exclusively undergo either SOC screening or MCED testing. The concurrent utilisation of both MCED and SOC screening for individual patients is not captured within the current SD framework.
- For individuals who undergo MCED testing and receive a positive signal for one of the four cancers with established SOC screening pathways, it is assumed they will adhere to the clinical protocol associated with SOC screening for further diagnostic confirmation and staging. Conversely, for those with detected signals of other cancer types, it is assumed they will be directed to special-

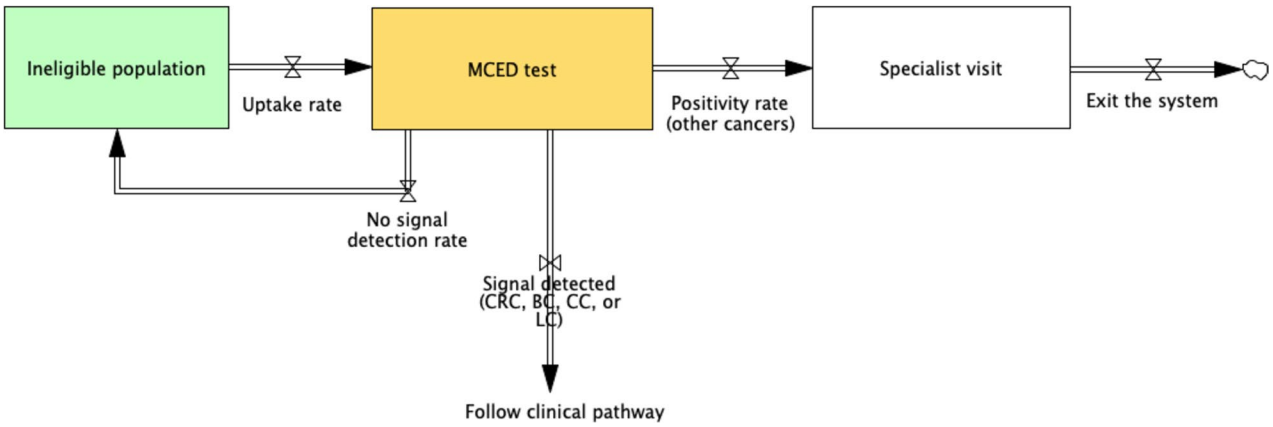

Fig. 7 Clinical pathway for ineligible population (SOC screening). BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; LC, lung cancer; MCED, multi-cancer early detection

ist care, after which they exit the system. This approach stems from the modelling complexities associated with delineating clinical pathways for an exhaustive list of cancer types within the Australian context.

- Cancer stage shift was assumed for individuals who received and were diagnosed through the MCED testing. This assumption was based on the premise that patients identified through the MCED testing approach are anticipated to be diagnosed at an earlier cancer stage compared with those diagnosed via the SOC screening method.

3.4 Study Perspective and Time Horizon

This study will be framed within the context of the Australian healthcare system, considering the costs and benefits (including the increase in diagnostic yield and detection rate) of using MCED tests. It will examine the above-mentioned scenarios at different screening intervals by examining the results of one-time screenings over 2 years. Furthermore, this model can be extended to evaluate long-term benefits over a 5-, 10- and 15-year time horizon, such as improvements in survival and the accrual of quality-adjusted life-years (QALYs), using the stage at which patients are diagnosed and the associated costs.

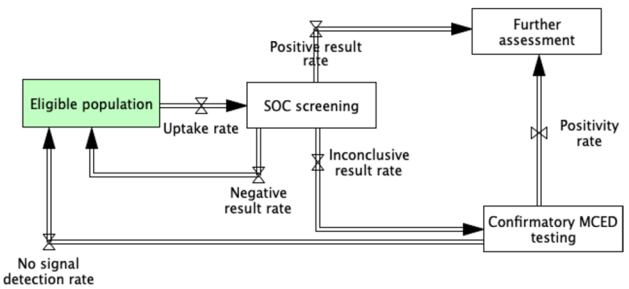

Fig. 8 Modelled pathway for MCED testing as a confirmatory diagnostic tool. MCED, multi-cancer early detection; SOC, standard of care

3.5 Input Parameters and Data Sources

3.5.1 Clinical Data

All clinical data relevant to colorectal, cervical and breast cancers, such as incidence and prevalence rates, eligible populations and uptake rates, will be extracted from the National Screening Programs monitoring reports published by the Australian Institute of Health and Welfare (AIHW). Missing data will be complemented by expert opinion (academics and clinicians engaged in the field of cancer early detection). Given that currently in Australia there is no national screening program for lung cancer, all clinical data relevant to lung cancer will be based on the assumptions submitted for the reimbursement of the lung cancer screening program submitted to the MSAC as well as from the Lung Cancer Screening Enquiry report, published by Cancer Australia in 2020 [39]. The enquiry was held to assess global evidence on the benefits and harms of lung cancer screening, target population groups and the design and effective delivery of a national lung cancer screening program in the Australian setting, where lung cancer is the leading cause of cancer death, accounting for nearly 20% of all cancer deaths. Diagnostic accuracy for the MCED tests will be obtained from the literature [47]. Various assumptions regarding the adoption rates of the MCED test by clinicians will be explored through distinct scenario analyses planned to be conducted.

3.5.2 Cost Data

Relevant cost data, including the cost of SOC screening, specialist visits and further assessments, will be extracted from the Australian Medicare Benefits Schedule (MBS) [48]. The

average cost of MCED testing will be estimated on the basis of the acquisition costs of various tests, which will be sourced from relevant manufacturers' online sources, and these costs will then be converted into Australian dollars.

3.5.3 MCED Testing Data

The eligible population for this study was defined as those currently eligible for SOC screening. As MCED testing is not yet in Australia, there are no existing data to inform the clinical pathways for MCED testing. Therefore, the positivity rate, defined as the number of MCED-positive cases among the eligible population, will be estimated by summing the true positives (TP) and false positives (FP). The TP and FP values were calculated on the basis of sensitivity, specificity and prevalence using the formulas provided below (1) and (2) [32].

$$TP = Sensitivity \times Prevalence \tag{1}$$

$$FP = (1 - Specificity) \times (1 - Prevalence) \tag{2}$$

3.5.4 Stage Shift Estimation

A critical assumption influencing the projected benefits of MCED is its potential to cause a stage shift in cancer diagnosis, specifically, the shift towards earlier-stage detection compared with the current standard-of-care (SOC) screening methods. The estimation of this stage shift is informed by the interception model developed by Hubbell et al. [15], which provides a probability matrix for each cancer type, indicating the likelihood of earlier stage detection through MCED. To evaluate the anticipated stage shift within the Australian healthcare context, these probabilities will be applied to existing Australian cancer stage distribution data. This approach aims to quantify the potential impact of MCED on the stage at diagnosis among Australian patients, thereby offering insights into its clinical utility and potential for improving cancer outcomes in Australia.

3.6 Model Validation

3.6.1 Internal Validity

The outputs of the SD model for various SOC screening pathways, which estimate annual cancer diagnoses, were internally validated using data from the AIHW screening program monitoring reports. The findings from this validation effort are shown in Fig. 9. This validation specifically compared the model's estimates of diagnosed patients with the actual reported numbers for CRC, breast cancer and cervical cancer after the first screening round within 1 year. Patients diagnosed in the second or subsequent screening rounds were excluded from the validation to simplify the validation process and ensure the model's accuracy.

The primary objective of utilising AIHW data in the validation process was to ensure the model's accuracy, particularly its ability to replicate results consistent with published data. This step was essential for verifying that the model behaves as expected when simulating the patient journey from screening through to diagnosis. However, we recognise the limitations of this approach, especially the risk of the model merely reproducing input data without fully testing its predictive accuracy.

To address this concern, we plan to incorporate additional validation strategies in any future analyses based on this model. These strategies will include cross-validation with external data sources, where independent datasets not used in the model's construction will be used for validation. This method will help ensure that the model's predictions are robust and not just a reflection of the input data. Additionally, sensitivity analyses will be conducted by systematically varying key model parameters and inputs, allowing us to evaluate the impact of different assumptions on the model's

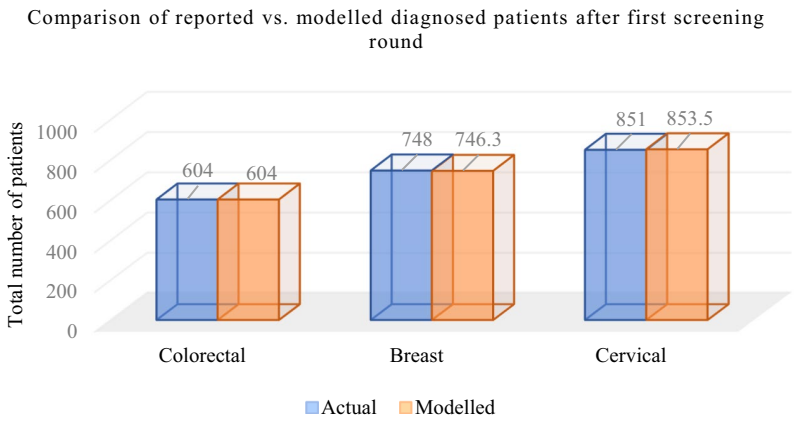

Fig. 9 Model validation results over 1 year. *Note: Since there is no existing lung cancer screening program in Australia, data on the number of patients diagnosed with lung cancer through such screenings are unavailable

outcomes. This approach will provide a deeper understanding of the model's reliability and stability across various scenarios.

3.6.2 Expert Involvement and Validation of Clinical Pathways

The development of the SD model was driven by a multidisciplinary team of experts, specifically selected for their roles as clinicians and researchers in cancer and precision oncology. This team included oncologists and early career researchers (J.S. and Y.H.T.), who were chosen on the basis of their experience in precision oncology. They played a pivotal role in refining the model and ensuring its clinical relevance by participating in meetings and round table discussions over two sessions. Their contributions were vital, providing expert insights into current diagnostic practices and the practical aspects of cancer screening and detection.

To ensure the relevance and applicability of the model, the clinical pathways proposed within the model were rigorously checked and validated by the expert team. This validation process involved comparing the modelled pathways against those outlined in the Australian Institute of Health and Welfare (AIHW) screening reports. This step was essential in confirming that the model accurately reflects the real-world clinical pathways used in the Australian healthcare system, thereby enhancing the reliability of the stage shift estimations generated by the model.

4 Discussion and Limitations

In discussing our modelling process, it is crucial to recognise certain limitations that we did not include in the model due to additional complexity. A primary challenge is to assess the potential consequences of overdiagnosis and overtreatment. This part of the analysis would entail evaluating the impacts of detecting cancers early in situations where further treatment or investigation might not be necessary. Overdiagnosed cancers are positive cases that would not have produced symptoms or led to premature mortality without screening. It is essential to distinguish these from false positives, where the screening test incorrectly identifies an average-risk, cancer-free individual as having the disease, potentially leading to unnecessary follow-up procedures such as biopsies.

One of the pivotal assumptions in this SD model is that the MCED test facilitates a stage shift in cancer diagnosis due to the assumption that adequate quantities of tumour DNA are present in the circulation, even in cases where the tumour has not extensively invaded surrounding tissues. This stage shift implies the transition of cancer stages from more advanced to earlier stages at the time of diagnosis (e.g. from stage IV to stages III, II or I). The degree to which the cancer is diagnosed at an earlier stage is contingent upon the rate of progression of the specific cancer type. Several studies have previously modelled the stage shift induced by MCED testing [15, 49–51]. In our study, the estimation of stage shift will be based on a previously published interception model [15]. The interception model of Hubbell et al. (2021), structured as a state-transition flow, calculated the proportion of cancers detected earlier due to MCED screening and incorporated inputs such as the frequency of MCED screening, estimated cancer dwell times by stage and the sensitivity of the MCED test across different cancer types and stages. Using these inputs, the study generated cancer-specific upper-triangular matrices that detail the probability of shifting from each cancer stage to all preceding stages [15].

Moreover, a crucial assumption in the model is that early cancer detection improves health outcomes, overlooking the micro-metastatic disease phenomenon. Micro-metastatic disease refers to the situation where cancer has already spread to distant sites at the time of initial diagnosis, but the metastatic deposits are too minute to be identified by standard staging investigations such as CT or PET–CT [52]. This scenario may result in an inaccurate diagnosis of early stage cancer, prompting the patient to undergo curative intent treatment, typically surgery, only for the disease to recur later, ultimately shortening their life. If an MCED test specifically identifies such cases, its capacity to enhance survival through early detection may be constrained. It is essential to acknowledge that the assumption of stage shift may not consistently yield better health outcomes due to the presence of micro-metastatic disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-024-00533-3.

Acknowledgments This research is underpinned by the Health Economics Platform of The Advanced Genomics Collaboration (TAGC), a partnership between Illumina and The University of Melbourne. Learn more at tagcaustralia.com.

The authors express their gratitude to medical oncologists, Jennifer Soon (MBBS) and Yat Hang To (MBBS), for their invaluable guidance and comprehensive review of the clinical pathways associated with cancer screening in Australia. Their expertise and insights have significantly enriched the discussion and refinement of the screening protocols discussed in this study.

Declarations

Conflict of Interest M.F. receives a PhD (unrestricted) scholarship through the Health Economics Platform of The Advanced Genomics Collaboration (TAGC), a partnership between Illumina and The University of Melbourne. H.K., S.Q.W., O.K., J.E. and M.J.I. have no competing interests to declare relevant to the content of this article. No funding was received to assist with the preparation of this manuscript.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability Not applicable.

Code Availability The system dynamics (SD) model described in this paper is available in the GitHub repository at https://github.com/mfagery/MCED-SD-Model.

Author Contributions All authors contributed to the study conception, design, and protocol review. The system dynamics model conceptual design was a collaborative effort by all authors. M.F. constructed the model in Vensim™ software (Ventana Systems Inc., Harvard, TA, USA), and it was subsequently approved by H.K., J.E., S.Q.W., O.K. and M.J.I. The first manuscript draft was composed by M.F. and underwent critical review by all other authors. All authors have read and approved the final version.

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