An exploratory analysis of the cost-effectiveness of a multi-cancer early detection blood test in Ontario, Canada

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Cancer is one of the main causes of death globally and early detection of tumors through screening is key to preventing morbidity and mortality. However, screening tools only exist for a few types of cancers, and so, many cancers go undetected until symptoms appear. New multi-cancer early detection (MCED) screening tools are currently being developed and have the potential to be cost-effective.

Research Objective: The main objective of this study is to determine the cost-effectiveness of including a MCED screening regimen together with existing provincial screening protocols for selected cancers that are prevalent in Ontario, Canada, among average risk persons aged 50 – 75 years. The selected cancers include breast, colorectal, lung, esophageal, liver, pancreatic, stomach and ovarian. The proposed intervention strategy was compared to current standard of care screening strategies for these selected types of cancers.

Methods: Cost-effectiveness was estimated using a cost-utility analysis from a provincial Ministry of Health perspective. To conduct this analysis, a state-transition Markov model representing the decision path of both the proposed and existing screening strategies along the natural history of the selected types of cancers was implemented. The incremental cost-effectiveness ratio (ICER) was calculated using data from available literature and the guidelines forwarded by the Canadian Agency for Drugs and Technologies in Health (CADTH) for conducting a cost-utility analysis, which included a discount rate of 1.5%. To test the robustness of the model, both univariate and probabilistic sensitivity analyses were conducted to determine the importance of selected input parameters.

Results: The analysis demonstrated that the adoption of MCED screening results in more diagnosed cases of each type of cancer, even at an earlier stage of disease. This was also associated with fewer related deaths compared to the standard of care option. Notwithstanding, the analysis revealed that the MCED intervention was not cost-effective (ICER: CAD$143,369 per Quality-adjusted life year (QALY)), given a willingness to pay (WTP) threshold of $100,000 per QALY. The model was most sensitive to the cost of screening and the level of specificity of the MCED and colorectal cancer screening tests. Notwithstanding, the probabilistic sensitivity analyses revealed that the MCED intervention strategy was at least 63% preferred to standard of care screening at the willingness to pay of $150,000 per QALY for both males and females.

Contribution: The main contribution of the study is to present and execute a methodological approach that can be adopted to test the cost-effectiveness of an MCED tool in the Canadian setting. The model is also sufficiently generic that it could be adapted to other jurisdictions, and with consideration for increasing the WTP threshold beyond the common $100,000 per QALY limit, given the life-threatening nature of cancer, to ensure that MCED interventions are cost-effective.

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List of Abbreviations

CADTH - Canadian Agency for Drugs and Technologies for Health

DELFI - DNA evaluation of fragments for early interception

DETECT-A - Detecting cancer earlier through elective mutation-based blood collection and testing

MCDT - Multi-cancer detection test

MCED - Multi-cancer early detection

QALY - Quality-adjusted life year

SOC – Standard of care

WTP - Willingness to pay

Introduction

Cancer is one of the main causes of death across the world, accounting for approximately 10 million deaths globally in 2020 (Ferlay et al., 2021). Lung, colorectal and breast are the most common types of cancers and causes of death, although, prostate, stomach and liver are more common among men, while cervical and thyroid cancers are more common among women (International Agency for Research on Cancer (IARC), 2020). Furthermore, in referencing Sen et al. 2009, Ahlquist highlighted that based on autopsy reports, tumors tend to be present in 7% - 11% of persons 50 – 75 years and that cancer may be a related cause of death in 3% - 5% of such persons (Ahlquist, 2018).

The burden associated with cancer extends beyond individual patient health and has far reaching social and economic consequences with respect to financing/health care costs, loss in productivity, and other impacts on families and the wider community (CCSAC, 2020; World Health Organization (WHO), 2022). Adjustments in modifiable risk factors like avoiding alcohol and tobacco consumption and maintaining a healthy diet and exercise are key in limiting the risk of developing cancer and mitigating the associated impacts (WHO, 2022). Early screening and detection also play an important role in preventing deaths by identifying and successfully treating precancerous lesions and early-stage cancers before metastasis occurs. In fact, IARC (2020), estimated that 30%-50% of cancer deaths can be avoided with these types of interventions.

Screening regimens are mainly available to target groups under organized screening programs for selected cancers where screening tools are cost-effective and contribute to reducing cancer mortality and morbidity (Cossu et al., 2018; Narayan et al., 2017; Tanner et al., 2020). Organized screening programs can either be national or state/province-led programs responsible for screening a particular (asymptomatic) population for a specific type of cancer and directing those with positive test results to appropriate follow-up clinical investigation and treatment (Dominitz & Levin, 2020; IARC, n.d.). The screening tools used under such programs are typically single-organ tests like mammography, colonoscopy, Papanicolaou test, and low-dose chest computed tomography that screen for cancers of the breast, colorectum, cervix and lungs, respectively (Black et al., 2014; US Preventive Services Task Force et al., 2016a, 2016b). Moreover, early screening of average risk groups[1] is only available for few cancers (colorectal, cervical and breast) in North America (Smith et al., 2019) and this ensures that a wider cross section of the population has access to these services. For many other types of cancers,

[1] "Average-risk individuals are defined as *those not known to be at substantially elevated risk, including those without known inherited predisposition, without comorbidities known to increase cancer risk, and without previous diagnosis of cancer or pre-cancer"* (Marcus et al., 2015).

however, early screening tools either do not exist (like for pancreatic and esophageal cancer) or are only available to high-risk groups (those with a higher-than-average chance of developing a particular type of cancer) as in the case of heavy smokers and lung cancer (Kwong et al., 2021; Siegel et al., 2020) or groups with higher risk identified by genetic testing (e.g., ovarian). This often contributes to late-stage cancer diagnoses at which point treatment options are less likely to be effective (Ahlquist, 2018; Smith et al., 2019).

Even with organized screening programs and screening tests with favourable diagnostic capabilities (like colonoscopy), screening participation within eligible groups across several countries is well below that which is required for screening benefits, namely, cost-effectiveness and lower mortality to be realised (Brouwers et al., 2011; D'Andrea et al., 2019). A minimum screening participation rate of 70% is generally recommended for these benefits to materialize. In fact, Cancer Care Ontario proposed a minimum uptake of 70% for mammography, while the US Preventive Services Task Force (USPSTF) recommended an uptake rate of at least 65% to 70% for colorectal cancer screening (Brouwers et al., 2011; USPSTF et al., 2016b).

Although the purpose of screening is to reduce cancer-related mortality by identifying cancers at a more treatable stage, where the chances of survival are notably better, the main challenge to disease management is that many cancers are not screened and are instead diagnosed at more advanced stages (Lorenzo et al., 2019; WHO, 2022). This is often the case because of one or more of the following factors: the prevalence of each of these cancers in the population is relatively low, screening and diagnostic tests are costly and invasive, testing tools are unreliable, screening programs are unavailable and screening compliance is low (Hall et al., 2018; Kisiel et al., 2022; Siegel et al., 2020; Yeh et al., 2010). Moreover, diagnostic tests are often triggered by the onset of symptoms in cancers like pancreatic, ovarian, and esophageal, which are not typically screened, and are diagnosed at points where prognoses are unfavorable (Kisiel et al., 2022). Studies have further explained that mortality and morbidity associated with cancers are due in part to late diagnoses when tumors have already metastasized, and treatment interventions are more expensive and less likely to be successful (Ahlquist, 2018; Siegel et al., 2020).

The challenges associated with unscreened cancers and late diagnoses have, therefore, spurred interest and motivated research in early cancer detection. The goal of early cancer screening, therefore, is to detect pre-symptomatic localized tumors that have not yet metastasized with the hope of increasing the likelihood of successful clinical interventions and reducing mortality (Cohen et al., 2018; Kwong et al., 2021; Siegel et al., 2020). Given that metastasis and late-stage disease for some cancers occur 20 – 30 years on average after the development of neoplastic cells, there is a large

window of opportunity to detect cancers while they remain localized (Singhi et al., 2019; Vogelstein et al., 2013; Yachida et al., 2012). During this period when the tumor burden is low, medical interventions including surgical resection, radiation and immunotherapy are most effective (Siegel et al., 2020). In fact, up to 50% of cancers can be cured with appropriate therapies provided that metastasis is not radiologically significant (Bozic et al., 2013; Huang et al., 2017; Moertel, 1995). However, medical interventions are less curative once distant tumors have formed (Bozic et al., 2013; Cohen et al., 2018; Huang et al., 2017).

Liquid biopsies, especially those using blood samples, have emerged as potential options to screen at the population level for multiple types of early-stage cancers, particularly those that are less prevalent, and those for which effective early screening tools do not exist (Ahlquist, 2018; Babayan & Pantel, 2018; Wan et al., 2017). The philosophy that drives multi-cancer early detection (MCED) is to increase the number of cancers that can be screened by virtue of a single test, so as to increase the overall prevalence of detectable cancers, and thus make the screening tool potentially more cost-effective for population-wide use, while ensuring that less prevalent cancers are also screened (Ahlquist, 2018; Liu et al., 2020). Ideally, MCED tests are less invasive than conventional single organ screening tools and require little patient preparation (Jiao et al., 2022).

Although technologies for MCED are not yet available for widespread clinical use (Cristiano et al., 2019), many tools are currently being developed and tested (Jiao et al., 2022; Oxnard et al., 2019). Some noteworthy tools that have been recently created include DETECT-A, CancerSEEK, GRAIL-Galleri, PanSeer and DELFI (Chen et al., 2020; Cohen, et al., 2018; Cristiano et al., 2019; Lennon et al., 2020; Liu., 2020). These tools rely on assay technologies and machine learning to identify low levels of cancer signatures and tumor sites (Chen et al., 2020; Cohen et al., 2018; Cristiano et al., 2019; Lennon et al., 2020; Liu et al., 2020). Specifically, assays are designed to detect cancer biomarkers and genetic mutations from a single draw of blood.

It is against this backdrop that this study asks the central question of whether including repeated MCED screening for selected cancers not currently being screened under organized screening programs, together with the current screening regimens for breast and colorectal cancers, would be cost-effective in Ontario, Canada, assuming that recommended screening participation rates are achieved. As such, the main objectives of this study are to present and execute a pragmatic economic evaluation model that can be adopted to test the cost-effectiveness of a hypothetical MCED test in the Ontario province of Canada.

Cost-effectiveness is an economic evaluation method used to assess the trade offs between the cost and effect of an intervention relative to a reference strategy (CADTH, 2017). This analysis is useful to inform decisions on whether certain health interventions are worth pursuing based on indicators of health and available budgetary resources that are measured against a predetermined willingness to pay threshold (CADTH, 2017). In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) has provided a framework of best practices to conduct economic evaluations, and this framework is adopted in this present study. Specifically, this study estimates cost-effectiveness using a cost-utility analysis that uses quality-adjusted life-years as the measure of utility associated with the intervention and reference strategies.

Furthermore, this study builds on the foundational work of Lipscomb et al. in exploring a new methodological approach to assessing the cost-effectiveness of a MCED tool. Lipscomb et al. examined the cost-effectiveness of one-time screening of a generic MCED tool using a decision tree analysis for three broad sets of hypothetical cancers (Lipscomb et al., 2022). This current research, however, proposes the use of more realistic and complex decision modelling techniques by incorporating Markov models and repeated screening of an average risk group, i.e., persons 50 - 75 years, as well as incorporating existing organized screening programs. Generally, this type of work is crucial in determining whether such tools can be incorporated into the clinical workup of cancer detection and care, even though many of these tools are still in early stages of development and are not yet available on a commercial scale. Furthermore, results from investigations of this nature will ultimately determine key parameters which will impact cost, health outcomes and overall cost-effectiveness of MCED screening (Etzioni et al., 2022; Jiao et al., 2022).

Literature Review & Background

There is a strong association between early screening and detection of cancers and the likelihood of survival with appropriate clinical interventions, especially for cancers with lower prevalence and higher mortality rates (Ahlquist 2018, Crosswell et al. 2010, Siegel et al. 2020). Unfortunately, many people who die from cancer are already symptomatic and are diagnosed only after the disease has spread from its original site to other parts of the body. Early screening is therefore seen as one strategy to limit mortality and morbidity associated with cancer, as medical interventions are more likely to be effective before metastasis has occurred (Brenner 2016, André et al. 2016). In fact, Hubbell et al. (2021) estimated that cancer-related deaths could be lowered by 26% with early screening and appropriate clinical care.

The current paradigm of cancer screening focuses primarily on cost-effective methods of single-organ screening of average risk adults under organized population-based screening programs (Kisiel et al., 2022); where average risk persons are defined as "*those not known to be at substantially elevated risk, including those without known inherited predisposition, without comorbidities known to increase cancer risk, and without previous diagnosis of cancer or pre-cancer"* (Marcus et al., 2015). Moreover, population-based cancer screening programmes are designed to detect cancers at an earlier stage among eligible persons, where eligibility is defined by patient characteristics, like age, sex and risk of developing disease (Sivaram et al., 2018). What makes these programs organized is the fact that they are managed and financed by a central body (Dominitz & Levin, 2020).

By definition, organized screening programs are either national or state/province-led programs with a clear mandate and requisite resources (human resources, infrastructure and screening tools) to screen a particular (asymptomatic) population for a specific type of cancer and to direct those with positive test results to appropriate follow-up testing and treatment (Dominitz & Levin, 2020; IARC, n.d.). Generally, the target group, the frequency with which eligible persons should be screened, and the tests used for screening form an integral part of the recommendation for screening.

The main types of cancers for which single-organ population-based screening is generally available are breast, cervical and colorectal (Kisiel et al., 2021). In the US specifically, screening for cancers of the breast, cervix, colorectum, and prostate is recommended by the American Cancer Society for average risk individuals because these types of cancers have sufficiently high prevalence rates to warrant population-level screening with existing detection tools (Smith et al., 2019). These tools range from colonoscopy for colorectal cancer, mammography for breast cancer, and pap smears for cervical cancer (Smith et al., 2019). Annual low dose computed tomography (LDCT) is recommended to screen

those with an elevated risk for lung cancer based on age and smoking history criteria (Smith et al., 2019).

On the other hand, for many other types of cancers, like pancreatic, ovarian and esophageal cancer, population-wide early screening is seldom conducted and not recommended because of low prevalence of disease, costly and unreliable screening tools, and issues related to availability and access to such tools (Ahlquist, 2018; Kisiel et al., 2022; Siegel et al., 2020). Consequently, these cancers are often detected at more advanced stages of diseases where symptoms are present, metastasis has occurred, and curative interventions are less likely to be successful (Ahlquist, 2018; Howlader et al., 2014).

However, in many cases where screening strategies are available, they are often recommended for high-risk persons or when symptoms appear. This is commonly referred to as opportunistic/risk-based screening where persons at higher-than-average risk of developing certain types of cancers that are less common among the general population are targeted for screening (Lorenzo et al., 2019). These risks include familial history of cancer, specific germline mutations, smoking history, ethnicity and geographical location (Brentnall et al., 1999; Lorenzo et al., 2019; Poruk et al., 2013). Persons with one or a combination of these risk factors are usually encouraged to undergo screening or routine monitoring under surveillance programs for pancreatic, lung and liver cancers, respectively (Kwong et al., 2021). As an example, opportunistic screening for lung cancer is provided for high-risk persons of 55-74 years who currently smoke or quit within the last 15 years and have a smoking history of at least 30 pack-years (CTFPHC, 2016). Generally, with opportunistic screening, tests are administered on the request of the patient and/or doctor depending on the presentation of symptoms and/or lifestyle (Lorenzo et al., 2019).

One key benefit of risk-based screening is that it allows for greater flexibility in screening regimens, as screening can be personalized according to individual patient risks and characteristics (Khan et al., 2021; Trentham-Dietz et al., 2016). Furthermore, the decision to undergo screening can be initiated either by the request of the patient or health professional. This is referred to as opportunistic screening (Dominitz & Levin, 2020). However, the challenge with this approach to screening is that it eludes those in the wider population who may also harbor disease, and where the incidence of deaths may also be high (Ahlquist, 2018; Kisiel et al., 2022).

Ahlquist (2018) noted other challenges of single-organ screening including those related to integrating the screening process into the clinical flow of cancer care, low screening compliance, low adherence to standard of care, and high screening and logistical costs. With respect to compliance with cancer

screening protocols, researchers have consistently reported low and variable levels (Cossu et al., 2018; Narayan et al., 2017). Sauer et al, in particular, reported a 42% rate of completion for screening of colorectal, breast and cervical cancers based on a national health interview survey in the US (Sauer et al., 2018). Additionally, Ahlquist (2018) suggested that single organ screening tends to be less efficient and less cost-effective for cancers with low prevalence in the population. Furthermore, even when approved screening methods are cost-effective as measured by willingness to pay, absolute cost can still be exorbitant (Ladabaum, 2020; Rim et al., 2019).

The limitations of single-organ screening mentioned above, along with the absence of organized screening programs for many types of cancers, have motivated research into early cancer screening and detection in order to reduce the health and economic burdens associated with malignancies. The goal of early screening is to shift the time of diagnosis of cancers to an earlier stage of disease compared to what would occur without organized screening or with opportunistic screening only (IARC, 2020). This is commonly known as 'stage-shift' and it is expected to shift the stage-distribution of diagnosed cancers away from more severe cases to more treatable, earlier stages (Connor et al., 1989; Hackshaw et al., 2021). As such, more cancers would be detected at Stage I, rather than Stage II; or at Stage II rather than Stage III, and so on; ultimately, shifting the stage of diagnosis from IV to I–III (Hackshaw et al., 2021; Lipscomb et al., 2022). Connor et al. (1989) further explained that "the stage at diagnosis is shifted from one stage to the next lower one or the stage of diagnosis is unchanged but the cancer is diagnosed earlier in the stage," in distinguishing between internal and external stage-shift. Generally, the consequence of this is a reduction in the incidence of advanced diagnoses as more cancers are detected when the tumor burden is more manageable, with the hope of increasing the likelihood of successful clinical interventions and reducing mortality (Cohen al., 2018; Kwong et al., 2021; Siegel et al., 2020).

As an alternative paradigm, universal cancer screening is a new approach (to cancer screening) that seeks to address the issues surrounding single-organ screening by offering a more cost-effective, broad-scope screening tool aimed at increasing patient participation and improving diagnostic performance (Ahlquist, 2018; Etzioni et al., 2022; Kisiel et al., 2022). With this approach to screening, multiple types of cancers are interrogated using a single tool that examines samples from the circulatory or excretory systems (Ahlquist, 2018). To this end, samples of blood, urine, stool, saliva and expired breath are tested for tumor materials. Also, critical to universal cancer screening is the ability to identify the location of tumors at an early stage to increase the chances of survival with appropriate medical intervention (Ahlquist, 2018; Etzioni et al., 2022).

Currently, tools for early screening of multiple cancers are in the experimental phase and are mainly based on technologies used for liquid biopsies (Kisiel et al., 2022). This, however, has its limitations as the technology was originally designed to detect developed tumors and not tumor precursors (Kisiel et al., 2021). In this respect, researchers agree that more effort is needed to improve the diagnostic performance of new technologies to ensure greater accuracy in cancer detection, especially at earlier stages (Ahlquist, 2018; Kisiel et al., 2022; Kwong et al., 2021). This would ultimately determine whether these tools can be integrated in the clinical pathway of cancer care and be adopted for population-wide use (Ahlquist, 2018; Kisiel et al., 2022).

Notwithstanding, liquid biopsies, especially those using blood samples, have emerged as potential options to screen for multiple types of early-stage cancers at the population level, particularly those that are less prevalent, and those for which effective early screening tools do not exist (Ahlquist, 2018; Babayan & Pantel, 2018; Wan et al., 2017). In fact, the MCED tests that have been developed are typically based on the same technology used to carry out liquid biopsies. Furthermore, the philosophy that drives multi-cancer early detection (MCED) is to increase the number of cancers that can be screened by virtue of a single test, so as to increase the overall prevalence of detectable cancers, and thus make the screening tool potentially more cost-effective for population-wide use, while ensuring that less prevalent cancers are also screened (Ahlquist, 2018; Liu et al., 2020). Ideally, MCED tests are less invasive than conventional single organ screening tools and require little patient preparation (Jiao et al., 2022).

Liquid biopsies were originally designed as investigative tools to inform treatment options, surveillance and prognoses of cancers that have already been diagnosed (CADTH 2019). They are minimally invasive tests that detect cancer material in body fluids like blood and urine (Canadian Cancer Society, 2017). Specifically, assays are used to identify cancer cells and genetic mutations in existing tumors. Furthermore, compared to tissue biopsies (where samples of tumors are collected and investigated to establish diagnosis), liquid biopsies are typically less expensive and involve less risky procedures to collect samples (Canadian Cancer Society, 2017).

Although in its infancy, the application of liquid biopsy in early cancer screening and detection has the potential to revolutionize oncology and cancer diagnostics (Babayan & Pantel, 2018; Wan et al., 2017). Scientists are currently developing new technologies to screen for multiple cancers using a single test for which tumors can be detected at very early stages of development; and especially for those where screening tools do not exist. This also opens new opportunities for early diagnosis of some cancers (like lung cancer and pancreatic cancer) where most diagnoses are made at later stages of disease (Canadian Cancer Society, 2017).

Focus has primarily been on developing minimally invasive blood-based liquid biopsy tools with higher levels of sensitivity and specificity to detect and locate tumors (Kisiel et al. 2021). More recent screening tools worth mentioning include CancerSEEK (an evolution of a previous test, DETECT-A), GRAIL-Galleri, PanSeer and DELFI (Chen et al., 2020; Cohen et al., 2018; Cristiano et al., 2019; Lennon et al., 2020; Liu et al., 2020). Although these tools differ, they share common features. Firstly, they test for early-stage cancer by applying techniques that check for mutation in cfDNA (Chen et al., 2020; Cohen et al., 2018; Cristiano et al., 2019; Lennon et al., 2020; Liu et al., 2020). Some tools (CancerSEEK and DELFI) also incorporate assays to detect biomarkers in blood samples to further increase sensitivity. Even though each tool evaluates a different subset of cancers, all the ones listed above are all able to detect colorectal, ovarian and lung cancer. In total, DETECT-A (an earlier version of CancerSEEK) evaluated 10 cancers while CancerSEEK and DELFI evaluated 8 and 7 cancers, respectively (Cohen et al., 2018; Cristiano et al., 2019; Lennon et al., 2020; Liu et al., 2020). GRAIL-Galleri, however, was designed to detect 50 different types of cancers (Lui et al., 2020). CancerSEEK can potentially detect significantly more types of cancers than that noted above, but published results of this are still not available. Furthermore, to identify the location of tumors, tools have applied machine learning (Cohen et al., 2018, Cristiano et al., 2019), confirmatory tests (Lennon et al., 2020) and other mechanisms to classify different types of cancers and establish an official diagnosis (Lui et al., 2020).

Notwithstanding the advances of liquid biopsy in early cancer detection, the widespread use of these technologies in clinical settings is yet to materialize, especially at the population level (CADTH, 2019; Jiao et al., 2022). More rigorous validation, and improved diagnostic performance, are required before clinical application is possible (CADTH, 2019; Etzioni et al., 2022; Kisiel et al., 2022). Further improvements are also needed to improve detection of early-stage tumors, even at the precancerous stage, and the location of such lesions to ultimately inform clinical follow-up for patients (Kwong et al., 2021).

Generally, proponents of universal cancer screening argue that the foundation of this approach to cancer screening is based on the principles of biology and epidemiology (Ahlquist, 2018; Hoadley et al., 2018; Kang et al., 2017). The biological principle argues that tumor markers share a similar biological process, i.e., they all shed contents into the circulatory systems even though markers may differ for a given type of cancer and even among various forms of cancers (Ahlquist, 2018; Kisiel et al., 2022). This common feature of the morphology of cancer has motivated scientists to further explore the application of tumor marker technology to detect early-stage cancer (Kisiel et al., 2022). To this end, single biopsy tests using assays and methylation have been proposed to identify tumor materials, including biomarkers such as cfDNA, cfRNA and ctDNA, across multiple types of cancers.

Using the principles of epidemiology, aggregating the prevalence of various forms of cancers based on multi-organ clusters or even the *universe* of cancers, has the potential benefit of making universal screening more cost-effective as the number of persons needed to be screened (NNS) to detect a positive case would be significantly lower than with single-organ screening, especially for less common cancers (Ahlquist, 2018; Kisiel et al., 2022). Screening strategies for individual cancers are often not cost-effective when the prevalence of the cancer in the wider population is relatively low. To further demonstrate, Ahlquist (2018) estimated that the NNS is notably higher for less prevalent individual cancers like esophageal cancer (1,000 persons) and stomach cancer (833 persons); and it reduces markedly when pan-gastrointestinal cancers (83 persons) or even the *universe* of cancers (33 persons) are screened. Relatedly, with universal screening, the likelihood that a person presents with cancer given a positive test result increases as multiple cancers are interrogated using a single test, irrespective of the level of the test's specificity. It is therefore in this light that Ahlquist (2018) described universal screening as more logical and inclusive compared to the traditional single organ approach.

Notwithstanding its benefits, there are a number of factors to consider in developing a universal cancer screening test suitable for population-wide application. These include defining the parameters of universal screening and the diagnostic capabilities of the screening tool itself.

In spite of its name, – *universal cancer screening* - researchers acknowledge that a single blood test will not be able to detect the 'universe' of cancers as some cancers, including skin cancer, leukaemia and cancers of the central nervous system, are less likely to be detected through such a medium (Kisiel et al., 2022). Instead, multi-cancer Blood Test (MCBT) or multi-cancer Early Detection (MCED) are more appropriate terms to describe the screening of multiple or a subset of different types of cancers from one test. In fact, given that several types of cancers undergo the same form of gene mutation, scientists face the critical decision of selecting which group of cancers to include in an individual test (Jiao et al., 2022). To this end, the inclusion and exclusion criteria for cancers in a multi-cancer screening test can be guided by screening priorities. For example, tests may target cancers that are more prevalent, those associated with higher mortality rates, those for which screening and detection rates are low, or those for which the chance of survival improves with early detection and treatment (Kisiel et al., 2022). Additionally, screening may be done along connected organs that follow a common route through which biomarkers may flow, like in the case of the gastrointestinal tract and the female reproductive system (Ahlquist, 2018).

Critical to the population-wide adoption of a multi-cancer early detection (MCED) screening tool is its diagnostic performance with respect to sensitivity, specificity and its ability to correctly identify the

location of tumors (Etzioni et al., 2022; Kisiel et al., 2022; Liu et al., 2020). Tests that perform favorably with respect to these criteria are more likely to be incorporated into the clinical pathway of cancer care because they are less likely to produce false positive and false negative results, thus minimizing undesirable outcomes including overdiagnosis, overtreatment, diagnostic odyssey and unnecessary anxiety associated with an incorrect test result (Kisiel et al., 2022; Kwong et al., 2021). Further research, however, is needed to validate the diagnostic performance of existing early detection tools before they can be fully integrated into the clinical flow of cancer screening and diagnostics (Etzioni et al., 2022; Jiao et al., 2022).

The sensitivity of a MCED test measures the probability of a positive test result given that a person has cancer. High sensitivity indicates that a test is more likely to accurately detect cancer materials from a particular medium. This is important because those who harbor tumors and precancerous lesions can be identified and directed through appropriate clinical pathways. An effective MCBT should, therefore, be able to detect early-stage neoplasm when clinical intervention is less invasive and outcomes are typically more favourable (Kisiel et al., 2022).

However, detecting precancerous materials using liquid biopsy technologies has its own challenges (Cohen et al., 2018; Kisiel et al., 2022). Specifically, Cohen and colleagues explained that cancers with less than one mutant molecule per millilitre of plasma are undetectable by most screening tools (Cohen et al., 2018). To address this problem, emerging technologies have focussed on improving sensitivity by incorporating different assays to screen for various tumor contents at low levels (Cohen et al., 2018; Kwong et al., 2021; Liu et al., 2020). To this end, tests for protein biomarkers and ctDNA are typically combined to boost a tool's sensitivity. In spite of these attempts, the sensitivity of many screening tools is either variable or low. Etzioni et al. (2021) explained that this variability is on account of the type of technology employed in developing the test, the type of cancer being screened and the stage of each cancer. For example, sensitivity ranges from an average of 33% for breast cancer to an average of 98% for ovarian cancer with CancerSEEK (Cohen et al., 2018) while sensitivity ranges between 57% and 99%, on average, for cancers for which the DELFI test was designed to detect (Cristiano et al., 2019).

With lower sensitivity, a screening test would detect fewer cancers and produce more false negative results. One consequence of this is that persons may be less likely to participate in follow-up standard of care procedures in the face of a negative test result believing that they are cancer-free even if symptoms appear (Lui et al. 2020, Kisiel 2021). Lui et al. (2020), however, argued that at least moderate sensitivity is acceptable for a MCBT as it would detect more cases of cancer than a single organ test which has high sensitivity.

Another important component of the diagnostic performance of an MCED test is its specificity. This measures the probability that a person without disease tests negative. High specificity is a prerequisite for population-level screening as it minimizes the number of false positive results along with subsequent outcomes like patient anxiety, diagnostic odyssey, overdiagnosis and overtreatment (Cohen et al., 2018; Etzioni et al., 2022; Kisiel et al., 2022; Lennon et al., 2020; Liu et al., 2020). Persons with false positive test results are unnecessarily channelled through clinical pathways that tend to be costly and invasive in order to confirm diagnoses (Cohen et al., 2018; Etzioni et al., 2022; Kisiel et al., 2022; Lennon et al., 2020). This problem is compounded in cases where cancers are benign and do not progress to critical states (Etzioni et al., 2021). In this vein, a test's specificity should distinguish between benign and malignant tumors (Etzioni et al., 2022; Kwong et al., 2021; Liu et al., 2020).

Yet another vital element of an effective screening tool is its ability to identify the location of tumors. Liquid biopsy alone, however, is limited in its ability to locate tissue of origin in mutation-based assays as the mutation process is common across many types of cancers (Cohen et al., 2018). Complementary approaches are, therefore, required to confirm the location of lesions. To this end, positron emission tomography - computerized tomography scans (PET-CT scans) and machine learning have proven to be instructive in locating tumors, especially in the CancerSEEK tests (Ahlquist, 2018; Cohen et al., 2018; Etzioni et al., 2022; Kisiel et al., 2022). More importantly, correctly locating the tissue of origin ensures more accurate detection, avoids diagnostic odyssey and informs the direction of clinical follow-up in light of a positive test result (Etzioni et al., 2022; Liu et al., 2020).

Even with favorable diagnostic capabilities, how an MCBT fits into the flow of cancer care is critical in defining the clinical pathway from detection to diagnosis to treatment (Kisiel et al., 2022). This begins with recognizing the difference between screening tests and diagnostic tests and acknowledging that MCBTs are designed to complement existing standard of care procedures rather than replace them (Etzioni et al., 2022; Kisiel et al., 2022; Lennon et al., 2020; Lipscomb et al., 2022).

It should be noted that a positive result from an initial screening test is not indicative of an official diagnosis. Rather, follow-up tests are required to confirm the initial screening results and to establish clinical diagnoses. The most common confirmatory tests are tissue biopsies and positron emission tomography - computer tomography (PET-CT) scans (CADTH, 2019). PET-CT scans are whole body imaging cancer diagnostic tools used to locate and confirm positive results from an initial cancer screening (Kisiel et al., 2022; Lennon et al., 2020). Although this tool has high sensitivity for detecting and locating early-stage cancers, and has FDA approval, scans expose patients to radiation levels beyond that which is standard (Lennon et al., 2020; Sachelarie et al., 2005; Schöder & Gönen, 2007).

On the other hand, tissue biopsy, which involves sampling of tissues/cells to determine the existence of and extent of disease, also has its inherent challenges. For example, some tumors are not easily accessible because of their location, as in the case of some lung cancers where some tumors may remain in the inner lining of the lung, making it difficult to access and sample for further testing (Siravegna et al., 2017). Additionally, tissue biopsies are generally invasive and can result in complications such as bleeding and cell seeding (el Achi et al., 2019). Cell seeding can occur during the process of tissue collection as tumor cells are displaced and circulate throughout the body, posing further problems for the patient by inducing metastasis. Moreover, considering the variability in the evolution of tumors, tissue biopsies may not be the most efficient diagnostic tool when metastasis has occurred, as biopsies must be repeated to evaluate prognosis (Siravegna et al., 2017). Furthermore, given that tissue biopsies are performed on fully developed tumors, their use in detecting earlier stage neoplasia is limited when tumor signatures are low (Canadian Cancer Society, 2017).

In considering the complementary role of MCED screening, MCED screening tests can be added to the current screening protocols of existing screening programs as a preliminary scan for a subset of prevalent cancers which can then trigger further cancer-specific screening and diagnostic work-up when there is an initial positive screening result. This can therefore be applied in the case where screening programs already exist like for colorectal, breast, cervical and lung cancer. This complementary role is supported by the fact that although MCED screening is designed to be less invasive, and would likely generate greater uptake than the currently available cancer screening programs, existing tools tend to be less effective at detecting precancerous lesions compared to tests for colorectal and breast cancer, for example. Nonetheless, MCED screening could prove advantageous in population-based lung cancer screening since the typical target group is more restricted and based on age and smoking history eligibility criteria.

Further to this, MCED also offers an opportunity to screen cancers that have a low prevalence in the wider population and those that lack cost-effective screening tools. Its utility is dependent on the prevalence of disease, the natural history of individual cancers, lifestyle, environmental risk factors, available therapeutics, the cost-effectiveness of the interventions and the target population (Etzioni et al., 2022; Kisiel et al., 2022).

Notwithstanding the advancements in MCED tests, researchers agree that more work is needed to validate the impact of MCED on early cancer screening and clinical outcomes, in order to justify adoption at the population-level (Etzioni et al., 2022; Jiao et al., 2022). While both retrospective and prospective studies can be identified from the literature, these types of research are not sufficiently

extensive with the necessary scientific evidence to support the inclusion of MCED screening into the clinical path of cancer care.

Retrospective studies report on cases of cancer that have already been diagnosed and are both symptomatic and at more advanced stages (Kisiel et al., 2022). Noteworthy retrospective studies identified in the literature include Cohen et al. (2018) and Cristiano et al. (2019), where the diagnostic performance of the respective MCED tests (CancerSEEK and DELFI) was evaluated on their ability to detect already diagnosed cases of cancer. The challenges with such studies are that the level of sensitivity of the screening test tends to be overestimated and the control groups are often not representative of the target population, which in turn influences the test's specificity (Cohen et al., 2018; Kisiel et al., 2022; Lennon et al., 2020). Cohen et al. (2018) further acknowledged that existing studies lacked large healthy control groups which they explained is vital for evaluating the specificity of screening tests.

To address the challenges of retrospective studies described above, prospective studies and randomized trials offer alternative approaches as they investigate screening of cancers in undiagnosed asymptomatic individuals as opposed to interrogating those who already have been diagnosed with disease (Etzioni et al., 2022; Kisiel et al., 2022; Lennon et al., 2020). Although the level of sensitivity of a test for such a group is expected to be lower than for those with diagnosed cancer, it would more accurately reflect the diagnostic parameters of the screening tool in a real-world setting (Etzioni et al., 2022; Kisiel et al., 2022; Lennon et al., 2020). Interventional studies are also equally important in assessing the impact of screening tests on clinical follow up and determining whether MCED tests can reduce cancer deaths and other related burdens (Lennon et al., 2020).

Published prospective studies identified from the literature include Lennon et al. (2020), Chen et al. (2020), and Liu et al. (2020). Lennon et al was a prospective interventional study with approximately 10,000 participants designed to determine whether an MCED test can be incorporated into the clinical work up of cancer care by detecting cancers not typically screened and directing patients with positive screening results to appropriate care that would lead to more desirable health outcomes (Lennon et al., 2020). In the case of Liu et al., a prospective case-control design was adopted to interrogate 6,689 participants for cancer signals using an MCED test that eventually detected over 50 types of cancers (Liu et al., 2020). Meanwhile, in Chen et al.'s longitudinal prospective study, 605 asymptomatic participants were followed over a 4-year period during which they were screened using an MCED test and ultimately 5 types of cancers were detected, namely colorectal, esophageal, liver, lung and stomach (Chen et al., 2020).

Three forthcoming prospective studies worth mentioning, albeit from GRAIL, LLC, are STRIVE [NCT03085888], SUMMIT [NCT03934866] and PATHFINDER [NCT04241796]. The first two studies generally seek to validate MCED screening in detecting multiple types of cancers at an earlier stage, and results from both studies are expected in 2025 and 2030, respectively (Janes et al., 2019; M. Liu et al., 2017). Likewise, the results from the PATHFINDER study [NCT04241796] - a perspective, longitudinal, interventional (clinical trial) which aims to evaluate the impacts of including MCED screening in the clinical path of cancer diagnosis – is expected in 2026 (Nadauld et al., 2021). The outcomes from the aforementioned studies would no doubt be instructive in building the knowledge base on the utility of MCED testing and in determining whether this form of screening can in be integrated into the clinic pathway of cancer detection and treatment.

Ultimately, the integration of an MCED test into the clinical pathway of cancer care would depend on whether it is cost-effective. While extensive research in this area is lacking, two recent studies are worth mentioning, namely, Lipscomb et al. (2022) and Tafazzoli et al. (2022). Lipscomb et al. (2022) is a seminal piece that investigated the cost-effectiveness of a generic MCED using a decision tree model. While these authors found the MCED test to be cost-effective in screening for three groups of hypothetical cancers, they explained that the purpose of the analysis was *purely illustrative* and not designed to *provide a definitive assessment* of cost-effectiveness. Tafazzoli et al. (2022), on the other hand, followed with a more detailed state-transition model with an integrated decision tree to measure clinical and economic outcomes of MCED screening for 19 types of cancers in the US population among persons 50-79 years of age from a third-party perspective. This study focused on estimating the maximum price of the MCED test that can be charged given a willingness to pay of US$100,000 per Quality-adjusted life year (QALY). This price was estimated at US$1,196. Notwithstanding the invaluable contributions of these studies to the literature on cost-effectiveness of MCED screening, further work is needed in this area to better inform policy makers on these matters.

MCED tests

The thrust towards early cancer screening and detection in the hope of improving long term clinical outcomes has motivated research into developing new cancer screening tools aimed at identifying precancerous lesions and early-stage tumors. This has resulted in the development of a number of liquid biopsy-based screening tools which interrogate blood samples for cfDNA in order to identify multiple types of cancers. Some of the more recent screening tools include, CancerSEEK, GRAIL-Galleri, PanSeer and DELFI (Chen et al., 2020; Cohen et al., 2018; Cristiano et al., 2019; Lennon et al., 2020;

Liu et al., 2020). While these MCED tools are neither available for widespread clinical use nor have approval from the U.S. Food and Drug Administration (FDA), they are indicators of the advancements made thus far in multi-cancer screening. [2]

The capacity of each of the aforementioned test differs in terms of diagnostic performance, the subset of cancers they can detect, and the procedure used to locate tumors. While each test was designed to detect different subsets of cancers, some cancers are commonly detected, including, colorectal, ovarian and lung cancer. See Tables 1 and 2 for a comparison of the selected MCED screening tests. These tests also use very different methods to locate tumor. For example, DETECT-A, which is the predecessor of CancerSeek, was designed to identify multiple types of cancers with the help of PET-CT imaging to locate tumor sites (Lennon et al., 2020). In a similar fashion, PanSeer was engineered to distinguish between tumor and non-tumor DNA, but follow-up testing is required to identify the location of tumors. Meanwhile, DELFI, CancerSEEK and GRAIL-Galleri utilize machine learning techniques to locate the origin of cancer tissues.

It therefore follows that a comparison of the performance of the aforementioned MCED tests must be done in the context of the study designs in which they were employed to evaluate the sensitivity and specificity of each test. On that note, it should be reiterated that while prospective studies are preferred to retrospective studies to more accurately determine the performance of MCED tests under real world conditions, the diagnostic performance of the tests will be less favourable in these types of studies because the incidence of cancer cases tend to be notable smaller. For example, the DETECT-A test, which is an earlier version of CancerSEEK, interrogated 10 types of cancer in a prospective, interventional study of 100,006 cancer-free women aged 65-75 years using diagnostic PET-CT to inform an official diagnosis and tissue of origin, had estimated levels of sensitivity and specificity of 15.6% and 99.6%, respectively (Lennon et al., 2020). In contrast, in the follow-up CancerSEEK study, Cohen et al., interrogated 8 types of cancers in a retrospective investigation of 1,005 patients already diagnosed with either stage I to III cancer who had not yet been administered neo-adjuvant chemotherapy. Unlike its earlier iteration which accounted for a complete diagnostic work-up by incorporating a PET-CT scan to identify tissue of origin, the CancerSEEK test as described by Cohen et al. relied on machine learning techniques to locate tumors (Cohen et al., 2018). The recorded sensitivity and specificity of this test in this study were 70% (median) and 99.14%, respectively.

[2] The GRAIL-Galleri test, however, has FDA Breakthrough Device Designation, which makes the test available to eligible persons.

Further evidence of prospective studies producing less favourable diagnostic results, particularly levels of sensitivity, can be gleaned from Table 1. For example, the MCED tests in the two prospective studies, Lennon et al. and Klein et al., produced sensitivity levels of 15.6% and 51.5%, respectively (Klein et al., 2021; Lennon et al., 2020); although when fewer cancers (12 cancers) were interrogated in the Klein et al study, sensitivity improved to 76.4% (Klein et al., 2021).[3] Conversely, in the case of the retrospective studies, Cohen et al., Cristiano et al. and Chen et al., the recorded levels of sensitivity were notably higher, 70%, 73% and 95%, respectively .

The CancerSEEK test was selected as the stylized MCED test in this study because it can detect a reasonable number of cancers with a favorable degree of accuracy with respect to sensitivity and specificity. Specifically, in the research by Cohen et al, the test was used to detect eight types of cancers, namely, breast, colorectal, esophageal, liver, lung, ovarian, pancreatic and stomach; although it can potentially detect several more types of cancers. According to these researchers, these types of cancers were selected because they are common in Western societies (which includes Canada) and they have far-reaching impacts for personal and public health (Cohen et al., 2018).

Table 1 Description of selected MCED tools

	Multi-cancer Early Detect Tool				
	DETECT-A	CancerSEEK	GRAIL-Galleri	DELFI	PanSeer
Types of cancers interrogated	10	8	>50	7	5
Sensitivity	15.6%	70%	51.5%	73%	95%
Specificity	99.6%	99.14%	99.5%	98%	96%
Tissue of origin	N/A	63%	88.9%	61%	N/A
Type of study	Prospective, interventional	Retrospective, case-control	Prospective, case-control, observational	Retrospective, case-control	Retrospective
Source:	Lennon et al. 2020	Cohen et al. 2018	Klein et al. 2021	Cristiano et al. 2019	Chen et al. 2020

[3] The subset of cancers includes anal, bladder, colorectal, esophageal, head and neck, liver/bile-duct, lung, lymphoma, ovarian, pancreatic, plasma cell neoplasm and stomach.

Table 2 Screening tests and cancers detected

	Multi-cancer Early Detection Tools				
Cancer type	DETECT-A[1]	CancerSEEK	GRAIL-Galleri[1]	DELFI	PanSeer
Lung	✓	✓	✓	✓	✓
Colorectal	✓	✓	✓	✓	✓
Ovary	✓	✓	✓	✓	
Liver/bile duct		✓	✓	✓	✓
Stomach		✓	✓	✓	✓
Pancreas		✓	✓	✓	
Breast	✓	✓	✓	✓	
Esophagus		✓	✓		✓

Source: Lennon et al. 2020, Cohen et al. 2018, Klein et al. 2021, Cristiano et al. 2019, Chen et al. 2020.
[1]The full lists of cancers interrogated by DETECT-A and GRAIL-Galleri are provided in Appendix A and B.

Cancer in Canada

In Canada, cancer accounted for 28.2% of total deaths in 2019 (Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, 2021). In fact, 23.4% of Canadians are expected to die from cancer with the majority of deaths (96%) to occur among persons 50 years and older (CCSAC, 2021). Lung, colorectal, pancreatic, breast and prostate cancers contribute to approximately 55% of all cancer deaths in the country, with lung cancer in particular accounting for a quarter of all cancer deaths in Canada (CCSAC, 2020). Between 2000 and 2018, the number of cancer deaths increased by 29.2% from over 62,000 deaths to approximately 81,000 deaths (Statistics Canada, 2022). Moreover, deaths are projected to increase further to 84,600 in 2021 (CCSAC, 2021). Although the number of deaths continue to increase, the associated mortality rate has declined over the last 7 years from 216.9 deaths per 100,000 in 2014 to 213.1 deaths per 100,000 in 2020 (Statistics Canada, 2022). This trend can be credited to improved strategies for screening and detection and general cancer care (CCSAC, 2021).

Like the trend in cancer mortality, the most diagnosed cancers are lung, breast, colorectal and prostate cancers, and they account for over 50% of all newly diagnosed cases in Canada (CCSAC, 2021). Moreover, approximately 90% of these cases occur among persons at least 50 years of age, which falls within the recommended screening age for many cancers in Canada (CCSAC, 2021). The annual number of cases of cancers has also increased over the years from 86,245 persons to 156,605 persons between 1992 and 2018: an increase of 81.6% (Statistics Canada, 2022). Cases are also projected to rise further to 229,100 persons in 2021 (CCSAC, 2021). Notwithstanding the rise in the number of

diagnoses, the age-standardized incidence rate decreased by 2.6% from 519.5 cases per 100,000 to 506.1 cases per 100,000 between 1992 and 2018; but is expected to rise marginally to 515.2 cases per 100,000 in 2021 (Statistics Canada, CCS 2021).[4]

The chances of surviving the disease have also increased for many types of cancers as the incidence and mortality rates decline. In particular, the 5-year net survival has increased from 55% to 64%, on average, between the 1990s and 2021 (CCSAC, 2021). Thyroid cancer and testicular cancer have the highest survival rate; both at 97%. However, survival of esophageal and pancreatic cancers remains low at 16% and 10%, respectively (CCSAC, 2021). Like mortality, survival is dependent on the availability of effective early screening tools as well as the type of cancer (CCSAC, 2021).

The costs associated with a cancer diagnosis are far reaching and include both medical and non-medical expenditures that burden the patient as well as, families, the government and society. The cost of cancer care in Canada, in particular, more than doubled over the 8-year period 2005 to 2012 from $2.9 billion to $7.5 billion, an increase of 158% (de Oliveira et al., 2013). Costs are expected to continue to rise as the number of cases and deaths increase. This is compounded by the fact that 43% of the Canadian population are expected to develop one form of cancer during their life. These trends are driven in part by population growth and population ageing (CCSAC, 2021). For example, the Canadian population is expected to grow annually at a rate of approximately 0.8% over the next 10 years, while the subpopulation of persons 60 years and older is expected to grow by 24% over the same period (United Nations, 2019). In light of this, it is estimated that annual cases of cancer would be almost 80% higher on average in the period 2028-2032 compared to 2003-2007 (Xie et al., 2015). This increase is expected for both males (84%) and females (74%). CCSAC (2021) further reported that changes in risk factors and cancer control policies have had a notable impact on the reduction in mortality but less so on the incidence of cancer cases.

Cancer in Ontario

Similar trends are also observed across the provinces, especially in Ontario where approximately 31,100 cancer-related deaths were projected in 2021, representing over a third of the total number of deaths in the country in that year (CCSAC, 2021). Also, the annual number of diagnosed cases of cancer rose from 42,700 to 82,965 persons between 1992 and 2018: an increase of 94.3% (Statistics

[4] Cancer incidence data for Quebec are not available for diagnosis years after 2010. For tables 13-10-0111-01 and 13-10-0747-01, annual case count and rate estimates for Quebec and Canada for the 2011 diagnosis year onward are not provided. Cancer incidence estimates for Canada excluding Quebec were produced for all diagnosis years in this table.

Canada, 2022). At the same time, the incidence rate grew by 3.5% from 513 cases per 100,000 to 531.8 cases per 100,000 over the same period (Statistics Canada, 2022). The province also has the highest number of cases of cancer projected for 2021 compared to other provinces with over 91,000 cases expected (CCSAC, 2021). This is driven in part by the fact that the province is the most populous throughout Canada, accounting for over 38% of the country's population (CCSAC, 2021). However, using the age standardized incidence rate (ASIR), Ontario ranked second highest in 2021 with 545.9 cases per 100,000 persons. Newfoundland and Labrador had a higher rate (559.8 cases per 100,000 persons) (CCSAC, 2021).

Cancer screening programs and recommendations in Canada

The Canadian Cancer Society defines screening as "checking for a disease in a group of people who don't show any symptoms of the disease" (asymptomatic) with the hope of detecting and successfully treating precancerous lesion and early-stage cancers. Further, the cancer screening landscape in Canada consists of organized and risk-based/opportunistic screening programs for selected types of cancers (colorectal, breast, cervical, lung), and no screening programs for other types of cancers (such as ovarian and pancreatic).

Organized screening programs are not available for all types of cancers in Canada and only selected cancers are screened through population-based or risk-based programs. Typically, screening is made available if it is deemed feasible and this depends on the incidence of cancer, the potential reduction in associated mortality and the cost-effectiveness of screening. In Canada, organized screening programs are available for colorectal and breast cancer, and these programs are guided by clear screening recommendations articulated by the Canadian Task Force on Prevention Health Care (CTFPHC). Some examples of organized screening programs in Canada are described below.

In Ontario, like many of the other Canadian provinces, fecal immunochemical testing (FIT) biennially is the recommended screening regimen for colorectal cancer for persons 50 – 74 years (Canadian Cancer Society, n.d.-a). Flexible sigmoidoscopy (FS) is an alternative, while colonoscopy (COL) is used as a follow-up procedure in the event of a positive FIT or FS test (Kalyta et al., 2021). These tests are not only recommended by the Canadian Association of Gastroenterology for average at-risk persons (aged 50 - 75 years) but have also been demonstrated to be the most cost-effective screening strategies in many Canadian-based studies (Heitman et al., 2010; Kalyta et al., 2021; Leddin et al., 2010). Heitman et al. (2010), for instance, illustrated that FIT has a cost saving of $68 CAD per patient and is associated with a 71% reduction in colorectal cancer cases and a 74% reduction in related

deaths. Similarly, Telford et al. estimated an ICER of $611 per QALY relative to no screening. Other cost-effective strategies mentioned in this study include FS and COL (ICER: $61 per QALY and $6,133 per QALY, respectively) (Telford et al., 2010).

With respect to breast cancer, in 2018, the Canadian Task Force on Prevention Health Care (CTFPHC) updated its 2011 recommendation for screening. While elements of the previous guidelines were maintained, (i.e., routine screening with mammography is not recommended for average risk women 40-49 years but conditionally recommended for women 50-69 years and 70-74 years every 2 – 3 years), the new policy states that *the decision to undergo screening is conditional on the relative value a woman places on possible benefits and harms from screening* (CTFPHC, 2018). The estimated ICERs for biennial and triennial mammography among women 50/55 to 74 years range from $28,921 per QALY to $94,762 per QALY in the Canadian setting (Mandelblatt et al., 2016; Mittmann et al., 2015; Pataky et al., 2014). In fact, according to Mandelblatt et al., 81% of the benefits of annual screening are achievable with biennial screening without the additional costs of more frequent screening (Mandelblatt et al., 2009).

In the case of lung cancer, there are no provincial or territorial screening programs at present in Canada, but pilot programs are in place in some provinces with anticipated roll out in the future. For example, in the province of Ontario, the pilot program titled Lung Cancer Screening Pilot for People at High Risk was established and is expected to be fully operational as an organized screening program over time (Darling et al., 2021; Tammemägi et al., 2021). In support of this, the CTFPHC has recommended annual low-dose computed tomography (LDCT) for screening lung cancer for 3 years among persons 50–74 years who are current smokers or former smokers who quit in the last 15 years and have smoked 30 pack-years. This is to be accompanied by cessation programs aimed at helping persons to quit smoking (CTFPHC, 2016).

In line with the recommendation for lung cancer screening, three noteworthy studies demonstrated the cost-effectiveness of LDCT in Canada (Cressman et al., 2017; Goffin et al., 2015; ten Haaf et al., 2017). These studies estimated ICERs of CAD$52,000 per QALY, CAD$41,136 per life-year gained and CAD$20,724 per QALY, respectively, in their base-case analyses. The first two studies adopted a third-party health care payer perspective and an age range of 55 to 74/75 years while the other was based on a risk prediction model. Nevertheless, all the studies demonstrated that cessation programs and more stringent inclusion criteria that screen those with a smoking history of ≥ 40 pack-years as opposed to ≥ 20 pack-years would further improve cost-effectiveness.

Organized cervical cancer screening is also available across the country. Women from the age of 21 years who are sexually active are encouraged to undergo screening using a Papanicolaou/Papanikolaou test every 1 to 3 years based on previous test results (Canadian Cancer Society, n.d.-b). Notwithstanding this recommendation, studies have focused on the effectiveness and cost-effectiveness of Human papillomavirus (HPV) testing along with Pap smears as the primary screening regimen for cervical cancer (Kulasingam et al., 2009; Vijayaraghavan et al., 2010). For instance, the results from the Canadian Cervical Cancer Screening Trial revealed that this combination of a Pap-smear and HPV testing improved sensitivity to 94.6% (compared to 55.4% with Pap smears only), although specificity fell marginally to 94.1% from 95% (Mayrand et al., 2006). Furthermore, in a follow-up study, Vijayarghavan et al. (2010) demonstrated that including HPV testing as part of the annual cervical cancer screening regimen was cost-effective with an associated ICER of $2,991 per QALY compared to other screening options.

Although organized screening programs exist for the aforementioned types of cancers, for many other types of cancers like pancreatic, stomach, liver, esophageal and ovarian, there are no existing approved organized screening programs in Canada (Canadian Cancer Society, n.d.-a). Generally, the incidence of each one of these types of cancers in Canada is relatively low, with age-sex incidence rates less than 20 per 100,000, and typically, population-based screening programs for cancers with such low incidence are not recommended because they are less likely to be cost-effective (Bhutani et al., 2009; Schwartz et al., 2021).

In the absence of organized screening programs, opportunistic screening is available for stomach, ovarian and lung cancer in Canada (Canadian Cancer Society, n.d.-a). For example, *H.pylori* tests, or upper gastrointestinal series (UGI) and gastroscopy are recommended for those at higher-than-average risk for gastric cancer (Canadian Cancer Society, n.d.-a). Likewise, pelvic exams, transvaginal ultrasound and cancer antigen 125 (CA125) are recommended for women at greater risk for ovarian cancer (Canadian Cancer Society, n.d.-a). Also, in the case of lung cancer, opportunistic screening using low-dose computer tomography and through pilot screening programs are available for selected high-risk groups across many provinces.

To summarize, Table 3 below presents the status of screening programs, screening recommendations and screening tools available in Canada (Ontario) for the cancers of interest in this study. It reveals that organized screening programs are only available for colorectal cancer and breast cancer with

attendant screening tools and recommendations[5]. Meanwhile, there are no existing approved organized screening programs for 6 of the 8 cancers (pancreatic, stomach, lung, liver, esophageal and ovarian). However, opportunistic screening exists for lung, stomach and ovarian cancer.

[5] A population-based cervical cancer screening program also exists. Women from the age of 21 years who are sexually active are encouraged to screen for cancer using a Papanicolaou test or Papanikolaou test every 1 to 3 years based on previous test results according to the Canadian Cancer Society.

Table 3 Screening program and tools for selected cancers in Canada

Cancer	Screening program	Recommendation	Tool
Colorectal	Yes	Stool test every 2 years for persons 50-74 years, at not high risk of colorectal cancer. Those ≥75 years should consult their doctor about screening.	• Fecal immunochemical test (FIT) - Ontario • Guaiac-based fecal occult blood test (gFOBT)
Breast	Yes	Biennial screening for women 50-74 year. Those 40-49 years and ≥ 75 years should consult their doctors on the risks, benefits and limitations of screening.	Mammography
Lung	No	The Canadian Task Force on Preventive Health Care (CTFPHC) recommends triennial screening for persons 50–74 years who are current smokers or former smokers who quit in the last 15 years and have smoked 30 pack-years. Program should include cessation component.	Low-dose Computer Tomography
Stomach	No	Frequent checks for those with higher-than-average risk.	• Breath or stool test for H. pylori • Upper gastrointestinal (GI) series • Upper GI endoscopy
Esophageal	No	NA	NA
Pancreatic	No	NA	NA
Liver	No	NA	NA
Ovarian	No	Those with higher-than-average risk should consult their doctor.	• Pelvic exam • Transvaginal ultrasound • Cancer Antigen 125 (CA125)

Source: Canadian Cancer Society

Individually, the incidence rates for stomach, esophageal, pancreatic, liver and ovarian cancer in Canada are low. Table 4 shows the projected age-standardized incidence rate (ASIR) for each of the selected cancers for the year 2021. For the aforementioned cancers, the ASIRs are less than 20 per 100,000, which Ferlay et al. (2013) described as low to intermediate risk.[6] Generally, population-based screening programs for cancers with low incidence are not recommended because they are less likely to be cost-effective (Bhutani et al., 2009; Schwartz et al., 2021). This is driven in part by the absence of effective screening tools and high false positive rates associated with existing tools which can then trigger patient anxiety, and lead to costly, unnecessary and invasive follow-up procedures (Kulkarni et al., 2020; Li et al., 2019). Yeh et al. further explained that screening would only be cost-effective if the incidence of these individual cancers were to increase by over threefold (Yeh et al., 2010). Additionally, the dearth of research, particularly randomized controlled trials, on screening options, is one reason for the absence of guidelines and consensus on screening cancers with such low incidence (Lee et al., 2014; Moss et al., 2018).

Table 4 Projected age-standardized incidence rate of selected cancers in Canada, 2021

Cancer	**Cases per 100,000**
Breast	66.5
Lung	59.5
Colorectal	54.9
Pancreatic	14.1
Ovarian	13.5
Stomach	12.3
Liver	7.1
Esophageal	5.6

Source: Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2021. Canadian Cancer Statistics 2021, Canadian Cancer Registry database at Statistics Canada

[6] Risk is defined by the age-standardized rate (ASR) of cancer where, ASR ≥ 20 per 100,000 is considered high risk, ASR < 10 per 100,000 is low risk and ASR between 10 and 19 per 100,000 is intermediate risk.

Risk-based screening

Justification for risk-based screening is based on the prevalence of disease among high-risk populations. The following discussion presents the rationale for risk-based screening for pancreatic, stomach, esophageal, liver and ovarian cancer.

In the case of pancreatic cancer, risk-based screening that targets "members of familial pancreatic cancer (FPC) kindred", those with new-onset diabetes (NOD) and those with specific germline mutations may hold greater promise of being cost-effective, given that the incidence of this type of cancer among these groups is greater than in the general population (Brentnall et al., 1999; Lorenzo et al., 2019; Poruk et al., 2013). Moreover, given that the lifetime risk of developing pancreatic cancer among those in these high-risk groups can be as high as 50%, targeted screening of these persons would be more feasible than population wide screening where these cases are rare (Lynch et al., 1996; Stoffel et al., 2019). For example, familial pancreatic cancer screening is motivated by the fact that 10% of cases of pancreatic cancer are hereditary (Stoffel et al., 2019). Additionally, germline mutations, including those that are familial in origin, are associated with up to 40% higher risk of developing pancreatic cancer (Canto et al., 2013; Hu et al., 2018). Also, it was estimated that 75% of patients with pancreatic cancer are also diabetic and that 25% of these patients are diagnosed with diabetes 6-36 months before the cancer diagnosis (Chari et al., 2005).

With respect to stomach cancer, the incidence of disease is notably higher among Asian countries than western counterparts. In fact, in 2020, the ASIRs for gastric cancer in Japan, Korea and China were 31.6, 27.9 and 23.4 per 100,000, respectively, compared to 4.4 and 4.2 per 100,000 for Canada and the US, respectively (International Agency for Research on Cancer, 2020). Moreover, 89% of cases of noncardia gastric cancer have a Helicobacter pylori (H. pylori or HP) etiology, which is a type of bacteria that affects many children and can cause stomach cancer later in life when serious infections occur (Kowada, 2019; Malfertheiner et al., 2012; Sarmasti et al., 2021). It therefore follows that an alternative, yet indirect approach to gastric cancer screening, is through testing for Helicobacter pylori (H. pylori or HP), which if detected, can be treated, thus limiting the likelihood of presenting with related cancers in the future (Malfertheiner et al., 2012).

In one meta-analysis/systematic review, researchers found that endoscopy was associated with a 40% reduction in deaths related to gastric cancer, thus justifying its recommendation for gastric cancer screening in high-risk Asian countries like China, Korea and Japan (Zhang et al., 2018). Relatedly, another study demonstrated that in countries with intermediate risk of gastric cancer like those in Europe, the use of upper endoscopy was only cost-effective (ICER: €30,908 per QALY) when combined

with a colonoscopy procedure because the burden associated with both tests is shared[7] (Areia et al., 2018).

Like stomach cancer, esophageal cancer is also common within the Asian region, with over 50% of global cases of the esophageal squamous cell carcinoma (ESCC) type, occurring in China, whereas the remaining cases are typically found in more developed countries and have an adenocarcinoma histology (Arnold et al., 2015). Screening recommendations should therefore be cognizant of these epidemiological and geographic characteristics along with the fact that those with gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE), particularly men, are at higher risk of developing esophageal cancer than those in the general population (Y. Li et al., 2020). In fact, men with GERD have a five times more likely chance of developing esophageal cancer than women (Benaglia et al., 2013).

Concerning liver cancer, screening guidelines across countries in Europe, Asia-Pacific and North America have targeted hepatocellular carcinoma (HCC), which is the most common type of primary liver cancer, accounting for 85-90% of the total number of cases of liver cancer globally (Bruix & Sherman, 2011; Cucchetti et al., 2013; European Association For The Study Of The Liver, 2012; Omata et al., 2010). High risk patients for liver cancer are defined as those with cirrhosis of the liver as well as those with chronic hepatitis B and C infections, where 90% of these cases tend to develop liver cancer (Lee et al., 2014). In fact, cirrhosis may stem from hepatitis infections and up to 30% of these patients may develop HCC (Bugianesi et al. 2002). Given that HBV is endemic in certain regions of Asia and Africa, the incidence of HCC is likely to be higher among persons in these regions and their diaspora (Howlader et al., 2014; Miller & Lee, 2016). In fact, of the over 900,000 cases of liver cancer reported globally in 2020, 73%, 9.6% and 7.8% occurred in Asia, Europe and Africa, respectively, with the ASIRs in these regions estimated at 11.6%, 5.2% and 8.8%, respectively (International Agency for Research on Cancer, 2020). Likewise, Hutton et al. noted that at least 10% of Asian-Pacific adult population in the US have HBV and over 60% of these individuals are not aware of their health status (Hutton et al., 2007). Other reports indicate that the incidence of HCC among Chinese American men is approximately 21.6 per 100,000, which is three times higher than that among white males (Chang et al., 2007; Howlader et al., 2014). To address the challenges associated with liver cancer, policy makers have chosen to focus on vaccination programs to reduce the rate of infections and hence the likelihood of chronic liver disease and ultimately mortality associated with HCC.

[7] This study's target population was Portuguese men and women aged 50 to 75 years and the results of the study extrapolated to other European countries with similar risk of gastric cancer.

Regarding ovarian cancer, Jacob and Menon (2004) explained that because of the low incidence of disease and a 2% risk of cancer development among the at-risk group (postmenopausal women age ≥ 50 years, those with familial history of malignancy, and those with BRCA1/2 mutations), strict criteria are necessary for a screening tool to be considered effective. These criteria include a positive predictive value (PPV) ≥ 10%, specificity ≥ 99.6%, and a high level of sensitivity that ensures clinical and preclinical disease can be detected (Jacobs & Menon, 2004). These parameters would also limit the number of false positives and the associated consequences as well as ensure that a greater percentage of those with the disease are detected and receive appropriate clinical care. Further to this, one systematic review, which covered North American and European countries, found that multimodal screening using CA-125, transvaginal ultrasound, and a risk of ovarian cancer algorithm in postmenopausal women was cost-effective for ovarian cancer screening, with ICER ranging from €9,800 to €81,400 per QALY (Sroczynski et al., 2020).

Screening Participation

Notwithstanding the recommendations previously mentioned, research in Canada revealed that reported rates of screening participation are less than desired levels, especially among minority groups, including immigrants (Ferreira et al., 2021; Vahabi et al., 2021). For example, participation rates for mammography are just above 50% for minority groups in Canada (Ferreira et al., 2021). Furthermore, in a study of approximately 1.2 million eligible women in Ontario, over the period April 2014 to March 2017, 15% had not participated in screening for either breast or cervical or colorectal cancers; and only 48% participated in screening for all three cancers (Vahabi et al., 2021). Another statistic revealed that 41.3% to 67.2% of the eligible population across Canadian provinces adhere to CTFPHC guidelines for colorectal cancer screening (Sweeney-Magee et al., 2022). Meanwhile, in the case of lung cancer, while there is only one pilot project for screening in Ontario, evidence, especially from opportunistic screening, suggests low screening rates within the province (Linehan et al., 2021). For example, 44% of lung cancer cases were reported to have “presented to the ER within a week of their diagnoses” (Habbous et al., 2021); and 69% of lung cancer cases are diagnosed at Stage 3 or 4 (Statistics Canada, 2018). Socioeconomic and demographic factors like age, education and income levels, along with factors that influence access and availability of screening services, like location, non-medical costs and insurance have been noted to contribute the low screening participation rates observed (D’Andrea et al., 2019; Vahabi et al., 2021).

A minimum participation rate of 70% is generally recommended for the benefits of screening to materialize, namely, cost-effectiveness and lower mortality (Brouwers et al., 2011; D’Andrea et al.,

2019). In fact, Cancer Care Ontario proposed a minimum uptake of 70% for mammography, while the US Preventive Services Task Force (USPSTF) recommended an uptake rate of at least 65% to 70% for colorectal cancer screening (Brouwers et al., 2011; USPSTF et al., 2016b).

Cancers of concern

The cancers that are of concern in this study are those for which the MCED test, CancerSEEK, can detect. This test was selected as the stylized MCED test. The list of cancers that the test can detect are breast, colorectal, esophageal, liver, lung, ovarian, pancreatic and stomach. As in other western countries, these cancers are of concern in Canada. They can be categorized based on incidence, mortality/survival rates and availability of screening tools. For example, breast cancer, lung cancer and colorectal cancer are among the most commonly diagnosed cancers in Canada with over 15,000 cases of each type of cancer expected to be diagnosed in 2021 (CCSAC, 2020). On the other hand, while the incidence of ovarian, liver, stomach, pancreatic and esophageal cancers are relatively lower, they are associated with higher mortality and lower survival rates. In fact, for each of these cancers, at least 1,000 related deaths are expected in 2021; and this number is greater than 4,000 for pancreatic cancer (CCSAC, 2021). Additionally, less than 50% of those diagnosed with these cancers are expected to survive the first 5-years after diagnosis. See Table 5. Also, there are no existing approved organized screening programs for 5 of the 8 cancers (pancreatic, stomach, liver, oesophageal and ovarian). However, population-based screening using mammography and FIT exist for breast cancer and colorectal cancer, respectively. Meanwhile, opportunistic screening exists for lung, stomach and ovarian cancer. It is also important to note that five of the cancers occur along the digestive tract, i.e., pancreas, stomach, liver, esophagus and colon/rectum.

Table 5 Summary of key cancer control and outcome characteristics by cancer type in Canada

Cancer	**Existing Detection Tool**	**Survival (5-year net survival)**	**Mortality (deaths)**	**Incidence (expected cases in 2021)**
Ovary	No	<50%	1,000-4,000	<5,000
Liver	No	<50%	1,000-4,000	<5,000
Stomach	No	<50%	1,000-4,000	<5,000
Pancreas	No	<50%	≥4,000	<15,000
Esophagus	No	<50%	1,000-4,000	<5,000
Colorectum	Yes	50%-79%	≥4,000	≥15,000
Lung	Yes	<50%	≥4,000	≥15,000
Breast	Yes	>80%	≥4,000	≥15,000

Source: CCSAC 2021

Specific Aims

The specific aim of this study is to determine whether including an MCED screening regimen (for lung, esophageal, liver, pancreatic, stomach and ovarian cancers), together with existing provincial screening protocols for breast and colorectal cancers in Ontario, Canada, among average risk persons 50 – 75 years would be cost-effective from a provincial Ministry of Health perspective, assuming a minimum screening participation rate of 75%, compared to standard of care for selected cancers. The cancers of interest are those that the CancerSEEK tool was designed to detect, namely colorectal, breast, lung, liver, stomach, pancreatic, esophageal and ovarian.

As a secondary goal, this study also seeks to estimate the potential value-based price (VBP) of the MCED test, which is the maximum price at which the test may be set to ensure that its intervention is cost-effective at a willingness to pay of CAD $100,000 per QALY. This threshold was set since it is widely used for cancer treatment (Cherla et al., 2020)

Methods

Study design

This study employed decision-based modelling techniques to assess the overall cost-effectiveness of incorporating a stylized MCED screening tool, loosely based on the characteristics of the CancerSEEK test, along with standard of care screening recommendations for breast and colorectal cancer in Ontario, Canada, compared to only standard of care screening protocols for selected cancers, namely breast, colorectal, esophageal, liver, lung, ovarian, pancreatic and stomach. Cost-effectiveness was assessed using a cost-utility analysis.

This analysis builds on the pioneering work of Lipscomb et al. (2022) where cost-effectiveness of one-time screening of a generic MCED tool was assessed using decision tree analysis for three sets of hypothetical cancers. While this study demonstrated that MCED screening was cost-effective compared to no screening (ICER: $22,494 per QALY), the authors explained that the purpose of the analysis was *purely illustrative* and not designed to *provide a definitive assessment* of cost-effectiveness (Lipscomb et al., 2022). It is therefore within these same parameters that the assumptions and limitations of this study are based. The main limitation of the Lipscomb et al. (2022) study is the use of a static decision tree framework for an economic evaluation that would benefit from the application of dynamic simulation techniques, especially since the analysis accounts for evolving health states. Another limitation stemming from the authors' choice of model is that the analysis could only account for one-time screening, when in reality, eligible persons may be subjected to multiple rounds of screening based on recommended screening intervals for specific types of cancers under organized screening programmes as in the case of breast, colorectal and cervical cancers. Other limitations include the use of hypothetical types of cancers, a generic cancer screening tool, and multiple assumptions on key input parameters. In acknowledging these drawbacks, the authors advocated for further work to improve upon modelling techniques and input parameters in order to produce more robust and reliable results to better inform policy makers on cost-effectiveness of MCED screening for specific subsets of cancers.

In recognizing the limitations stated above, the present study developed a decision model closely based on current clinical practices to compare the potential health benefits and costs of implementing repeated screening with an MCED tool in Ontario, Canada from a provincial Ministry of Health perspective. The analysis therefore improves upon its predecessor by accounting for: the natural history of a selected group of cancers, repeated screening of asymptomatic persons, and more evidence-based input parameters. It applies modeling techniques to represent both the decision path

of repeated screening of the proposed strategy compared to standard of care, along with the natural history of the selected cancers in order to evaluate overall cost-effectiveness of the intervention.

The diagnostic characteristics of the CancerSEEK test formed the basis of the hypothetical MCED test that is used in this analysis, including its sensitivity and specificity. In this case, the average sensitivity levels for each type of cancer as published by the Cohen et al. study were used. Cohen et al. reported the average sensitivity of the MCED test over disease stages I to III for each type of cancer. However, it should be noted that sensitivity is likely to differ at each stage of disease, with lower levels at early-stage disease and higher levels at more advanced stages of disease.

CancerSEEK was designed to detect breast, colorectal, esophageal, liver, lung, ovarian, pancreatic and stomach cancers. According to the architects of the tool, these cancers were selected because they are associated with either high prevalence rates and/or high mortality rates in Western societies; and currently no blood-based test exists to detect them, especially at an early stage (Cohen et al., 2018). This is also the case in Canada where these types of cancers are either among the most diagnosed cancers or are associated with higher mortality rates (described earlier). Moreover, of these 8 types of cancers, organized screening programs using single-organ tests only exists for two- breast and colorectal- and MCED screening is still not available for any of the above cancers.

It should be mentioned that while there are several parallels between this current study and Tafazzoli et al. (2022) in terms of model structure and estimation techniques, unknown to both groups of researchers at the time of investigation, the two studies are different in study site (Ontario, Canada versus US population, respectively), and cancer test used (CancerSEEK versus GRAIL-Galleri). These similarities and differences are covered in more detail in the discussion section.

Strategies

The two screening strategies considered in this study are:

1. Strategy 1: Standard of care screening for the selected types of cancer in Ontario, Canada, and
2. Strategy 2: MCED screening (for esophageal, liver, lung, ovarian, pancreatic and stomach cancers) plus screening for breast and colorectal cancers as recommended under their respective organized screening programs in Ontario, Canada. These screening strategies are described in more detail below.

Strategy 1 represents standard of care, or the current status of screening programs as articulated by the Canadian Cancer Society for the respective cancers of concern in this study. For simplicity, the status of a screening program is described as either "*organized screening available",* where a population-based screening program exists at the provincial level, or "*no organized screening available",* where such a screening program does not exist. Accordingly, colorectal and breast cancers are included in the first group since organized screening programs are available for these types of cancers at the provincial level in Canada, where FIT and mammography are the respective recommended screening tools for these types of cancers. Meanwhile, in the latter group, which includes lung, ovarian, liver, stomach, pancreatic and esophageal cancer, organized screening programs do not currently exist, although opportunistic screening may be provided based on individual patient risks, as in the case of lung, stomach and ovarian cancers.

Strategy 2 is proposed as an alternative (to Strategy 1), where both MCED screening (for liver, lung, stomach, pancreatic, esophageal and ovarian cancers), and standard of care screening (for breast and colorectal cancers) are offered contemporaneously. This means that although the MCED test can detect both colorectal and breast cancer, this is not accounted for in the model as it is assumed that current organized screening programs will likely identify cases of these cancers, especially since the associated single-organ screening tests for these respective cancers outperform the MCED test with respect to reported levels of sensitivity. Under MCED screening, a hypothetical test based on the diagnostic characteristics of the CancerSEEK tool was adopted and is referred to as MCED-CancerSEEK henceforth.

CancerSEEK

CancerSEEK is a single multi-analyte blood test that detects multiple cancers at an early stage using assays that interrogate gene mutations and protein biomarkers (Cohen et al., 2018). It uses a polymerase chain reaction (PCR)-based assay with 61 amplicon panels and 8 proteins[8] to test for mutated driver genes (circulating tumor DNA- ctDNA) commonly found in many types of cancers, even at low levels. As such, the presence of either a genetic mutation and/or elevated levels of the selected proteins will trigger a positive test result, indicating the existence of a tumor. Specifically, the test can potentially detect a number of cancers, including the eight cancers investigated in the Cohen et al study, namely, breast, colorectal, esophageal, liver, lung, ovarian, pancreatic, and stomach. It also

[8] These proteins include cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), prolactin (PRL), hepatocyte growth factor (HGF), osteopontin (OPN), myeloperoxidase (MPO), and tissue inhibitor of metalloproteinases 1 (TIMP-1).

employs machine learning technology to predict the organ from which a tumor originates. It is estimated that the test will cost approximately $500 (Cohen et al., 2018).

The tool was developed as an initial screening option to direct those with positive tumor signals along the clinical path of diagnosis, treatment and surveillance. Based on an examination of 1,005 patients already diagnosed with at least stage I cancer, the CancerSEEK test demonstrated relatively high sensitivity and specificity, 70% and > 99%, respectively, and also identified the tissue of origin (TOO) or location of tumors with an accuracy of 63% (Cohen et al., 2018). Notwithstanding, the diagnostic performance of the test varies with respect to sensitivity and TOO prediction across the various types of cancers, and presumably across the different stages of disease for each type of cancer, but this was not officially reported in the Cohen et al, study. Table 6 below provides further details. The tool is most accurate at correctly identifying ovarian and liver cancers, with sensitivity levels of 98.1% and 97.7%, respectively, compared to breast and lung cancers, with sensitivity levels of 33.4% and 58.7%, respectively (Cohen et al., 2018).

Table 6 Diagnostic Performance of CancerSEEK

Cancer	Sensitivity	Specificity	TOO prediction
Ovary	98.1%	>99%	79%
Liver	97.7%	>99%	44%
Stomach	72%	>99%	46%
Pancreas	72%	>99%	81%
Esophagus	68.8%	>99%	46%
Colorectum	67%	>99%	84%
Lung	58.7%	>99%	39%
Breast	33.4%	>99%	63%

Source: Cohen et al. 2018

It is rationalised that strategy 2, which combines MCED screening together with existing organized screening programs, is feasible, as it is unlikely that MCED would replace existing screening tests like mammography and FIT which outperform MCED with respect to sensitivity and specificity. For example, the sensitivity of digital mammography is estimated to be between 70-90% while its specificity is 95-98% depending on breast density (Geisel & Philpotts, 2014; Jochelson, 2012; Lei et al., 2014; Salim et al., 2020). Likewise, the sensitivity and specificity of FIT are 85% and 94%, respectively (Levi et al., 2007; Yoshinaga et al., 1995) . Conversely, the sensitivity of CancerSEEK for breast and colorectal cancers is 33.4% and 67%, respectively. However, the overall specificity for CancerSEEK is over 99% (Cohen et al., 2018).

Cohort

A hypothetical cohort of 100,000 persons who are at average risk of developing each of the selected cancers that the proposed screening tool is expected to detect will be considered for the analysis. Drawing from Marcus et al., average risk is defined as "*those not known to be at substantially elevated risk, including those without known inherited predisposition, without comorbidities known to increase cancer risk, and without previous diagnosis of cancer or pre-cancer*" (Marcus et al., 2015). This group includes clinically asymptomatic individuals aged 50 - 75 years and overlaps substantially with the population that is eligible to participate in cancer screening programs that are currently available in Canada according to Cancer Care Ontario (Kalyta et al., 2021). Therefore, for the proposed model, screening is set to begin at age 50 years.

Model

To conduct the cost-utility analysis, a state-transition (Markov) model with an integrated decision tree was developed to represent both the screening decision and disease health states through which cohort members may transition. This model was implemented in TreeAge Pro (Healthcare Version 2022) and elements of this overall model are illustrated in Figures 1 to 3, which capture, in a general sense, the structure of the model and modelling techniques implemented in TreeAge Pro.

The flowchart in Figure 1 depicts the screening and detection paths of the selected cancers of this study. The initial decision facing members of the cohort is whether to undergo screening using Strategy 1 or Strategy 2 (as described earlier). Under Strategy 1, individuals may participate in organized screening programs for breast cancer (in the case of women) and colorectal cancer (for both men and women) since these are the only available provincial-wide organized screening programs for the selected types of cancers focused on in this study. For the remaining types of cancers, organized screening programs are not yet available and so these cancers are assumed to be symptom detected, although they can be detected through opportunistic screening which occurs infrequently, and so is not accounted for in this study. These cancers include ovarian, lung, stomach, pancreatic, esophageal, and liver cancer.

For persons who undergo screening, test results may either be positive or negative. A true positive test result, as measured by the test's sensitivity, indicates that the targeted cancer is detected while a false positive result gives rise to a screening odyssey, unnecessary patient anxiety, and over-diagnosis as the target cancer is not present. Conversely, in the case of a negative test result, the

outcome may be a true negative result, as measured by the test's specificity, in which the screened cancer is not present. Meanwhile, a false negative test result suggests that the screening tool failed to detect one of the underlying cancers that may be present.

Under Strategy 2, individuals may either test positive or negative for one of the eight cancers of concern using the MCED test (for ovarian, lung, stomach, pancreatic, esophageal, and liver cancers), and FIT and mammography for colorectal and breast cancer, respectively, under their respective organized screening programs. The screening outcomes under this strategy are the same as those described in Strategy 1 with respect to true positive, true negative, false positive and false negative results.

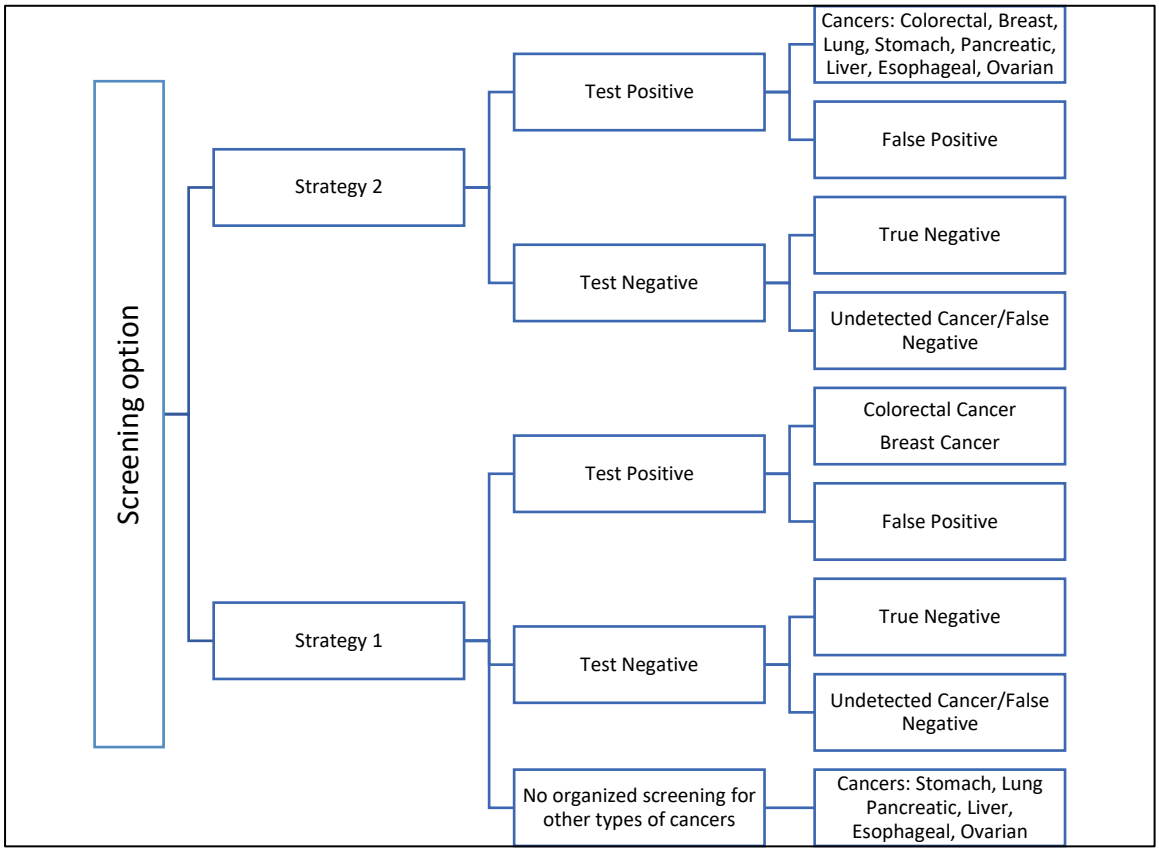


Figure 1 Initial screening decision, results and outcomes

Figure 2 builds on Figure 1 by presenting in more detail, the initial screening decisions and subsequent outcomes based on screening (and non-screening) results. In this diagram, the eight selected cancers are subdivided into their respective categories as described earlier: those for which organized screening programs are currently available, and those for which organized screening programs do not exist. This diagram also illustrates that individuals who received false negative results, or those who were correctly identified as having none of the selected cancers, will be eligible for repeated rounds of screening in the following screening cycle either with the MCED-CancerSEEK test or through available organized screening programs based on prescribed screening intervals so long as cancer is not detected up until the end age for screening. Furthermore, those with a false negative result may be symptom detected in a subsequent cycle.

Meanwhile, those with a positive test result from screening for one of the selected cancers (whether a true positive or false positive) will follow up with a standard cancer-specific diagnostic test to confirm the initial result. It is assumed that a false positive result from screening will likely be later disconfirmed by a diagnostic test and such persons may present for another round of screening in a subsequent period.

Additionally, in strategy 1, the five types of cancers for which organized screening programs are not yet available are assumed to be symptom detected. Symptom detection occurs when the onset of symptoms triggers diagnostic testing, and there is a higher probability of this in later than earlier stages of cancer.

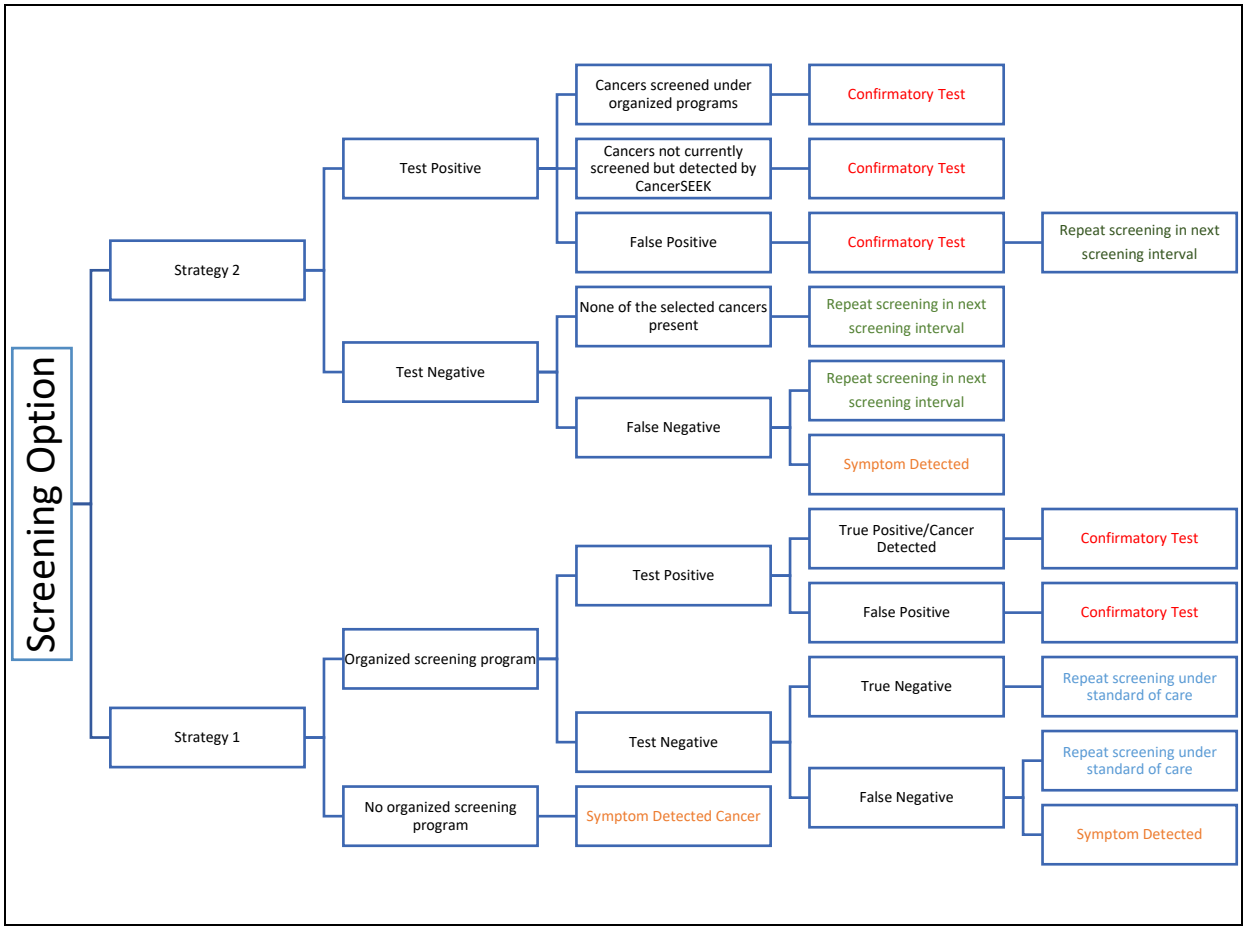


Figure 2 Initial screening decision, results and subsequent clinical follow-up

To represent the progression of disease, the state-transition diagram in Figure 3 depicts, in a stylized manner, the flow of the natural history of the selected cancers. The simplified health states through which individuals can transition over 1-year cycles include healthy, early-stage cancer (preclinical and clinical), late-stage cancer (preclinical and clinical), (defined below) and death either from one of the selected types of cancers or other causes. Death from other causes includes deaths from other types of cancers not (likely) detected by the MCED test. The preclinical health states represent disease states that have not been previously diagnosed while clinical health states represent disease states have been officially diagnosed.

For each annual cycle, healthy persons may either remain healthy or transition to early-stage cancer or die from other causes. Those with early-stage cancer may either remain in this state as preclinical early-stage cancer if disease is not symptom detected or identified through screening, or be diagnosed as clinical early-stage cancer and treated after screening, or transition to preclinical late-stage cancer, or die from other causes in a subsequent cycle. Those with preclinical late-stage cancer will eventually

be diagnosed and treated accordingly, with screening and/or without screening through symptom detection, while others will die from their disease or from other causes.

Ongoing surveillance is reserved for those who received treatment and are being monitored. Under surveillance, patients receive treatment and are routinely monitored for 5 years to determine the progression of their health and this may involve repeated testing for signs of cancer remission or recurrence as prescribed by North American cancer societies (American Cancer Society, n.d.; National Cancer Institute, n.d.-b). The model further assumes that persons who do not experience cancer relapse after 5 years will return to the healthy health state while those who experience relapse will again travers through the state transition model depending on the stage at which the cancer is detected.

Figure 3 also captures repeated screening of both healthy individuals and asymptomatic, undiagnosed patients whether at early stage or late stage of disease. The accuracy of the screening result will determine the paths through which individuals may traverse within the state-transition diagram. These paths were described above and relate to whether persons pursue follow-up confirmatory tests and eventual treatment or return for screening at periodic intervals or are symptom detected in a subsequent cycle.

The natural history of each type of cancer is represented by two stages of disease, namely early-stage and late-stage. This representation is based on two staging systems commonly adopted in the oncology community: the number staging system and the category staging system. The number staging system is typically used by medical practitioners, and identifies 5 stages of cancer development, numbered from 0 to 4. These stages include:

1. Stage 0. In this stage, abnormal cells, which are in situ, are precancerous and can be treated with a high rate of success.

2. Stage 1. In this stage, cancer has developed but is small and remains localized to the tissue of origin.

3. Stage 2. The cancer has grown further but has not spread to nearby tissues or lymph nodes.

4. Stage 3. The cancer tumor is larger and has possibly spread to surrounding tissues and or the lymph nodes.

5. Stage 4. Metastasis has occurred where the cancer has spread to other organs and/or other parts of the body (National Cancer Institute, n.d.-a; National Health Services, n.d.).

Meanwhile, the category staging system, commonly known as the Surveillance, Epidemiology, and End-Results (SEER) General Summary Staging System, is predominantly used by cancer registries, and like the number staging system, identifies 5 stages of cancer development, namely;

1. In situ
2. Localized, where the cancer has not spread and remains where it originated.
3. Regional, where the cancer has spread to nearby lymph nodes, tissues, or organs.
4. Distant, where the cancer has spread to other parts of the body.
5. Unknown, where there is insufficient information to determine the stage of disease (National Cancer Institute, n.d.-a; National Health Services, n.d.).

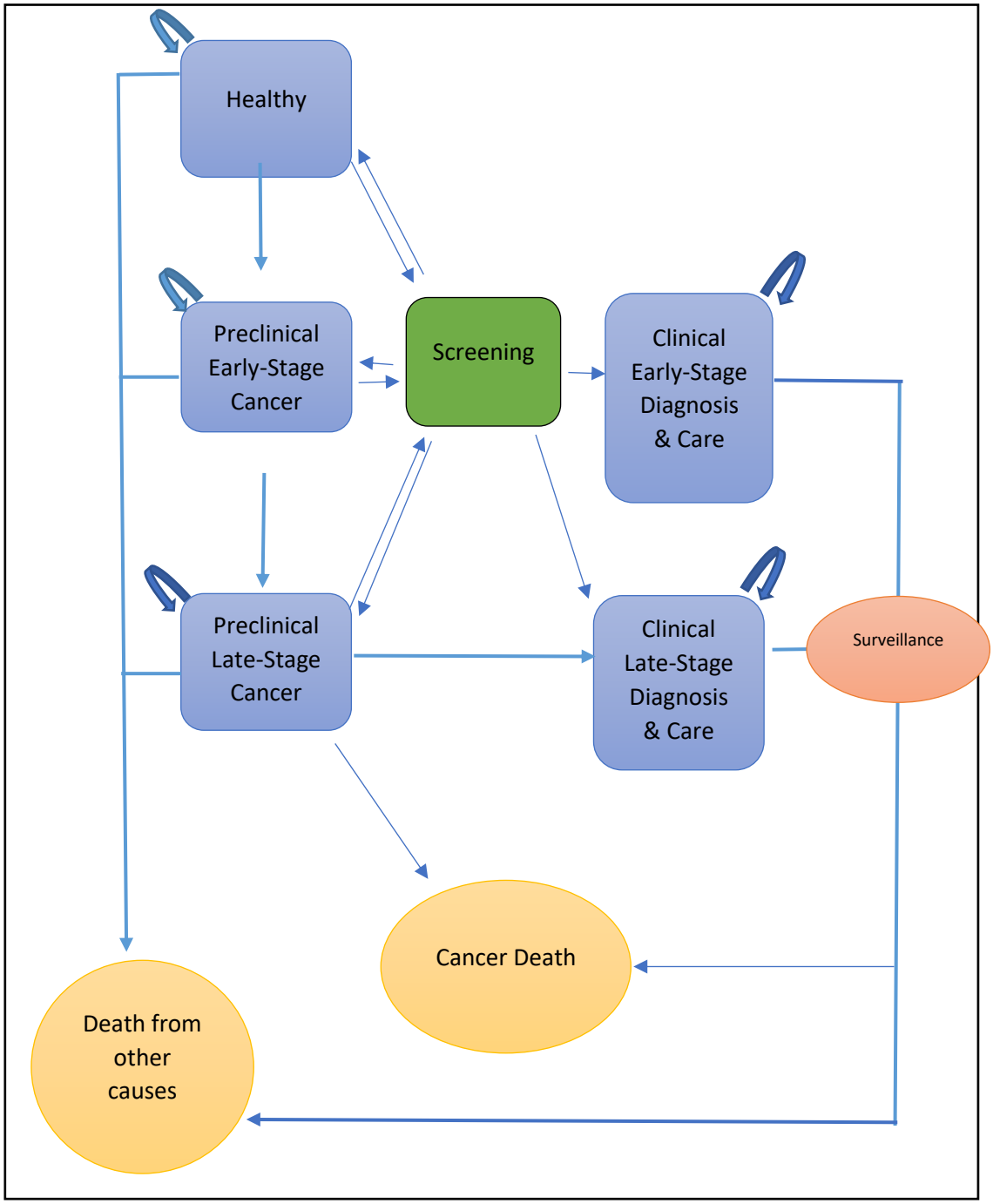


Figure 3 Markov model of natural history of selected cancers

Based on the aforementioned staging systems, this study describes early-stage cancer as the state of disease before regional spread and metastasis occurs while late-stage is described as the disease state once regional spread or metastasis occur. Early-stage cancer will therefore include precancerous legions and localized cancer while late-stage cancer will include both regional and distant cancer stages. These assumptions were made to accommodate the simplified structure of the proposed

model and to derive suitable parameter estimates to populate the said model, although in some cases, as described later, these assumptions were further adjusted to calculate more reasonably accurate parameter values.

The model also assumes that all cohort members enter the state-transition Markov model at one of the independent health states based on the population probability of that health state and then move to other health states based on transition probabilities. The respective screening strategies are superimposed onto the natural history of the various types of cancers to assess cost-utility for the target group, which is assumed to be a closed block group ensuring that no new participant enters and no existing member leaves except through death. A time-horizon of 25 years was modelled where screening begins at age 50 years and continues periodically until cancer is detected, or a person reaches the screening end age of 75 years, or death occurs, whichever occurs first. In terms of the screening interval, the model assumes that colorectal and breast cancers are screening biennially in keeping with Canadian Cancer Society recommendations, while MCED screening is set to occur annually because of the ease with which the test can be administered. Overall, it is expected that organized screening, whether using CancerSEEK or standard of care, will alter the clinical stage distribution of disease where more cancers are detected at an earlier stage than at a more advanced stage. See Appendix C for excerpts of the implemented model in Treeage Pro. This is provided for the colorectal arm of the model under the MCED intervention.

Further model assumptions

It is important to reiterate that Figures 1 to 3 represent, in part, the more detailed Markov model developed in Treeage Pro, and they are presented here as individual illustrations to demonstrate and simplify the different complex conceptual elements of the proposed model. It should also be noted that because of this simplified approach, other key model parameters are not included in the presentations above but were incorporated in the final model. One such parameter is screening participation/uptake/compliance. While accounting for screening participation is pivotal in determining the cost-effectiveness of screening as well as the number of potential deaths that can be avoided, it is well documented that participation rates within Canada are well below the level needed for these benefits to be maximized (Brouwers et al., 2011; D'Andrea et al., 2019). However, this current study employs the minimum rate of 75% of the eligible populations for both standard of care

screening and MCED screening, which is just above the lower limit of 70% recommended for screening benefits to be achieved (Brouwers et al., 2011; Siu & U.S. Preventive Services Task Force, 2016).[9]

It is also reasonable to expect that women will be screened for colorectal and breast cancer in standard care while men will be screened for only colorectal cancer, based on current screening guidelines recommended in Ontario, Canada. Standard care also includes screening for women with cervical cancer, but it is not included here, because standard care is expected to be more sensitive than a MCED test. Furthermore, the incidence rates of the cancers of concern in this study differ for men and women, and, as such, separate cost-effectiveness analyses were conducted for both sexes. Even further, while breast cancer can also occur in men, it does so at rates very much lower than for women, and is not considered in this model. Only a few men are currently covered by the organized breast cancer screening program.

Another caveat relates to lung cancer where a pilot program is currently available for screening at-risk persons in Ontario according to the CTFPHC recommendation described earlier. Based on this screening recommendation, which has strict inclusion criteria based on age and smoking history, it is likely that a potential organized screening program for lung cancer would only target above-average risk populations. Furthermore, since the present study focuses on an average-risk group that is not currently eligible for screening under the present CTFPHC guidelines, it is envisioned that MCED screening for lung cancer will then target this broader population. Even further, this study does not model the possibility of opportunistic screening for various cancers (e.g. ovarian cancer based on family history and genetic predisposition), which is an additional simplifying assumption.

For the analysis, it was also assumed that an individual can only present with at most one of the selected cancers at any one screening interval, and as such, cases of a second primary cancer occurring concurrently are not considered. This assumption limits the complexity of the proposed model.

The dwell time of each type of cancer at each stage of disease was not explicitly modelled in this study. Accounting for this variable would have notably added to the model's complexity and so it is assumed that the dwell time of diagnosed cases of cancer are essentially established by the annual transition probabilities of each type of cancer as health states transition from healthy to early-stage to late-stage disease. Adopting such a simplifying assumption is pragmatic since the natural history of some of the selected cancers are still unknown.

[9] It should be noted that the eligible population for lung cancer screening, currently, is much smaller than the eligible population expected to benefit from MCED screening.

Input data

Input parameters were sourced from the literature and the Surveillance, Epidemiology, and End Results (SEER) national US cancer database and supplemented by expert opinion where necessary. Specific input parameters include the characteristics of the screening and diagnostic tests (their sensitivity and specificity), the natural history of the eight cancers, point prevalence of each health state and the selected types of cancers, sex-specific incidence rates, transition probabilities between health states, mortality rates, screening participation rates, cost-related indicators and utilities associated with the different stages of disease. These datasets along with any relevant literature were sourced through SCOPUS, PubMed, Google Scholar and clinical databases. Articles published within the period 2010-2022 were prioritized. Table 7 provides a list of input parameters used in the state-transition model along with their associated references. The 95% confidence intervals (and ±25% spread where the 95% confidence interval was not available) for these input parameters are presented in Appendix D-F. A more detailed discussion on some of the more key input parameters is provided below.

Table 7 List of parameter estimates and references

					Source
Incidence rate (per 100,000), Female, Age 50 -74 years					
Cancer type	Localized	Regional	Distant		
Breast	506.8	167.8	38.6		SEER
Colorectal	60.4	56.7	35.2		SEER
Esophageal	2.5	3.3	3.7		SEER
Liver	13.7	7.7	7.6		SEER
Lung	88.9	62.7	122.4		SEER
Ovarian	9.3	9.6	28.8		SEER
Pancreatic	10.4	20	31.7		SEER
Stomach	9.9	5.6	8.5		SEER
Incidence rate (per 100,000), Male, Age 50 -74 years					
Cancer type	Localized	Regional	Distant		
Colorectal	85.2	80.5	51.7		SEER
Esophageal	9.4	15.3	17.9		SEER
Liver	39.4	27.8	18.5		SEER
Lung	83.3	73.5	161.5		SEER
Ovarian	0	0	0		SEER
Pancreatic	13.1	24.5	44.7		SEER
Stomach	15	13.4	18		SEER
Prevalence of cancer among persons 50-74 years (%)					

	Total Male	Total Female			
Cancer type					
Breast	-	11.572			SEER
Colorectal	2.571	2.122			SEER
Esophageal	0.146	0.037			SEER
Liver	0.252	0.091			SEER
Lung	1.001	1.045			SEER
Ovarian	0	0.657			SEER
Pancreatic	0.167	0.131			SEER
Stomach	0.261	0.165			SEER
Cancer Detection by Stage					
	Early Stage	Late Stage			
Cancer type					
Breast	0.94	0.06			CancerNet
Colorectal	0.25	0.75			Telford et al. 2010
Esophageal	0.4471	0.5529			CancerNet
Liver	0.43	0.57			CancerNet
Lung	0.25	0.75			Goffin et al.
Ovarian	0.16	0.84			CancerNet
Pancreatic	0.13	0.87			CancerNet
Stomach	0.38	0.62			CancerNet
Probability of cancer recurrence (%)					
Cancer type	Early Stage	Late Stage			
Breast	0.09	0.92			Cancer Treatment Centers of America & Eldridge 2022
Colorectal	0.05	0.35			Health Match
Esophageal	0.18	0.48			Pape et al. 2021
Liver	0.12	0.12			Kim et al. 2020
Lung	0.3	0.7			Eldridge 2022
Ovarian	0.2	0.825			Ovarian Cancer Research Alliance
Pancreatic	0.38	0.46			Fischer et al. 2012
Stomach	0.426	0.338			Jiao et al. 2020
Cancer mortality					
Cancer Site	**Gender**	**1-Year Early Stage**	**1-Year Late Stage**		
Breast	Female	0.005	0.085		NHS Digital 2022 & author's calculation
	Male	0.058	0.542		NHS Digital 2022 & author's calculation
Colorectal	Female	0.038	0.355		Author's calculation
Liver	Male	0.359	0.816		NHS Digital 2022 & author's calculation

	Female	0.402	0.804		NHS Digital 2022 & author's calculation
	Male	0.296	0.814		NHS Digital 2022 & author's calculation
Lung	Female	0.251	0.761		NHS Digital 2022 & author's calculation
	Male	0.54	0.751		NHS Digital 2022 & author's calculation
Esophagus	Female	0.54	0.763		NHS Digital 2022 & author's calculation
Ovary	Female	0.125	0.447		NHS Digital 2022 & author's calculation
	Male	0.226	0.763		NHS Digital 2022 & author's calculation
Stomach	Female	0.239	0.775		NHS Digital 2022 & author's calculation
	Male	0.58	0.915		SEER & author's calculation
Pancreas	Female	0.58	0.915		SEER & author's calculation
Screening tests					
	Sensitivity	Specificity			
MCED					
Breast	0.334	0.9914			Cohen et al. 2018
Colorectal	0.67	"			Cohen et al. 2018
Esophageal	0.688	"			Cohen et al. 2018
Liver	0.977	"			Cohen et al. 2018
Lung	0.587	"			Cohen et al. 2018
Ovarian	0.981	"			Cohen et al. 2018
Pancreatic	0.72	"			Cohen et al. 2018
Stomach	0.72	"			Cohen et al. 2018
Breast - Digital Mammography	0.76	0.96			Song et al. 2019
Colorectal - Fecal Immunochemical Test	0.85	0.94			Telford et al. 2010
Diagnostic test					
Breast-Diagnostic Mammography	0.878	0.905			Breast Cancer Surveillance Consortium
Colorectal-Colonoscopy	0.93	1			Telford et al. 2010
Esophageal-Upper GI + Endoscopic biopsy	0.909	1			Bloomfeld et al. 2005 & Nagai et al. 2014
Liver-CT scan	0.775	0.913			Nadarevic et al. 2021
Lung-CT scan + biopsy	0.9007	1			Baratella et al. 2022
Ovarian-Transvaginal ultrasound + biopsy	0.894	0.998			Menon et al. 2009
Pancreatic -CT scan + biopsy	0.95	0.92			Dabizzi et al. 2011
Stomach- Upper GI + biopsy	0.86	0.93			Jiang et al. 2021

Screening uptake	0.75				Coverage parameter
Participation in diagnostic testing	0.84				Telford et al. 2010
Medical cost (Female) (CAD)	Diagnostic	Initial Treatment	Annual Surveillance	Terminal Phase	
Breast	1,581	15,885	8,763	24,171	de Oliveira et al 2016 & author's calculation
Colorectal	705	32,195	6,954	40,456	de Oliveira et al 2016 & author's calculation
Esophageal	287	55,455	8,767	67,246	de Oliveira et al 2016 & author's calculation
Liver	3,761	25,130	10,093	36,205	de Oliveira et al 2016 & author's calculation
Lung	2,661	28,058	8,126	46,363	de Oliveira et al 2016 & author's calculation
Ovarian	1,937	29,292	5,330	45,071	de Oliveira et al 2016 & author's calculation
Pancreatic	2,231	41,539	11,354	69,316	de Oliveira et al 2016 & author's calculation
Stomach	885	38,922	3,458	68,316	de Oliveira et al 2016 & author's calculation
Medical cost (Male) (CAD)	Diagnostic	Initial Treatment	Annual Surveillance	Terminal Phase	
Colorectal	358	32,679	7,080	42,130	de Oliveira et al 2016 & author's calculation
Esophageal	1,063	54,037	7,528	70,660	de Oliveira et al 2016 & author's calculation
Liver	4,395	27,762	15,540	39,345	de Oliveira et al 2016 & author's calculation
Lung	2,383	29,132	6,933	51,013	de Oliveira et al 2016 & author's calculation
Pancreatic	2,460	38,973	8,185	70,398	de Oliveira et al 2016 & author's calculation
Stomach	1,102	41,912	4,328	69,820	de Oliveira et al 2016 & author's calculation
Costs associated with preclinical cancer deaths (CAD)					
Breast	3,338				de Oliveira et al 2013 & author's calculation
Colorectal	3,712				de Oliveira et al 2013 & author's calculation
Esophageal	2,844				de Oliveira et al 2013 & author's calculation
Liver	4,945				de Oliveira et al 2013 & author's calculation
Lung	3,822				de Oliveira et al 2013 & author's calculation
Ovarian	3,817				de Oliveira et al 2013 & author's calculation
Pancreatic	4,208				de Oliveira et al 2013 & author's calculation
Stomach	3,515				de Oliveira et al 2013 & author's calculation

Cost of Screening (CAD)					
MCED	874				Cohen et al. 2018 & author's calculation[1]
FIT	38.27				Goede et al. 2017 & author's calculation[2]
Mammography	314.70				Author's calculation[3]
Utility					
	Early stage	Late stage			
Breast	0.845	0.4			Pourrahmat et al. 2021
Colorectal	0.745	0.3			Pourrahmat et al. 2021
Esophageal	0.815	0.405			Pourrahmat et al. 2021
Liver	0.772	0.404			Author's estimation
Lung	0.835	0.465			Pourrahmat et al. 2021
Ovarian	0.62	0.45			Havrilesky et al. 2009
Pancreatic	0.772	0.404			Author's estimation
Stomach	0.773	0.404			Lee et al. 2018
Surveillance	0.8	0.5			Assumption
Utility decrement	-0.1				Telford et al. 2010

[1]Cohen et al estimated the cost of the MCED test be US$500. The estimate provided in the table above is adjusted for medical inflation and the exchange rate. [2] The cost of FIT was estimated to be $31.11 CAD (2013 prices) by Goede et al. 2017. The estimate used in this analysis was adjusted to 2022 prices by accounting for medical inflation. [3] This is the approximate equivalent to a two-breast mammography test in the US.
N.B. See Appendix 4-6 for the 95% confidence interval and ±25% spread where appropriate for selected parameters in the table above.

Prevalence and incidence

Data on the prevalence of each type of cancer (disaggregated by sex) were collected from the SEER database. These data values were multiplied by the stage-specific detection rates associated with each type of cancer to estimate the prevalence of preclinical early-stage and late-stage disease for each type of cancer. The stage-specific detection rates were derived from Kayla et al., 2021 for colorectal cancer, Goffin et al., 2015 for lung cancer and the American Society of Clinical Oncology (ASCO) patient information website Cancer.Net for all other selected types of cancers. Cancer.Net is a peer-reviewed website designed to disseminate up-to-date cancer-related information to patients and families. Goffin et al, meanwhile, is a Canadian-based study that examined the cost-effectiveness of using LDCT scanning to screen for lung cancer from a publicly funded healthcare system perspective, while Kayla et al, reviewed colorectal cancer screening guidelines in Canada and compared them to best practices in jurisdictions with similar epidemiological profiles.

The formula below illustrates how the prevalence rates of preclinical early-stage and late-stage disease for each type of cancer were calculated.

$$P_{PC_{Sij}} = P_{ij} \times \beta_{si}$$

P_{PC} - prevalence of preclinical cancer

P - prevalence of cancer

i - type of cancer, where *i* = 1, 2, 3…8. 1 = breast cancer, 2 = colorectal cancer, 3 = esophageal cancer, 4 = liver cancer, 5 = lung cancer, 6 = ovarian cancer, 7 = pancreatic cancer, and 8 = stomach cancer

j - sex where j = 0 for males and 1 for females

s - stage of detection where s = 0 for early stage and 1 for late stage

β - proportion of a particular cancer detected at a given stage

Transition probabilities

Transition probabilities were estimated by converting age-specific incidence rates for each type of cancer at each stage of disease into annual probabilities using the *ratetoprob* function in Treeage Pro. This is a function which transforms annual incidence rates into annual probabilities. The age-specific incidence rates for each type of cancer for each stage of disease were also obtained from SEER, where cancer stages are defined as local, regional and distant. This study made the assumption that the probability of transitioning from a state of full health to early-stage disease is consistent with the incidence of localized cancer. In a similar vein, it is assumed the that the transition from early-stage disease to late-stage disease is consistent with the incidence of regional and/or distant cancer.

Mortality

Data on cancer-related deaths were sourced from the NHS Digital 2022 report titled *Cancer Survival in England.* This report provided estimates of survival rates of diagnosed cancers in England between 2015 and 2019 (NHS Digital, 2022). Among other indicators, one-year survival rates of various types of cancers at each stage of disease are presented in this report. This indicator was used to estimate one-year-stage-specific death rates for each type of cancer by subtracting the survival rate from 100-percent. One-year-stage specific death rates are chosen because the present model operates on annual cycles. Further, to reflect the cancer-stage description adopted in this study and to derive estimates consistent with SEER and Canadian Cancer Statistics Advisory Committee, disease stages 1

to 3 were grouped (using a simple average) and defined as early-stage disease while disease stage 4 was defined as late-stage disease.[10]

The formula below explains how the cancer-related death rates were calculated.

$$D_{is} = 100 - SR_{is}$$

D = one-year death rate

i = type of cancer, where *i* = 1, 2, 3…8. 1 = breast cancer, 2 = colorectal cancer, 3 = esophageal cancer, 4 = liver cancer, 5 = lung cancer, 6 = ovarian cancer, 7 = pancreatic cancer[11], and 8 = stomach cancer

s = stage of cancer detection where s = 0 for early stage and 1 for late stage

SR = one-year survival rate

The probability of death from other causes was derived from Statistics Canada life tables for the year 2020. Again, death from other causes may include death from other types of cancers not likely to be detected by the modeled screening tool.

Relapse

Relapse rates were obtained from available literature and databases. Table 7 provides the reference for these rates for each type of cancer at each stage.

Screening participation rate

This study employed a reasonable screening participation rate of 75% of the eligible populations for both standard of care screening and MCED screening. This minimum participation rate is informed by the recommendations of the USPSTF and Cancer Care Ontario for breast and colorectal cancer, respectively. The USPSTF explained that screening compliance rates more than 65%-70% *would be required for any stool or blood-based screening modality to match the benefits of colonoscopy* (Siu &

[10] With this approach, it was believed that the mortality rates for esophageal cancer were underestimated, especially for early-disease, so this estimate was recalibrated to better reflect the 5-year survival/death rates reported by the Canadian Cancer Statistics Advisory Committee. A similar process was conducted for colorectal cancer among females. Additionally, for estimates for breast cancer, grouping stages 1 and 2 represent early-stage disease and using an estimate 0.085 for late-stage disease derived from a calibration process yielded more reliable results for the validation procedure.

[11] NHS Digital did not estimate the stage-specific 1-year survival rates for pancreatic cancer, so this study relied on a calibration process to estimate the death rate of early-stage and late-stage pancreatic cancer that would generate an associated 5-year mortality rate similar to the one reported by the Canadian Cancer Society.

U.S. Preventive Services Task Force, 2016). Likewise, Cancer Care Ontario proposed a minimum screening rate of 70% for mammography for the benefits of screening, including cost-effectiveness and a reduction in associated mortality, to be achieved (Brouwers et al., 2011). Evidence, however, has revealed that actual screening rates are well below the recommended levels. Notwithstanding, proposing a screening rate of 75% provides a reasonable parameter within which cost-effectiveness can be achieved, and this is varied subsequently in the sensitivity analysis.

Relatedly, the model assumes that 84% of those with a positive test result from screening would comply with follow-up testing to establish diagnosis. This estimate was adopted also by Telford et al. (2010) in a cost-effectiveness study of colorectal cancer screening in Canada.

Sensitivity and specificity

The diagnostic performance of screening and confirmatory tests, in terms of their sensitivity and specificity, was also sourced from available literature. Table 7 provides a list of the references for the sensitivity and specificity of each screening and diagnostic tool.

At present, of the cancers of concern in this study, screening under organized screening programs is only available for breast and colorectal cancer, with digital mammography and fecal immunochemical test (FIT) as the respective screening tests. The sensitivity and specificity for screening digital mammography (76% and 96%, respectively) was derived from Song et al. (2019), which is a systematic review and meta-analysis consisting of 13 studies comparing digital and screen-film mammography (SFM) for breast cancer screening. The authors noted that digital mammography outperformed its SFM predecessor in screening women over the age of 50 years. Meanwhile, with respect to FIT, the estimates of sensitivity and specificity (85% and 94%, respectively) were obtained from the Telford et al. 2010 study, which estimated the cost-effectiveness of 10 colorectal screening strategies, including FIT, from a Canadian third-party payer perspective (Telford et al., 2010).

The diagnostic performance of the proposed MCED screening tool was based on the results of the Cohen et al. (2018) study. This was a retrospective study designed to assess the diagnostic ability of the CancerSEEK test on 1,005 patients with eight specific types of previously diagnosed cancers: breast, colorectal, esophageal, liver, lungs, ovarian, pancreatic and stomach. The sensitivity and specificity of this test were 70% (median) and >99%, respectively. Further details concerning the CancerSEEK, including the sensitivity associated with detecting specific cancers were discussed in an earlier section.

Following a positive result from an initial cancer screening or physician referral based on the presentation of particular symptoms, patients are directed to establish a diagnosis from a battery of follow-up tests. The most common tests used to diagnose the cancers of concern in this study are presented in Table 8 below. Using the Canadian Cancer Society and the American Cancer Society as references, these tests were identified as the most likely procedures patients may undergo in the clinical path following a positive result from screening, although additional tests may be conducted depending on specific circumstances.

Table 8 Common baseline diagnosis test for selected types of cancers

Cancer Type	Baseline Diagnostic Procedures
Breast	• Diagnostic Mammography • Core needle biopsy (CNB)
Colorectal	• Diagnostic Colonoscopy • Endoscopic biopsy (removes polyps and small tissue), or • Core biopsy to sample tumors
Esophageal	• Upper GI series (Barium swallow test) • Upper GI Endoscopy + Endoscopic Ultrasound • Endoscopic biopsy
Liver	• Ultrasound (first step) • CT scan. No need for biopsy if cancer is found from the scan. • If result from scan is inclusive, core needle biopsy is used.
Lung	• CT scan + CT guided needle biopsy (Fine Needle Aspiration)
Ovarian	• Trans-vaginal ultrasound • Biopsy is done after tumor is removed during laparotomy – large incision to access the abdomen.
Pancreatic	• CT scan: Multiphase CT scan or Pancreatic Protocol CT scan • Endoscopic Ultrasound (new) to guide needle biopsy (FNA)
Stomach	• Upper GI endoscopy (esophagogastroduodenoscopy/gastroscopy) + endoscopic biopsy • Endoscopic ultrasound (EUS) -done during an Upper GI endoscopy + EUS-guided needle biopsy

Source: Canadian Cancer Society and American Cancer Society

The literature was then consulted to obtain sensitivity and specificity of the diagnostic tests identified above in Table 8. Generally, data on the sensitivity and specificity of each diagnostic work-up were taken from retrospective studies, systematic reviews, randomised controlled trials and other databases. For example, sensitivity and specificity of CT-guided core-needle biopsy used to diagnose

lung cancer was derived from the Baratella et al study, which is a retrospective study that assessed 350 thoracic biopsies (Baratella et al., 2022). Likewise, Bloomfeld et al. provided data on the diagnostic accuracy of upper endoscopy to detect esophageal cancer in over 100 patients who were previously diagnosed (Bloomfeld et al., 2005).

Meanwhile, values of sensitivity and specificity for diagnostic work-up were obtained from research reviews of cancers of the stomach, pancreas and liver. Specifically, a systematic & meta-analysis for early gastric cancer diagnosis was used as the main data source to account for the diagnostic accuracy of endoscopy in diagnosing stomach cancer. This study demonstrated that diagnoses are more accurate when artificial intelligence (AI) technology is used alongside endoscopic procedures (Jiang et al., 2021). Meanwhile, the systematic review by Nadarevic et al. was the main source for data on the diagnostic accuracy of CT scans for diagnosing adult liver cancer, especially among those with chronic liver disease (Nadarevic et al., 2021). While for pancreatic cancer, a review of diagnostic management practices for patients authored by Dabizzi et al. proved to be informative (Dabizzi et al., 2011).

In the case of ovarian cancer, results from the randomised controlled trial, United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), proved useful in estimating the sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer. The main goal of this trial was to evaluate the impact of screening regimens on related mortality (Menon et al., 2017).

For breast cancers, estimates were collected from the Breast Cancer Surveillance Consortium – which is a network of breast cancer registries tasked with the responsibility to improve breast cancer screening and associated health outcomes throughout the United States (Breast Cancer Surveillance Consortium, n.d.). Meanwhile, in the case of colorectal cancer, estimates were derived from the Telford et al. 2010 study, which was described earlier.

Cost

Given the Ontario provincial Ministry of Health perspective, only direct medical costs were incorporated into the analysis. Estimates of these costs were drawn from the available literature and expressed in 2022 Canadian dollars using the health and personal care consumer price index for Canada published by Statistics Canada. Any costs recorded in US-dollars were converted to Canadian dollars using an appropriate exchanges rate (purchasing power parity).

Components of costs considered in this present study were those associated with screening, diagnosis and treatment, as well as the cost included in facility and professional fees and care at different stages

of diseases. Specifically, clinical costs were derived from the de Oliveira et al. 2016 and 2013 studies. These are phase-based, descriptive costing studies that estimated the mean net direct medical costs throughout the pre- and post-diagnosis phases of cancer care for patients 18 years and older for 21 common types of cancers in Ontario between 1997 and 2007 from a provincial government perspective. These authors defined the pre-diagnosis phase as the 3-month period where tests are conducted to determine cancer diagnosis. The post-diagnosis phase, meanwhile, was subdivided into three categories by de Oliveira et al. (2016), namely: 1) the initial phases, which accounts for the first 6 months of care from the date of diagnosis where frontline therapy and adjuvant therapy are administer; 2) continuing phase, which captures annual surveillance and any treatment for recurring cancer or new primary cancers; and 3) the terminal phase which represents the care services offered during the 12 months preceding a cancer-related death (de Oliveira et al., 2016). In adopting a similar approach to describe the clinical path of cancer, this current study assumes the following clinical phases: a diagnosis phase, initial treatment, surveillance and a terminal phase. It is assumed that expenses incurred in the diagnosis phase include all the costs associated with the diagnostic procedures presented in Table 8. Overall, it is believed that the value of this phase-based approach to costing lies in its ability, in part, to account for the natural history of the different types of cancer, reflect the various phases of treatment, and facilitate the estimation of cost over time (de Oliveira et al., 2016).

Meanwhile, the de Oliveira et al. (2013) study estimated medical costs associated with "pre- and post-diagnosis periods for patients who died within 1 year after diagnosis and patients who survived beyond 1 year after diagnosis" (de Oliveira et al, 2013). This study defined the pre-diagnosis phase as the 3-month period before an official diagnosis is determined. The cost associated with this pre-diagnosis period for patients who died within 1 year was used to estimate the medical cost incurred by those who have either early or late-stage preclinical cancer in the current study who also died without receiving an official diagnosis but may have sought clinical intervention.

It is assumed (following Cohen et al. (2018) that the cost of the MCED-CancerSEEK test kit will be US$500. This was later adjusted using an appropriate inflation rate and exchange rate.

Utilities

Utility was measured using quality-adjusted life years (QALYs). This measure ranges from zero which represents death, to one, which represents perfect health or at least asymptomatic patients or patients without cancer (S. C. Shah et al., 2020). In the case of cancer, health utility is linked to the

stage of disease, disease progression and the site of the tumor, where more ill-health is experienced during late-stage disease (Pourrahmat et al., 2021). Additional morbidity may arise with intensive immunotherapy treatment options where patient health may at least be temporarily compromised.

Generally, utility values for each Markov health state were obtained from the literature (sources are cited in Table 8). Also based on the literature, decrements or disutilities were assigned to cases of cancer relapse.

Utility values for four of the eight cancers of concern were sourced from Pourrahmat et al., 2021 - a systematic literature review which summarized reported stage-specific health state utility values (HSUV) for selected cancers, including breast, colorectal esophageal and lung. Pourrahmat et al provided a mean range of HSUVs for each disease stage (specifically stages 1 to 4) for the respective cancers. In adopting these health utility values into the current study, the average of the upper-limit health utility values for stages 1 and 2 was calculated to represent health utility of early-stage disease, while the average of the lower-limit health values for stages 3 and 4 was calculated to reflect health utility of late-stage disease. The formulae below illustrate further how these estimates were derived.

$$HSUV_{iE} = (HSUV_{i1} + HSUV_{i2})/2$$

$$HSUV_{iL} = (HSUV_{i3} + HSUV_{i4})/2$$

$HSUV$ = health state utility value

i = type of cancer, where *i* = 1, 2, 3…8. 1 = breast cancer, 2 = colorectal cancer, 3 = esophageal cancer, 4 = liver cancer, 5 = lung cancer, 6 = ovarian cancer, 7 = pancreatic cancer, and 8 = stomach cancer

E = early-stage cancer which combines stages 1 and 2 disease states

L = late-stage cancer which combines stages 3 and 4 disease states

For ovarian cancer, health utilities were taken from the Havrilesky et al 2009 study. This study estimated the quality of life-related utilities along the clinical path of ovarian cancer screening, diagnosis and treatment in a case-control setting by interviewing participants about their utility preference with respect ovarian cancer using two methods of valuing health states: the visual analog score method and time trade-off method (Havrilesky et al., 2009). Estimates from the former method were used in this current study as they were more intuitive and easier to incorporate in the proposed state-transition model in this study since health was measured on a scale 0 to 100, where 100 represents perfect health and 0 represents death. The specific indicators selected from Havrilesky et

al. to represent utilities at early and late-stage disease were early ovarian cancer- newly diagnosed, and advanced ovarian cancer – newly diagnosed.

In the case of stomach cancer, estimates of utilities were obtained from Lee et al. (2018). The objective of this study was to calculate stage and treatment-specific utility weights for gastric cancer-related health states using the standard gamble (SG) method from a general population perspective (Lee et al., 2018). Particularly, utilities were selected from two key health states: (1) early gastric cancer [EGC] with endoscopic surgery to represent early-stage utility, and (2) metastatic gastric cancer with palliative chemotherapy to represent late-stage utility.

Utility values for liver and pancreatic cancer were not readily available, so the average utility for the six other types of cancers under study for which utility values were available were estimated and used to represent the utility associated with both liver and pancreatic cancer both at early and late-stage disease. These values were 0.772 and 0.404 for early-stage and late-stage disease, respectively.

Outcomes and Data Analysis

The primary outcomes of the analysis include cost, QALYs and the incremental cost-effectiveness ratio (ICER) comparing Strategy 2 and Strategy 1. All costs and utilities were discounted at an annual rate of 1.5% as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH), with a half-cycling correction (CADTH, 2017).

ICER was calculated as the quotient of the difference in cost to the difference in QALYs associated with screening Strategy 2 compared to screening Strategy 1/standard of care. ICER measures the additional cost for each extra unit of QALY gained from Strategy 2 and is expressed as the cost per QALY. It is calculated for men and women separately, and then combined using a simple average to derive an overall ICER for both sexes. See formulae below.

$$ICER_j = \frac{Cost_{Stategy\,2} - Cost_{Strategy\,1}}{QALY_{Strategy\,2} - QALY_{Strategy\,1}}$$

j = sex where j = 0 for males and 1 for females

$$ICER_{average} = (ICER_0 + ICER_1)/2$$

$ICER_{average}$ = average ICER for males and females combined

Using the estimates of each input parameter, base-case ICERs were calculated for men and women separately, and then an overall ICER was estimated using a simple average of the sex-specific ICERs. Overall cost-effectiveness was evaluated by comparing the results against a commonly used willingness to pay threshold of $100,000 per QALY. This threshold has been recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH), which has provided a template of best practices for conducting cost-effectiveness analyses on health interventions in Canada (CADTH, 2017). Comparator studies - Lipscomb et al. and Tafazzoli et al. (discussed earlier) - have also used the same threshold level in evaluating the cost-effectiveness of MCED screening under various conditions (Lipscomb et al., 2022; Tafazzoli et al., 2022).

The potential value-based price (VBP) of the MCED test was also calculated. This is an estimate of the maximum price at which the test may be set to ensure that its intervention is cost-effective at a willingness to pay of $100,000 per QALY.

To complement these findings, other outcomes including the number of early cancers detected and the number of cancer-related deaths avoided were also estimated.

Validation method

Validation of the proposed model in the study was conducted by comparing the estimated 5-year cancer-related mortality rate of the model under Strategy 1, which represents standard of care under current screening participation rates, with that published by the Canadian Cancer Statistic Advisory Committee in its special report, *Canadian Cancer Statistics 2021* (Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, 2021). For this comparison, a maximum difference of 20% between the estimated mortality rate and the published mortality rate was assumed to be acceptable.

Sensitivity Analysis

To assess the uncertainty of parameter estimates, two main sensitivity analyses were conducted, namely, one-way/univariate sensitivity analysis and probabilistic sensitivity analysis. For the one-way sensitivity analysis, key parameter estimates were varied independently (within a +/-25% range or 95% confidence interval where such information were available), while holding other variables fixed

to test the robustness of base-case results and to identify the most influential variables to the model. The associated tornado diagrams were interrogated to inform this analysis.

To further test the robustness of the model, probabilistic sensitivity analysis was employed where all model parameters were allowed to vary simultaneously. Assessing the associated cost-effectiveness acceptability frontier allowed for assessing the likelihood of MCED screening being cost-effective, given the willingness to pay threshold. To conduct this analysis, input variables were converted to probability distributions and their respective means and standard deviations estimated, in order to re-evaluate ICER using Monte-Carlo simulation with 10,000 iterations. Specifically, clinical probabilities and utilities were transformed to beta distributions, while cost variables were converted to gamma distributions. All other variables were converted to normal distributions.

Results

Validation results

The 5-year cancer mortality rate estimated by the model was compared with that published by the Canadian Cancer Statistic Advisory Committee in its special report, *Canadian Cancer Statistics 2021*. This comparison is presented in Tables 9 and 10 below. Generally, there is a marginal difference between the mortality rates estimated by the model for both males and females and those reported by the Canadian Cancer Society. Moreover, for each type of cancer, this difference is below the accepted level of 20%. The measured difference in the estimates from the model and that reported by the Canadian Cancer Society can be accounted for by the fact that epidemiology data were collected from two different countries - the US and the UK – and so country specific characteristics not typical of the Canadian experience may be embedded in the data.

Table 9 Five-year cancer mortality rate, male

	Model Estimate (Strategy 1)	Canadian Cancer Society	Difference (%)
Colorectal	0.4004	0.34	17.8
Esophageal	0.788	0.84	-6.19
Liver	0.7025	0.78	-9.94
Lung	0.71	0.81	-12.35
Pancreatic	0.8805	0.9	-2.17
Stomach	0.6435	0.73	-11.85

Table 10 Five-year cancer mortality rate, female

Cancer	Model Estimate (Strategy 1)	Canadian Cancer Society	Difference (%)
Breast	0.1145	0.11	4.090909
Colorectal	0.2905	0.33	-11.9697
Esophageal	0.7915	0.83	-4.63855
Liver	0.7235	0.78	-7.24359
Lung	0.673	0.74	-9.05405
Ovarian	0.484	0.56	-13.58
Pancreatic	0.881	0.91	-3.18681
Stomach	0.657	0.68	-3.38235

Clinical outcome projections

In the case of clinical outcome projections, it was also estimated that Strategy 2, which includes MCED screening for the selected cancers, resulted in an average of 76.5% more cancers being diagnosed at an earlier stage of disease (135% for males and 18% for females). It should be noted that although the early-stage incidence of cancer among males doubles as more cancers are detected at an earlier stage, the rate remained relatively low increasing from 0.0032 per 100,000 to 0.00751 per 100,000. Similarly, among females, the incidence rate for early-stage cancer increased from 0.02565 per 100,000 to 0.02842 per 100,000 as the rate of early detection increased. These estimates indicate that in independent cohorts of 100,000 persons, approximately 431 and 277 additional cases of cancers can be detected at the early stage of disease under the MCED screening strategy among males and females, respectively, resulting in a total of 708 additional cases of diagnosed cancer across both groups. It can be reasoned that fewer additional cancers were detected in the female group because organized screening for breast cancer is already available.

Also, under Strategy 2, 51% more cancers are diagnosed at a later stage on average (41% for males and 61% for females). This result suggests that cohort members with preclinical late-stage cancer are more likely to be detected through MCED screening rather than through symptom detection.

In the case of mortality, 11.5% less cancer-related deaths are expected (10% less for males and 13% less for females). At the same time, an average of 45% less preclinical cancer deaths (i.e., deaths that occur before an official cancer diagnosis) are expected when MCED screening is included as part of the standard cancer screening regimen for the selected cancers.

Table 11 Changes in selected outcome indicators resulting from MCED screening (%)

Strategy 2 vs Strategy 1	Male	Female	Average
Early diagnosis cases	135	18	76.5
Late diagnosis cases	41	61	51
Cancer deaths	-10	-13	-11.5
Preclinical deaths	-45	-45	-45

Base case analysis

From the base case analysis, the average cost of including annual MCED screening with current screening regimens for colorectal and breast cancer was estimated to be approximately $3,709 CAD ($2,287 for males and $5,130 for females), while the average cost of the standard of care screening strategy was estimated to be $2,195 CAD ($575 for males and $3,814 for females). Likewise, the average QALY for the intervention strategy was estimated at 19.385 (19.11 for males and 19.66 for females). Meanwhile, the average QALY for the standard of care was approximately 19.375 (19.10 for males and 19.65 for females).

The higher cost and higher QALY associated with the intervention strategy for the female cohort can be credited to the fact that MCED screening for this group interrogates all eight cancers for which the test can potentially detect, compared to the male cohort where only 6 of the 8 selected cancers are screened. The higher cost in this case would be driven by expenditure on care services once a cancer diagnosis has been established.

Overall, in comparison to standard of care screening, including MCED screening with current screening regimens for colorectal and breast cancer is not cost-effective with ICER: $143,369 CAD per QALY (ICER: $144,012 per QALY for males and ICER: $142,726 per QALY for females) given a willingness to pay threshold of $100,000 per QALY.

Table 12 ICER calculation for male model

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
SOC	575		19.101		
MCED + SOC for breast & colorectal cancer	2,287	1,712	19.113	0.012	144,012

Table 13 ICER calculation for female model

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
SOC	3,814		19.650		
MCED + SOC for breast & colorectal cancer	5,130	1,317	19.659	0.009	142,726

Given the base-case input values, the estimated maximum average price at which the MCED test can be set to achieve a willingness to pay threshold of $100,000 per QALY was estimated to be $451 ($443 from the male model and $459 from the female model).

Regarding the sensitivity analysis, similar variables were the most sensitive in both the male and female models. Specifically, the one-way sensitivity analysis, as illustrated in the tornado diagrams below, revealed that the cost of screening, and the specificity of FIT and MCED are the most sensitive variables in both the male and female models. Higher screening costs are associated with a worsening ICER, but this improves as these costs reduce. Meanwhile, ICER is more favorable with higher levels of specificity for FIT and MCED but deteriorates as these levels fall. Other variables that impact both the male and female models to a lesser extent than the aforementioned include the probability of dying from early-stage colorectal cancer, screening frequency, utility associated with the surveillance of early-stage colorectal cancer, the cost of the MCED test, utility associated with early-stage colorectal cancer, the sensitivity of FIT, the sensitivity of the diagnostic test for colorectal cancer, screening participations, the likelihood of those with a positive screening engaging in diagnostic work-up, the utility associated with preclinical early-stage lung cancer and the sensitivity of the MCED test to identifying lung cancer. All other variables were less sensitive in both the male and female models.

Use the variable descriptors in Table 14 to review Figures 4 and 5.

Table 14 Variables and their descriptors

Variable	**Description**
c_screening	Cost of the MCED test plus FIT
c_screening_MCED	Cost of MCED test only
p_deathCRC_ES	Probability that a cohort member dies from early-stage colorectal cancer
p_diagnostictest	Probability that a cohort member with a positive screen result pursues diagnostic follow-up
p_screening	Probability that a cohort member participates in a screening program
p_sensitivityDT_CRC	Sensitivity associated with a colonoscopy
p_sensitivity_FIT	Sensitivity of FIT
p_sensitivity_MCED_Lung	Sensitivity of the MCED test in detecting lung cancer
p_specificity_FIT	Specificity of FIT
p_specificity_MCED	Specificity of the MCED test
screenfreq	Screening interval
u_ESC	Utility associated with early-stage colorectal cancer
u_PcESC	Utility associated with preclinical early-stage colorectal cancer
u_ESC_Lung	Utility associated with preclinical early-stage lung cancer
u_SurveilES	Utility associated with those under surveillance having been diagnosed with early-stage colorectal cancer

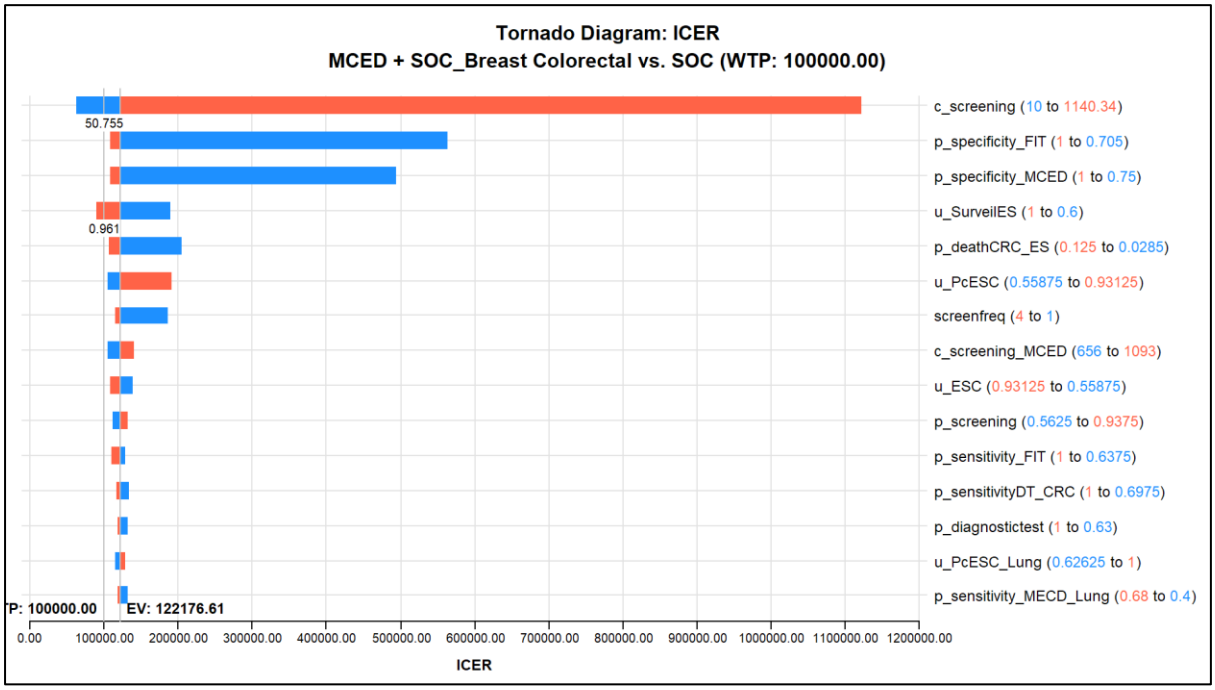


Figure 4 Tornado diagram: strategy 2 vs strategy 1, females

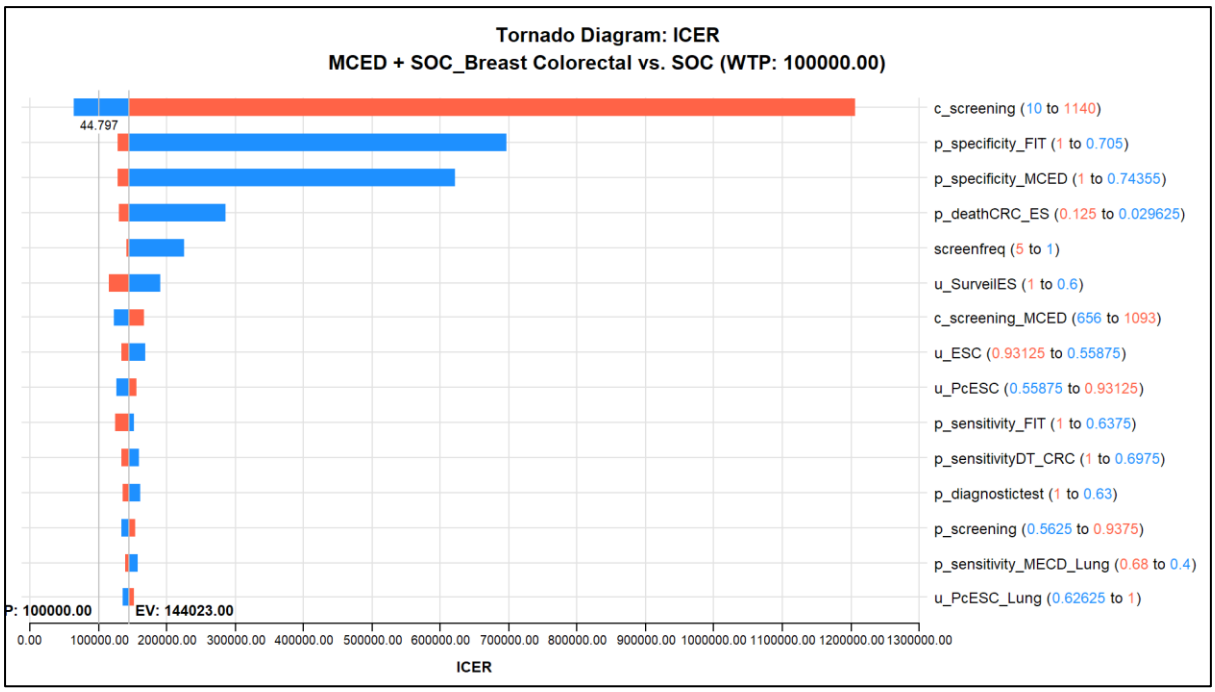


Figure 5 Tornado diagram: strategy 2 vs strategy 1, males

For females, the probabilistic sensitivity analysis using Monte Carlo simulation for 10,000 iterations revealed that standard of care is preferred 98.28% of the times at a willingness to pay threshold of $100,000 per QALY compared to the intervention strategy (which involves MCED screening). However, at a willingness to pay threshold of $150,000 per QALY or higher, the intervention strategy is preferred to only standard of care at least 63% of the times.

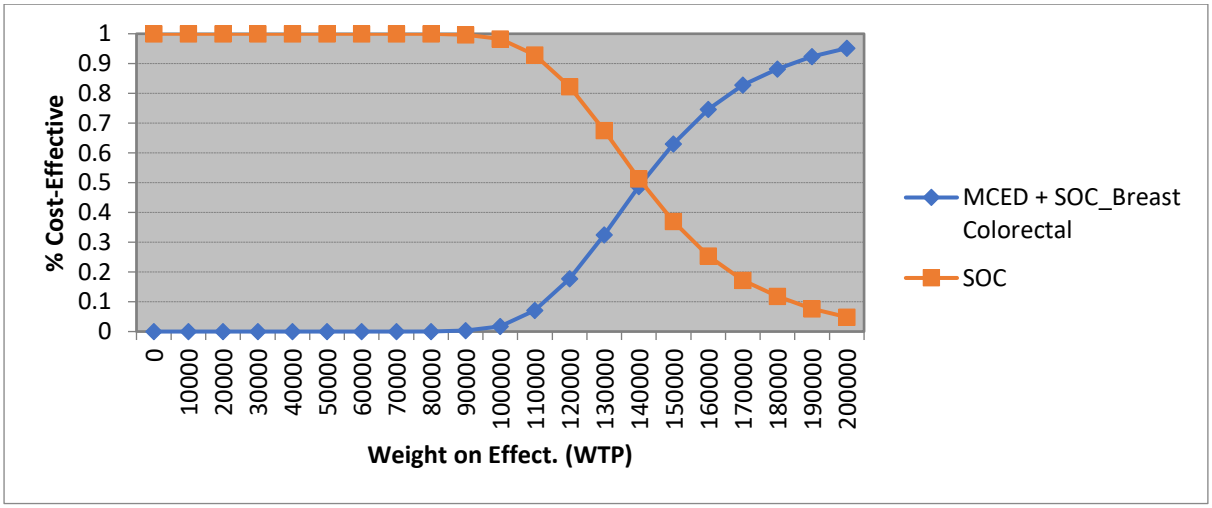


Figure 6 Cost-effectiveness acceptability curve: females

Similarly, in the case of males, the probability sensitivity analysis revealed that at a willingness to pay threshold of $100,000 per QALY, standard of care is preferred to the intervention strategy 98.28% of the times. However, at a willingness to pay threshold of $150,000 per QALY, the intervention strategy is preferred to standard of care at least 63.2% of the times.

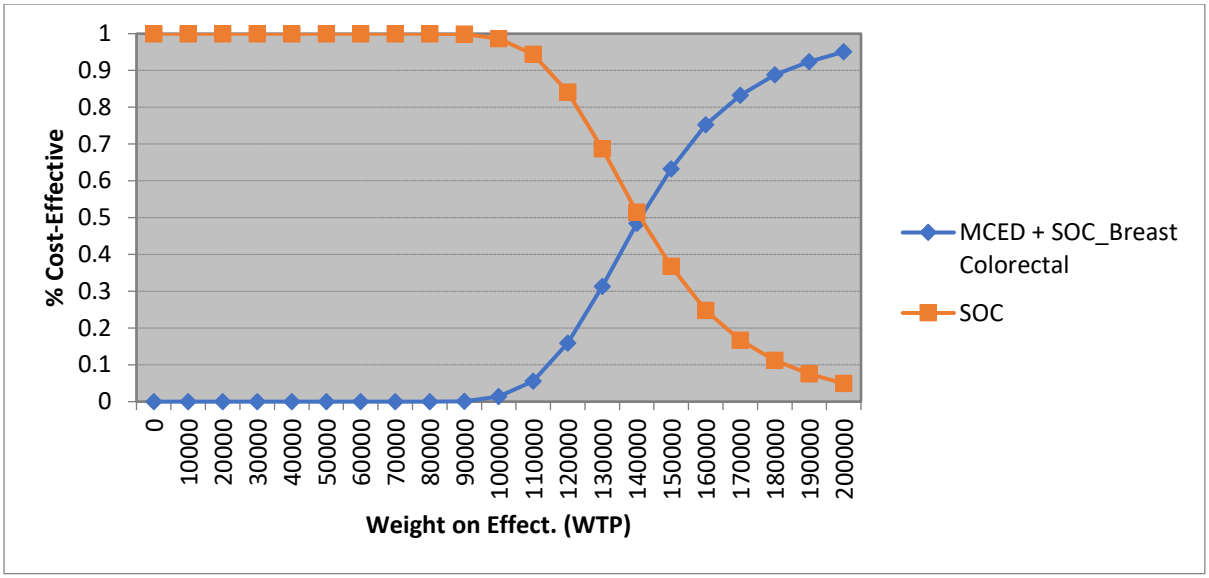


Figure 7 Cost-effectiveness acceptability curve: males

Discussion: Contributions and Limitations

In building on the foundational work of Lipscomb et al. (2022), this study presented and executed a methodological approach that can be adopted to test the cost-effectiveness of an MCED tool. More specifically, an MCED screening regimen was superimposed onto a state-transition Markov model which represented the progression of malignant tumors in order to evaluate both incremental cost and incremental benefits of MCED screening so as to determine its overall cost-effectiveness compared to standard of care screening for selected types of cancers.

Although independently developed, the model presented in this study is similar conceptually to the one created by Tafazzoli et al. (2022), in that they both provide a framework for investigating the cost-effectiveness of MCED screening using economic evaluation techniques, i.e., Markov modelling. Both studies used an integrated state-transition Markov model and decision tree to capture cases of diagnosed cancers and estimate the associated clinical and economic outcomes of these diagnoses. Other noteworthy similarities include the proposed screening strategies and study perspectives. Both studies compared the clinical and economic outcomes associated with MCED screening coupled with standard of care screening for cancers like breast and colorectal, compared to only standard of care for selected types of cancers, where the latter may involve no screening where screening programs are unavailable. Tafazzoli et al. described this as “usual care only”. Meanwhile, the main differences between Tafazzoli et al. and this current study stem from the cohort population (US vs Ontario province), screening age (50-79 years vs 50-75 years), number of cancers potentially detected (19 vs 8), study horizon (lifetime vs 25 years), discount rate (3% vs 1.5%), MCED screening compliance (90% vs 75%), and the natural history of disease (stages I to IV vs early to late-stage). Tafazzoli et al. also explicitly accounted for stage and time shift associated with early diagnosis with MCED as well as the consequences of overdiagnosis. Conversely, these features are not explicitly accounted for in this current study but are assumed to be reflected in transition probabilities and the sensitivity of cancer screening tests.

Where the current model appears to be superior to its contemporary is in accounting for the pre-clinical cases of cancer and how they may transition through the natural history ending in death if not detected through screening. Additionally, the model assumes a more realistic, yet conservative screening uptake based on trends in current screening participation in Canada. It also accounts for screening among men and women independently since both groups are affected by different subsets of cancers. This current study also conducted probabilistic sensitivity analysis, which is a more robust and highly recommended sensitivity test in executing cost-effectiveness analyses, whereas Tafazzoli et al. only used one-way sensitivity analysis in their study.

Overall, the preceding analysis revealed that MCED screening has the potential to diagnose additional cancers not typically screened, resulting in fewer related deaths compared to standard screening regimes. Similar results were also reported in Tafazzoli et al. (2022). In fact, in the case of the CancerSEEK test, even more types of cancers (those not investigated in this study) can potentially be detected according to its architects.

The estimated ICER in this present study, however, revealed that MCED screening was not cost-effective, exceeding the prescribed threshold level of $100,000 per QALY. The comparator study reported an even higher ICER (US$205,444 per QALY) when MCED screening focused solely on cancers not typically screened (Tafazzoli et al., 2022). Meanwhile, although the ICER estimated in the Lipscomb et al (2022) was more favorable ($22,494 per QALY), this study only accounted for one-time screening in a decision tree model with other limiting assumptions surrounding input variables.

In spite of the unfavorable result with respect to the estimated ICER in this study, the recent discourse on threshold analysis has pointed towards considering higher threshold levels for life-threatening diseases like cancer to ensure that clinical interventions are more cost-effective, especially from a patient's perspective where much needed health services can be provided (Safari et al., 2022). In a similar vein, the pan-Canadian Oncology Drug Review Process (pCODR) under the Canadian Agency for Technology Health (CADTH) has demonstrated its support for a higher threshold level with some studies proposing an upper threshold limit of CAD $140,000 per QALY (Binder et al., 2022; Y. Y. R. Li et al., 2020; Skedgel et al., 2018). Assuming that this upper limit is the new standard for assessing cost-effectiveness, then the results generated in this study may be acceptable and provide justification for including MCED testing in the clinical path of care for the selected cancers in this study.

While there is no consensus on an appropriate willingness to pay threshold for cancer interventions and whether a premium is justified, other indicators may prove useful. For example, WHO recommends a threshold level of at most 3-times a country's GDP per capita as an alternative benchmark for assessing cost-effectiveness (Aguiar et al., 2019; K. K. Shah, 2017; WHO, 2003). Furthermore, complementary measures as found in a league table, which ranks interventions based on their cost-effectiveness, and in the budget impact analysis, which is an affordability measure that estimates the absolute short-term cost of an intervention to a patient, can be considered (Aguiar et al., 2019).

According to the sensitivity analysis conducted in this present study, cost-effectiveness is most sensitive to screening costs and the specificity of screening tools. This suggests that lower screening costs, particularly the cost of MCED, will result in a more favorable ICER. In fact, in this study, a

maximum average value-based price of CA$451 for the MCED test was estimated to ensure a willingness to pay threshold of $100,000 per QALY. This value is more consistent with the US$500 originally estimated by Cohen et al. (2018) and is a more conservative value compared to the US$1,196 estimated by Tafazzoli et al. (2022). Ultimately, these results are instructive for policy makers and manufacturers of MCED screening tests in implementing appropriate pricing strategies for these tests in different jurisdictions.

Equally as important, high screening specificity suggests that fewer cases of false positive results would occur. This implies that screening will correctly identify those who do and those who do not have disease, thus limiting unnecessary patient anxiety, diagnostic odyssey, overdiagnosis, over treatment and the costs associated with these outcomes (Cohen et al., 2018; Etzioni et al., 2022, Kisiel et al., 2022; Lennon et al., 2020).

Generally, the model developed in this study can be used by other researchers and policy makers in the future to evaluate cost-effectiveness of other MCED tools as compared to standard of care. As such, the model can be adapted to different numbers of additional cancers, and also, standard care and costs can be varied according to different jurisdictions. This is made possible given that the proposed model accounts for key variables such as the prevalence rates of each health state of the selected types of cancers, disease transition, diagnosis rates, treatment, screening participation rates, costs and health outcomes. It would also be possible, in subsequent analyses, to relax some of the assumptions which were made here to facilitate a less computationally complex analysis.

However, it is with these assumptions in mind that caution should be taken in interpreting the results of the current study. Some notable assumptions in the analysis pertain to the methods adopted to estimate some key parameters like mortality rates, transition probabilities, utilities and the sensitivity levels used for each type and stage of cancer. Other assumptions to be mindful of include those used to represent cancer health states (i.e., early-stage and late-stage disease), setting a screening participation rate of 75% and a participation rate in follow-up testing of 84%, and assuming only one primary cancer can potentially occur for an individual cohort member in the state-transition model.

The challenge with adopting a more streamlined state-transition Markov model to represent the natural history of the selected cancers, as done in this study, is that in reality, the progression of each type of cancer is invariably different, and even for a given type of cancer, disease progression may vary from patient to patient (Siravegna et al., 2017). Furthermore, there has been little consensus on the natural history of cancers that are not typically screened like those of the pancreas, ovary and

liver, since there are much less data on these cancers in early stages. Notwithstanding, it is argued that the natural history proposed in this study was reasonable given the research objectives.

Assuming that only primary cancers are detected is yet another limitation of the study when in fact, a second primary cancer may also develop over time. However, this is an important assumption as it limits the model's complexity.

Although MCED compliance rates are unknown because these tools are not yet commercially available, it is expected that a greater number of persons would be more inclined to use these tests over the traditional single-organ screening tests because they are less invasive (Etzioni et al., 2022). The results of this current study were based on an assumed screening participation rate of 75%. This rate is proposed as it is viewed as a minimum requirement for the benefits of screening, including cost-effectiveness and lower mortality, to materialize (Brouwers et al., 2011; D'Andrea et al., 2019). However, it is acknowledged that actual participation rates in organized screening programs are less than optimal to achieve these benefits (Brouwers et al., 2011; US Preventive Services Task Force et al., 2016b).

Yet another caution to note is the fact that the results of this study are based on the sensitivity and specificity levels of an MCED test generated from a retrospective study - Cohen et al. 2018; and further, the average sensitivity levels rather than the stage-specific sensitivity levels were used for each type of cancer as this data were not readily available. As highlighted earlier, retrospective studies tend to overestimate the diagnostic performance of the MCED test because the study parameters are less representative of conditions in the real world. However, this study relied on the results of the Cohen et al. study because the sensitivity and specificity of the MCED test for the individual cancers were not available in the prospective study done by Lennon et al. Future research on the CancerSEEK test would therefore benefit from a prospective, interventional case-control approach (as done in the Lennon et al. study) where a PET-CT scan will follow a positive screening result to locate the issue of origin. It is envisioned that this diagnostic work-up may increase diagnostic costs but would also have positive tradeoffs with respect to cost-effectiveness as the MCED test can potentially identify a larger subset of cancers.

It should also be noted that the data employed in this study were collected from multiple country sources because they were not readily available for Canada. For instance, epidemiology data were sourced mainly from US and UK databases, namely SEER and the NHS for cancer incident rates and mortality rates, respectively. Meanwhile, cost-related data were derived from Canadian-based

studies. It is acknowledged that incorporating data points from these disparate sources may account for any disparities between the results of the study and published Canadian data.

Also, regarding the data on medical costs associated with cancer diagnosis and care, estimates were drawn from the de Oliveira et al. studies. These studies were based on data from 1997 to 2007 and would have accounted for the intervention tools at that time. It is acknowledged that since then, medical interventions along the clinical path of cancer care have improved and even become more costly; and so while this current study has updated the costs associated with medical interventions by accounting for medical inflation, it did not account for the change in cost associated with improvements in medical interventions.

Not explicitly accounting for the dwell time of the stages of each type of cancer is another limitation of the current study. However, this position was taken to maintain a more simplified state-transition model where dwell time was assumed to be a component of the disease transition probabilities of each type of cancer considered in the study. Cancer dwell time refers to the period spent in each stage of disease before transitioning to the next stage. It can be used as a measure of the burden of disease and varies for each type of cancer. Cancers with long dwell times progress slowly while those with short dwell times are more aggressive with poor prognoses (Broder et al., 2021). Border further noted that cancers of the esophagus, lung, liver, and pancreas can be considered as fast progressing with an average dwell time (for the most part) of less than a year between the respective stages of diseases (Broder et al., 2021). Meanwhile, breast, colorectal, ovarian and stomach cancers progress more gradually with average dwell times of 3 and 2 years for stages I and II cancer, respectively (Broder et al., 2021).

Notwithstanding these limitations, it is hoped that this study will motivate further research on the cost-effectiveness of MCED testing with particular focus on improving model structure and other important parameter assumptions. This may require more complex modeling techniques to account for the nuances in the natural history of specific types of cancers, the diagnostic abilities of specific screening tools and the care regimens for the different types of cancers.

It is also worth mentioning that should MCED screening prove to be cost-effective, its role in the clinical flow of cancer care would be complementary at best. This means that MCED screening tools would unlikely replace existing single-organ screening tests that have more favourable levels of sensitivity and specificity, like FIT and mammography for colorectal and breast cancer, respectively. Instead, it is feasible to have MCED screening work alongside these conventional tests as a less invasive primary screening intervention that is likely to increase screening uptake among eligible

persons not currently participating in organized screening programs, and so detect additional cases of breast, colorectal and lung cancers, especially if MCED were undertaken annually and standard of care testing biennially (Ahlquist, 2018; Jiao et al., 2022; Liu et al., 2020). At the same time, for cancers for which screening tools are not yet available, MCED screening offers an opportunity to identify and treat more cases of early-stage cancer with a greater degree of success (Ahlquist, 2018).

References

Aguiar, P. N., Adashek, J. J., Roitberg, F., Noia Barreto, C. M., Del Giglio, A., & Lopes, G. L. (2019). In the Era of Cost-Effectiveness Analysis, Affordability Is a Limiting Factor for Patients' Access to Innovative Cancer Treatments. *Value in Health Regional Issues*, *20*, 47–50. https://doi.org/10.1016/j.vhri.2018.12.003

Ahlquist, D. A. (2018). Universal cancer screening: revolutionary, rational, and realizable. In *npj Precision Oncology* (Vol. 2, Issue 1). Nature Publishing Group. https://doi.org/10.1038/s41698-018-0066-x

American Cancer Society. (n.d.). *Cancer surveillance programs in the United States*. Retrieved July 23, 2022, from https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/cancer-surveillance-programs-and-registries-in-the-united-states.html#:~:text=Cancer%20surveillance%20is%20the%20ongoing,%2C%20survival%2C%20and%20cancer%20deaths

Areia, M., Spaander, M. C. W., Kuipers, E. J., & Dinis-Ribeiro, M. (2018). Endoscopic screening for gastric cancer: A cost-utility analysis for countries with an intermediate gastric cancer risk. In *United European Gastroenterology Journal* (Vol. 6, Issue 2, pp. 192–202). SAGE Publications Ltd. https://doi.org/10.1177/2050640617722902

Arnold, M., Soerjomataram, I., Ferlay, J., & Forman, D. (2015). Global incidence of oesophageal cancer by histological subtype in 2012. *Gut*, *64*(3), 381–387. https://doi.org/10.1136/gutjnl-2014-308124

Babayan, A., & Pantel, K. (2018). Advances in liquid biopsy approaches for early detection and monitoring of cancer. *Genome Medicine*, *10*(1), 21. https://doi.org/10.1186/s13073-018-0533-6

Baratella, E., Cernic, S., Minelli, P., Furlan, G., Crimì, F., Rocco, S., Ruaro, B., & Cova, M. A. (2022). Accuracy of CT-guided core-needle biopsy in diagnosis of thoracic lesions suspicious for primitive malignancy of the lung: a five-year retrospective analysis. *Tomography*, *8*(6), 2828–2838. https://doi.org/10.3390/tomography8060236

Benaglia, T., Sharples, L. D., Fitzgerald, R. C., & Lyratzopoulos, G. (2013). Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. *Gastroenterology*, *144*(1). https://doi.org/10.1053/j.gastro.2012.09.060

Bhutani, M. S., Verma, D., Guha, S., Lee, J. H., Richards-Kortum, R. R., & Fleming, J. B. (2009). Is endoscopic ultrasound "sound" for pancreatic cancer screening? *Journal of Clinical Gastroenterology*, *43*(9), 797–802. https://doi.org/10.1097/MCG.0b013e3181b3ab58

Binder, L., Ghadban, M., Sit, C., & Barnard, K. (2022). Health Technology Assessment Process for Oncology Drugs: Impact of CADTH Changes on Public Payer Reimbursement Recommendations. *Current Oncology*, *29*(3), 1514–1526. https://doi.org/10.3390/curroncol29030127

Black, W. C., Gareen, I. F., Soneji, S. S., Sicks, J. D., Keeler, E. B., Aberle, D. R., Naeim, A., Church, T. R., Silvestri, G. A., Gorelick, J., & Gatsonis, C. (2014). Cost-effectiveness of CT screening in the National Lung Screening Trial. *New England Journal of Medicine*, *371*(19), 1793–1802. https://doi.org/10.1056/nejmoa1312547

Bloomfeld, R. S., Bridgers, D. I., & Pineau, B. C. (2005). Sensitivity of upper endoscopy in diagnosing esophageal cancer. *Dysphagia*, *20*(4), 278–282. https://doi.org/10.1007/s00455-005-0025-x

Bozic, I., Reiter, J. G., Allen, B., Antal, T., Chatterjee, K., Shah, P., Moon, Y. S., Yaqubie, A., Kelly, N., Le, D. T., Lipson, E. J., Chapman, P. B., Diaz, L. A., Vogelstein, B., & Nowak, M. A. (2013). Evolutionary dynamics of cancer in response to targeted combination therapy. *ELife*, *2*. https://doi.org/10.7554/eLife.00747

Breast Cancer Surveillance Consortium. (n.d.). *Diagnostic mammography sensitivity, specificity & false positive rate*. Retrieved January 4, 2023, from https://www.bcsc-research.org/statistics/diagnostic-performance-benchmarks/diagnostic-mammography-sensitivity-specificity

Brentnall, T. A., Bronner, M. P., Byrd, D. R., Haggitt, R. C., & Kimmey, M. B. (1999). Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Annals of Internal Medicine*, *131*(4), 247–255. https://doi.org/10.7326/0003-4819-131-4-199908170-00003

Broder, M. S., Ailawadhi, S., Beltran, H., Blakely, L. J., Budd, G. T., Carr, L., Cecchini, M., Cobb, P. W., Gibbs, S. N., Kansal, A., Kim, A., Monk, B. J., Schwartzberg, L. S., Wong, D. J. L., & Yermilov, I. (2021). Estimates of stage-specific preclinical sojourn time across 21 cancer types. *Journal of Clinical Oncology*, *39*(15_suppl), e18584–e18584. https://doi.org/10.1200/JCO.2021.39.15_suppl.e18584

Brouwers, M. C., de Vito, C., Bahirathan, L., Carol, A., Carroll, J. C., Cotterchio, M., Dobbins, M., Lent, B., Levitt, C., Lewis, N., Mcgregor, E., Paszat, L., Rand, C., & Wathen, N. (2011). What implementation interventions increase cancer screening rates? a systematic review. *Implementation Science*, *6*(111). http://www.implementationscience.com/content/6/1/111

Bruix, J., & Sherman, M. (2011). Management of hepatocellular carcinoma: An update. *Hepatology*, *53*(3), 1020–1022. https://doi.org/10.1002/hep.24199

CADTH. (2017). *Guidelines for the economic evaluation of health technologies: Canada 4th edition CADTH methods and guidelines service line*.

CADTH. (2019). *An overview of liquid biopsy for screening and early detection of cancer: CADTH issues in emerging health technologies*.

Canadian Cancer Society. (n.d.-a). *Cancer types*. Retrieved July 19, 2022, from https://cancer.ca/en/cancer-information/cancer-types

Canadian Cancer Society. (n.d.-b). *Screening for cervical cancer*. Retrieved July 19, 2022, from https://cancer.ca/en/cancer-information/cancer-types/cervical/screening

Canadian Cancer Society. (2017). *Liquid biopsy for early cancer detection*. https://www.cancer.ca/en/research-horizons/1/8/f/liquid-biopsy-for-early-cancer-detection/.

Canadian Cancer Statistics Advisory Committee. (2020). *Canadian cancer statistics: A 2020 special report on lung cancer*.

Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, S. C. and the P. H. A. of C. (2021). *Canadian Cancer Statistics 2021*. http://cancer.ca/Canadian-Cancer-Statistics-2021-EN

Canadian Task Force on Prevention Health. (2018). *Recommendations on screening for breast cancer in women 40-74 years of age who are not at increased risk*. https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update/

Canadian Task Force on Preventive Health Care. (2016). *Lung Cancer*. https://canadiantaskforce.ca/guidelines/published-guidelines/lung-cancer/

Canto, M. I., Harinck, F., Hruban, R. H., Offerhaus, G. J., Poley, J.-W., Kamel, I., Nio, Y., Schulick, R. S., Bassi, C., Kluijt, I., Levy, M. J., Chak, A., Fockens, P., Goggins, M., Bruno, M., & International Cancer of Pancreas Screening (CAPS) Consortium. (2013). International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*, *62*(3), 339–347. https://doi.org/10.1136/gutjnl-2012-303108

Chang, E. T., Keegan, T. H. M., Gomez, S. L., Le, G. M., Clarke, C. A., So, S. K. S., & Glaser, S. L. (2007). The burden of liver cancer in Asians and Pacific Islanders in the Greater San Francisco Bay Area, 1990 through 2004. *Cancer*, *109*(10), 2100–2108. https://doi.org/10.1002/cncr.22642

Chari, S., LEIBSON, C., RABE, K., RANSOM, J., DEANDRADE, M., & PETERSEN, G. (2005). Probability of pancreatic cancer following diabetes: A population-based study. *Gastroenterology*, *129*(2), 504–511. https://doi.org/10.1016/j.gastro.2005.05.007

Chen, X., Gole, J., Gore, A., He, Q., Lu, M., Min, J., Yuan, Z., Yang, X., Jiang, Y., Zhang, T., Suo, C., Li, X., Cheng, L., Zhang, Z., Niu, H., Li, Z., Xie, Z., Shi, H., Zhang, X., … Jin, L. (2020). Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nature Communications*, *11*(1). https://doi.org/10.1038/s41467-020-17316-z

Cherla, A., Renwick, M., Jha, A., & Mossialos, E. (2020). Cost-effectiveness of cancer drugs: Comparative analysis of the United States and England. *EClinicalMedicine*, *29–30*, 100625. https://doi.org/10.1016/j.eclinm.2020.100625

Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., Douville, C., Javed, A. A., Wong, F., Mattox, A., Hruban, R. H., Wolfgang, C. L., Goggins, M. G., Dal Molin, M., Wang, T.-L., Roden, R., Klein, A. P., Ptak, J., Dobbyn, L., … Papadopoulos, N. (2018). *Detection and localization of surgically resectable cancers with a multi-analyte blood test* (Vol. 17). http://science.sciencemag.org/

Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., Douville, C., Javed, A. A., Wong, F., Mattox, A., Hruban, R. H., Wolfgang, C. L., Goggins, M. G., Molin, M. D., Wang, T. L., Roden, R., Klein, A. P., Ptak, J., Dobbyn, L., … Papadopoulos, N. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*, *359*(6378), 926–930. https://doi.org/10.1126/science.aar3247

Connor, R. J., Chu, K. C., & Smart, C. R. (1989). Stage-shift cancer screening model. *Journal of Clinical Epidemiology*, *42*(11), 1083–1095. https://doi.org/10.1016/0895-4356(89)90050-4

Cossu, G., Saba, L., Minerba, L., & Mascalchi, M. (2018). Colorectal cancer screening: The role of psychological, social and background factors in decision-making process. *Clinical Practice and Epidemiology in Mental Health : CP & EMH*, *14*, 63–69. https://doi.org/10.2174/1745017901814010063

Cressman, S., Peacock, S. J., Tammemägi, M. C., Evans, W. K., Leighl, N. B., Goffin, J. R., Tremblay, A., Liu, G., Manos, D., MacEachern, P., Bhatia, R., Puksa, S., Nicholas, G., McWilliams, A., Mayo, J. R., Yee, J., English, J. C., Pataky, R., McPherson, E., … Lam, S. (2017). The cost-effectiveness of high-risk lung cancer screening and drivers of program efficiency. *Journal of Thoracic Oncology*, *12*(8), 1210–1222. https://doi.org/10.1016/j.jtho.2017.04.021

Cristiano, S., Leal, A., Phallen, J., Fiksel, J., Adleff, V., Bruhm, D. C., Jensen, S. Ø., Medina, J. E., Hruban, C., White, J. R., Palsgrove, D. N., Niknafs, N., Anagnostou, V., Forde, P., Naidoo, J., Marrone, K., Brahmer, J., Woodward, B. D., Husain, H., … Velculescu, V. E. (2019). Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature*, *570*(7761), 385–389. https://doi.org/10.1038/s41586-019-1272-6

Cucchetti, A., Cescon, M., Erroi, V., & Pinna, A. D. (2013). Cost-effectiveness of liver cancer screening. In *Best Practice and Research: Clinical Gastroenterology* (Vol. 27, Issue 6, pp. 961–972). Bailliere Tindall Ltd. https://doi.org/10.1016/j.bpg.2013.08.021

Dabizzi, E., Assef, M. S., & Raimondo, M. (2011). Diagnostic Management of Pancreatic Cancer. *Cancers*, *3*(1), 494–509. https://doi.org/10.3390/cancers3010494

D'Andrea, E., Ahnen, D. J., Sussman, D. A., & Najafzadeh, M. (2019). *Quantifying the impact of adherence to screening strategies on colorectal cancer incidence and mortality*. https://doi.org/10.1002/cam4.2735

Darling, G. E., Tammemägi, M. C., Schmidt, H., Buchanan, D. N., Leung, Y., McGarry, C., & Rabeneck, L. (2021). Organized lung cancer screening pilot: Informing a province-wide program in Ontario, Canada. *The Annals of Thoracic Surgery*, *111*(6), 1805–1811. https://doi.org/10.1016/J.ATHORACSUR.2020.07.051

de Oliveira, C., Bremner, K. E., Pataky, R., Gunraj, N., Chan, K., Peacock, S., & Krahn, M. D. (2013). Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. *CMAJ Open*, *1*(1), E1–E8. https://doi.org/10.9778/cmajo.20120013

de Oliveira, C., Pataky, R., Bremner, K. E., Rangrej, J., Chan, K. K. W., Cheung, W. Y., Hoch, J. S., Peacock, S., & Krahn, M. D. (2016). Phase-specific and lifetime costs of cancer care in Ontario, Canada. *BMC Cancer*, *16*(1), 809. https://doi.org/10.1186/s12885-016-2835-7

Dominitz, J. A., & Levin, T. R. (2020). What Is Organized Screening and What Is Its Value? *Gastrointestinal Endoscopy Clinics of North America*, *30*(3), 393–411. https://doi.org/10.1016/j.giec.2020.02.002

el Achi, H., Khoury, J. D., & Loghavi, S. (2019). Liquid biopsy by next-generation sequencing: a multimodality test for management of cancer. *Current Hematologic Malignancy Reports*, *14*(5), 358–367. https://doi.org/10.1007/s11899-019-00532-w

Etzioni, R., Gulati, R., & Weiss, N. S. (2022). Multicancer early detection: Learning from the past to meet the future. *Journal of the National Cancer Institute*, *114*(3), 349–352. https://doi.org/10.1093/jnci/djab168

European Association For The Study Of The Liver, & E. O. for R. and T. of C. (2012). EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*, *56*(4), 908–943. https://doi.org/10.1016/j.jhep.2011.12.001

Ferreira, C. S., Rodrigues, J., Moreira, S., Ribeiro, F., & Longatto-Filho, A. (2021). Breast cancer screening adherence rates and barriers of implementation in ethnic, cultural and religious minorities: A systematic review. *Molecular and Clinical Oncology*, *15*(1). https://doi.org/10.3892/mco.2021.2301

Geisel, J. L., & Philpotts, L. E. (2014). Breast tomosynthesis: a replacement or an adjunct to conventional diagnostic mammography? *Current Breast Cancer Reports*, *6*(2), 132–137. https://doi.org/10.1007/s12609-014-0146-z

Goffin, J. R., Flanagan, W. M., Miller, A. B., Fitzgerald, N. R., Memon, S., Wolfson, M. C., & Evans, W. K. (2015). Cost-effectiveness of lung cancer screening in Canada. *JAMA Oncology*, *1*(6), 807–813. https://doi.org/10.1001/jamaoncol.2015.2472

Habbous, S., Khan, Y., Langer, D. L., Kaan, M., Green, B., Forster, K., Darling, G., & Holloway, C. M. B. (2021). The effect of diagnostic assessment programs on the diagnosis and treatment of patients with lung cancer in Ontario, Canada. *Annals of Thoracic Medicine*, *16*(1), 81–101. https://doi.org/10.4103/atm.ATM_283_20

Hackshaw, A., Cohen, S. S., Reichert, H., Kansal, A. R., Chung, K. C., & Ofman, J. J. (2021). Estimating the population health impact of a multi-cancer early detection genomic blood test to complement existing screening in the US and UK. *British Journal of Cancer*, *125*(10), 1432–1442. https://doi.org/10.1038/s41416-021-01498-4

Hall, I. J., Tangka, F. K. L., Sabatino, S. A., Thompson, T. D., Graubard, B. I., & Breen, N. (2018). Patterns and trends in cancer screening in the United States. *Preventing Chronic Disease*, *15*, E97. https://doi.org/10.5888/pcd15.170465

Heitman, S. J., Hilsden, R. J., Au, F., Dowden, S., & Manns, B. J. (2010). Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Medicine*, *7*(11), e1000370. https://doi.org/10.1371/journal.pmed.1000370

Hoadley, K. A., Yau, C., Hinoue, T., Wolf, D. M., Lazar, A. J., Drill, E., Shen, R., Taylor, A. M., Cherniack, A. D., Thorsson, V., Akbani, R., Bowlby, R., Wong, C. K., Wiznerowicz, M., Sanchez-Vega, F., Robertson, A. G., Schneider, B. G., Lawrence, M. S., Noushmehr, H., … Laird, P. W. (2018). Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. *Cell*, *173*(2), 291-304.e6. https://doi.org/10.1016/j.cell.2018.03.022

Howlader, N., Noone, A., Krapcho, M., Miller, D., Bishop, K., Kosary, C., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D., Chen, H., Feuer, E., & Cronin, K. (2014). *SEER Cancer Statistics Review, 1975-2014*. https://seer.cancer.gov/csr/1975_2014/

Hu, C., Hart, S. N., Polley, E. C., Gnanaolivu, R., Shimelis, H., Lee, K. Y., Lilyquist, J., Na, J., Moore, R., Antwi, S. O., Bamlet, W. R., Chaffee, K. G., DiCarlo, J., Wu, Z., Samara, R., Kasi, P. M., McWilliams, R. R., Petersen, G. M., & Couch, F. J. (2018). Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA*, *319*(23), 2401. https://doi.org/10.1001/jama.2018.6228

Huang, D., Pastagia, M., & Ericsson, C. (2017). Issues for travelers. In S. Tyring, O. Lupi, & U. Hengge (Eds.), *Tropical Dermatology* (2nd ed., pp. 14–22). Elsevier.

Hutton, D. W., Tan, D., So, S. K., & Brandeau, M. L. (2007). *Cost-effectiveness of screening and vaccinating Asian and Pacific islander adults for Hepatitis B*. www.annals.org

International Agency for Research on Cancer. (n.d.). What is an “organized” screening programme? In *European code against cancer: 12 ways to reduce your cancer risk*. Retrieved July 19, 2022, from https://cancer-code-europe.iarc.fr/index.php/en/ecac-12-ways/screening-recommandation/key-points-about-cancer-screening/213-what-is-an-organized-screening-

programme#:~:text=Organized%20screening%20programmes%20are%20designed,testing%2C%20support%2C%20and%20treatment.

International Agency for Research on Cancer. (2020). Cancer fact sheets. In *Global Cancer Observatory*. World Health Organization. https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf

Jacobs, I. J., & Menon, U. (2004). Progress and challenges in screening for early detection of ovarian cancer. In *Molecular and Cellular Proteomics* (Vol. 3, Issue 4, pp. 355–366). https://doi.org/10.1074/mcp.R400006-MCP200

Janes, S., Dickson, J., Devaraj, A., Horst, C., Quaife, S., Levermore, C., Gyertson, K., Mullin, A., Farrelly, L., & Allen, B. (2019, September). Trial in progress: Cancer screening study with or without low dose lung CT to validate a multi-cancer early detection blood test: SUMMIT. *International Association for the Study of Lung Cancer*.

Jiang, K., Jiang, X., Pan, J., Wen, Y., Huang, Y., Weng, S., Lan, S., Nie, K., Zheng, Z., Ji, S., Liu, P., Li, P., & Liu, F. (2021). Current evidence and future perspective of accuracy of artificial intelligence application for early gastric cancer diagnosis with endoscopy: a systematic and meta-analysis. *Frontiers in Medicine*, *8*, 629080. https://doi.org/10.3389/fmed.2021.629080

Jiao, B., Gulati, R., Katki, H. A., Castle, P. E., & Etzioni, R. (2022). A quantitative framework to study potential benefits and harms of multi-cancer early detection testing. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *31*(1), 38–44. https://doi.org/10.1158/1055-9965.EPI-21-0380

Jochelson, M. (2012). Advanced imaging techniques for the detection of breast cancer. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting*, 65–69. https://doi.org/10.14694/EdBook_AM.2012.32.223

Kalyta, A., de Vera, M. A., Peacock, S., Telford, J. J., Brown, C. J., Donnellan, F., Gill, S., & Loree, J. M. (2021). Canadian colorectal cancer screening guidelines: Do they need an update given changing incidence and global practice patterns? *Current Oncology (Toronto, Ont.)*, *28*(3), 1558–1570. https://doi.org/10.3390/curroncol28030147

Kang, S., Li, Q., Chen, Q., Zhou, Y., Park, S., Lee, G., Grimes, B., Krysan, K., Yu, M., Wang, W., Alber, F., Sun, F., Dubinett, S. M., Li, W., & Zhou, X. J. (2017). Cancer locator: non-invasive cancer diagnosis and tissue-of-origin prediction using methylation profiles of cell-free DNA. *Genome Biology*, *18*(1), 53. https://doi.org/10.1186/s13059-017-1191-5

Khan, S. A., Hernandez-Villafuerte, K. V., Muchadeyi, M. T., & Schlander, M. (2021). Cost-effectiveness of risk-based breast cancer screening: A systematic review. *International Journal of Cancer*, *149*(4), 790–810. https://doi.org/10.1002/ijc.33593

Kisiel, J. B., Papadopoulos, N., Liu, M. C., Crosby, D., Srivastava, S., & Hawk, E. T. (2022). Multicancer early detection test: Preclinical, translational, and clinical evidence–generation plan and provocative questions. In *Cancer* (Vol. 128, Issue S4, pp. 861–874). John Wiley and Sons Inc. https://doi.org/10.1002/cncr.33912

Klein, E. A., Richards, D., Cohn, A., Tummala, M., Lapham, R., Cosgrove, D., Chung, G., Clement, J., Gao, J., Hunkapiller, N., Jamshidi, A., Kurtzman, K. N., Seiden, M. v., Swanton, C., & Liu, M. C. (2021). Clinical validation of a targeted methylation-based multi-cancer early detection test

using an independent validation set. *Annals of Oncology*, *32*(9), 1167–1177. https://doi.org/10.1016/j.annonc.2021.05.806

Kowada, A. (2019). Cost-effectiveness of Helicobacter pylori test and eradication versus upper gastrointestinal series versus endoscopy for gastric cancer mortality and outcomes in high prevalence countries. *Scandinavian Journal of Gastroenterology*, *54*(6), 685–689. https://doi.org/10.1080/00365521.2019.1627408

Kulasingam, S. L., Rajan, R., St Pierre, Y., Atwood, C. V., Myers, E. R., & Franco, E. L. (2009). Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: A cost-effectiveness analysis. *BMC Medicine*, *7*. https://doi.org/10.1186/1741-7015-7-69

Kulkarni, N. M., Mannelli, L., Zins, M., Bhosale, P. R., Arif-Tiwari, H., Brook, O. R., Hecht, E. M., Kastrinos, F., Wang, Z. J., Soloff, E. v., Tolat, P. P., Sangster, G., Fleming, J., Tamm, E. P., & Kambadakone, A. R. (2020). White paper on pancreatic ductal adenocarcinoma from society of abdominal radiology's disease-focused panel for pancreatic ductal adenocarcinoma: Part II, update on imaging techniques and screening of pancreatic cancer in high-risk individuals. In *Abdominal Radiology* (Vol. 45, Issue 3, pp. 729–742). Springer. https://doi.org/10.1007/s00261-019-02290-y

Kwong, G. A., Ghosh, S., Gamboa, L., Patriotis, C., Srivastava, S., & Bhatia, S. N. (2021). Synthetic biomarkers: a twenty-first century path to early cancer detection. In *Nature Reviews Cancer* (Vol. 21, Issue 10, pp. 655–668). Nature Research. https://doi.org/10.1038/s41568-021-00389-3

Ladabaum, U. (2020). Cost-effectiveness of current colorectal cancer screening tests. *Gastrointestinal Endoscopy Clinics of North America*, *30*(3), 479–497. https://doi.org/10.1016/j.giec.2020.02.005

Leddin, D. J., Frcpc, M. B., Enns, R., Hilsden, R., Plourde, V., Rabeneck, L., Frcpc, M., Sadowski, D. C., Singh, H., & Frcpc, M. D. (2010). Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. In *Can J Gastroenterol* (Vol. 24).

Lee, Y. H., Choi, K. S., Jun, J. K., Suh, M., Lee, H. Y., Kim, Y. N., Nam, C. M., Park, E. C., & Cho, W. H. (2014). Cost-effectiveness of liver cancer screening in adults at high risk for liver cancer in the Republic of Korea. *Cancer Research and Treatment*, *46*(3), 223–233. https://doi.org/10.4143/crt.2014.46.3.223

Lei, J., Yang, P., Zhang, L., Wang, Y., & Yang, K. (2014). Diagnostic accuracy of digital breast tomosynthesis versus digital mammography for benign and malignant lesions in breasts: a meta-analysis. *European Radiology*, *24*(3), 595–602. https://doi.org/10.1007/s00330-013-3012-x

Lennon, A. M., Buchanan, A. H., Kinde, I., Warren, A., Honushefsky, A., Cohain, A. T., Ledbetter, D. H., Sanfilippo, F., Sheridan, K., Rosica, D., Adonizio, C. S., Hwang, H. J., Lahouel, K., Cohen, J. D., Douville, C., Pate, A. A., Hagmann, L. N., Rolston, D. D., Malani, N., … Papadopoulos, N. (2020). Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science*, *369*(6499). https://doi.org/10.1126/science.abb9601

Levi, Z., Rozen, P., Hazazi, R., Vilkin, A., Waked, A., Maoz, E., Birkenfeld, S., Leshno, M., & Niv, Y. (2007). A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Annals*

of Internal Medicine, *146*(4), 244–255. https://doi.org/10.7326/0003-4819-146-4-200702200-00003

Li, F., Li, X., Guo, C., Xu, R., Li, F., Pan, Y., Liu, M., Liu, Z., Shi, C., Wang, H., Wang, M., Tian, H., Liu, F., Liu, Y., Li, J., Cai, H., Yang, L., He, Z., & Ke, Y. (2019). Estimation of cost for endoscopic screening for esophageal cancer in a high-risk population in rural China: Results from a population-level randomized controlled trial. *PharmacoEconomics*, *37*(6), 819–827. https://doi.org/10.1007/s40273-019-00766-9

Li, Y., Du, L., Wang, Y., Gu, Y., Zhen, X., Hu, X., Sun, X., & Dong, H. (2020). Modeling the cost-effectiveness of esophageal cancer screening in China. *Cost Effectiveness and Resource Allocation*, *18*(1), 33. https://doi.org/10.1186/s12962-020-00230-y

Li, Y. Y. R., Mai, H., Trudeau, M. E., Mittmann, N., Chiasson, K., Chan, K. K. W., & Cheung, M. C. (2020). Reimbursement Recommendations for Cancer Drugs Supported by Phase II Evidence in Canada. *Current Oncology*, *27*(5), 495–500. https://doi.org/10.3747/co.27.6489

Linehan, V., Harris, S., & Bhatia, R. (2021). An audit of opportunistic lung cancer screening in a Canadian province. *Journal of Primary Care and Community Health*, *12*. https://doi.org/10.1177/21501327211051484

Lipscomb, J., Horton, S., Kuo, A., & Tomasetti, C. (2022). Evaluating the impact of multicancer early detection testing on health and economic outcomes: Toward a decision modeling strategy. *Cancer*, *128 Suppl 4*, 892–908. https://doi.org/10.1002/cncr.33980

Liu, M. C., Oxnard, G. R., Klein, E. A., Swanton, C., Seiden, M. v, & CCGA Consortium. (2020). Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *31*(6), 745–759. https://doi.org/10.1016/j.annonc.2020.02.011

Liu, M. C., Oxnard, G. R., Klein, E. A., Swanton, C., Seiden, M. v., Liu, M. C., Oxnard, G. R., Klein, E. A., Smith, D., Richards, D., Yeatman, T. J., Cohn, A. L., Lapham, R., Clement, J., Parker, A. S., Tummala, M. K., McIntyre, K., Sekeres, M. A., Bryce, A. H., … Berry, D. A. (2020). Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Annals of Oncology*, *31*(6), 745–759. https://doi.org/10.1016/j.annonc.2020.02.011

Liu, M., Cummings, S., Vachon, C., Kerlikowske, K., Couch, F. J., Morris, E., Olson, J., Polley, E., Conners, A., & Ellis, R. (2017, December 5). Development of cell-free nucleic acid-based tests for detection of invasive breast cancer: The STRIVE study. *San Antonio Breast Cancer Symposium*.

Lorenzo, D., Rebours, V., Maire, F., Palazzo, M., Gonzalez, J.-M., Vullierme, M.-P., Aubert, A., Hammel, P., Lévy, P., & de Mestier, L. (2019). Role of endoscopic ultrasound in the screening and follow-up of high-risk individuals for familial pancreatic cancer. *World Journal of Gastroenterology*, *25*(34), 5017–5219. https://www.wjgnet.com

Lynch, H. T., Smyrk, T., Kern, S. E., Hruban, R. H., Lightdale, C. J., Lemon, S. J., Lynch, J. F., Fusaro, L. R., Fusaro, R. M., & Ghadirian, P. (1996). Familial pancreatic cancer: a review. *Seminars in Oncology*, *23*(2), 251–275.

Malfertheiner, P., Megraud, F., O'Morain, C. A., Atherton, J., Axon, A. T. R., Bazzoli, F., Gensini, G. F., Gisbert, J. P., Graham, D. Y., Rokkas, T., El-Omar, E. M., Kuipers, E. J., & European Helicobacter

Study Group. (2012). Management of helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut*, *61*(5), 646–664. https://doi.org/10.1136/gutjnl-2012-302084

Mandelblatt, J. S., Cronin, K. A., Bailey, S., Berry, D. A., de Koning, H. J., Draisma, G., Huang, H., Lee, S. J., Munsell, M., Plevritis, S. K., Ravdin, P., Schechter, C. B., Sigal, B., Stoto, M. A., Stout, N. K., van Ravesteyn, N. T., Venier, J., Zelen, M., Feuer, E. J., & Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. (2009). Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Annals of Internal Medicine*, *151*(10), 738–747. https://doi.org/10.7326/0003-4819-151-10-200911170-00010

Mandelblatt, J. S., Stout, N. K., Schechter, C. B., van den Broek, J. J., Miglioretti, D. L., Krapcho, M., Trentham-Dietz, A., Munoz, D., Lee, S. J., Berry, D. A., van Ravesteyn, N. T., Alagoz, O., Kerlikowske, K., Tosteson, A. N. A., Near, A. M., Hoeffken, A., Chang, Y., Heijnsdijk, E. A., Chisholm, G., … Cronin, K. A. (2016). Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. *Annals of Internal Medicine*, *164*(4), 215–225. https://doi.org/10.7326/M15-1536

Marcus, P. M., Freedman, A. N., & Khoury, M. J. (2015). Targeted cancer screening in average-risk individuals. *American Journal of Preventive Medicine*, *49*(5), 765–771. https://doi.org/10.1016/j.amepre.2015.04.030

Mayrand, M.-H., Duarte-Franco, E., Coutlée, F., Rodrigues, I., Walter, S. D., Ratnam, S., Franco, E. L., & CCCaST Study Group. (2006). Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). *International Journal of Cancer*, *119*(3), 615–623. https://doi.org/10.1002/ijc.21897

Menon, U., McGuire, A. J., Raikou, M., Ryan, A., Davies, S. K., Burnell, M., Gentry-Maharaj, A., Kalsi, J. K., Singh, N., Amso, N. N., Cruickshank, D., Dobbs, S., Godfrey, K., Herod, J., Leeson, S., Mould, T., Murdoch, J., Oram, D., Scott, I., … Jacobs, I. J. (2017). The cost-effectiveness of screening for ovarian cancer: Results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *British Journal of Cancer*, *117*(5), 619–627. https://doi.org/10.1038/bjc.2017.222

Miller, Z. A., & Lee, K. S. (2016). Screening for hepatocellular carcinoma in high-risk populations. *Clinical Imaging*, *40*(2), 311–314. https://doi.org/10.1016/j.clinimag.2015.11.010

Mittmann, N., Stout, N. K., Lee, P., Tosteson, A. N. A., Trentham-Dietz, A., Alagoz, O., & Yaffe, M. J. (2015). Total cost-effectiveness of mammography screening strategies. *Health Rep.*, *23*(12), 16–25. www.cisnet.cancer.gov/breast/

Moertel, C. G. (1995). Fluorouracil plus Levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Annals of Internal Medicine*, *122*(5), 321. https://doi.org/10.7326/0003-4819-122-5-199503010-00001

Moss, H. A., Berchuck, A., Neely, M. L., Myers, E. R., & Havrilesky, L. J. (2018). Estimating cost-effectiveness of a multimodal ovarian cancer screening program in the United States: Secondary analysis of the UK collaborative trial of ovarian cancer screening (UKCTOCS). *JAMA Oncology*, *4*(2), 190–195. https://doi.org/10.1001/jamaoncol.2017.4211

Nadarevic, T., Giljaca, V., Colli, A., Fraquelli, M., Casazza, G., Miletic, D., & Štimac, D. (2021). Computed tomography for the diagnosis of hepatocellular carcinoma in adults with chronic

liver disease. *Cochrane Database of Systematic Reviews*, *2021*(10). https://doi.org/10.1002/14651858.CD013362.pub2

Nadauld, L. D., McDonnell, C. H., Beer, T. M., Liu, M. C., Klein, E. A., Hudnut, A., Whittington, R. A., Taylor, B., Oxnard, G. R., Lipson, J., Lopatin, M., Shaknovich, R., Chung, K. C., Fung, E. T., Schrag, D., & Marinac, C. R. (2021). The PATHFINDER Study: Assessment of the implementation of an investigational Multi-Cancer Early Detection Test into clinical practice. *Cancers*, *13*(14). https://doi.org/10.3390/cancers13143501

Narayan, A., Fischer, A., Zhang, Z., Woods, R., Morris, E., & Harvey, S. (2017). Nationwide cross-sectional adherence to mammography screening guidelines: national behavioral risk factor surveillance system survey results. *Breast Cancer Research and Treatment*, *164*(3), 719–725. https://doi.org/10.1007/s10549-017-4286-5

National Cancer Institute. (n.d.-a). *Diagnosis and staging*. Retrieved July 23, 2022, from https://www.cancer.gov/about-cancer/diagnosis-staging/staging

National Cancer Institute. (n.d.-b). *Dictionary of cancer terms*. Retrieved July 23, 2022, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/surveillance

National Health Services. (n.d.). *What do cancer stages and grades mean?* Retrieved July 23, 2022, from https://www.nhs.uk/common-health-questions/operations-tests-and-procedures/what-do-cancer-stages-and-grades-mean/

Omata, M., Lesmana, L. A., Tateishi, R., Chen, P.-J., Lin, S.-M., Yoshida, H., Kudo, M., Lee, J. M., Choi, B. I., Poon, R. T. P., Shiina, S., Cheng, A. L., Jia, J.-D., Obi, S., Han, K. H., Jafri, W., Chow, P., Lim, S. G., Chawla, Y. K., … Sarin, S. K. (2010). Asian Pacific Association for the study of the liver consensus recommendations on hepatocellular carcinoma. *Hepatology International*, *4*(2), 439–474. https://doi.org/10.1007/s12072-010-9165-7

Oxnard, G. R., Klein, E. A., Seiden, M. V., Hubbell, E., Venn, O., Jamshidi, A., Zhang, N., Beausang, J. F., Gross, S., Kurtzman, K. N., Fung, E. T., Allen, B., Fields, A. P., Liu, H., Sekeres, M. A., Richards, D. A., Yu, P. P., Aravanis, A. M., Hartman, A.-R., & Liu, M. C. (2019). Simultaneous multi-cancer detection and tissue of origin (TOO) localization using targeted bisulfite sequencing of plasma cell-free DNA (cfDNA). *Annals of Oncology*, *30*, v912. https://doi.org/10.1093/ANNONC/MDZ394.074

Pataky, R., Phillips, N., Peacock, S., & Coldman, A. J. (2014). Cost-effectiveness of population-based mammography screening strategies by age range and frequency. *Journal of Cancer Policy*, *2*(4), 97–102. https://doi.org/10.1016/j.jcpo.2014.09.001

Poruk, K. E., Firpo, M. A., Adler, D. G., & Mulvihill, S. J. (2013). Screening for pancreatic cancer: why, how, and who? *Annals of Surgery*, *257*(1), 17–26. https://doi.org/10.1097/SLA.0b013e31825ffbfb

Rim, S. H., Allaire, B. T., Ekwueme, D. U., Miller, J. W., Subramanian, S., Hall, I. J., & Hoerger, T. J. (2019). Cost-effectiveness of breast cancer screening in the National Breast and Cervical Cancer Early Detection Program. *Cancer Causes and Control*, *30*(8), 819–826. https://doi.org/10.1007/s10552-019-01178-y

Sachelarie, I., Kerr, K., Ghesani, M., & Blum, R. H. (2005). Integrated PET-CT: evidence-based review of oncology indications. *Oncology (Williston Park, N.Y.)*, *19*(4), 481–490; discussion 490-2, 495–496.

Safari, H., Poder, T. G., Afshari, S., Nahvijou, A., Arab-Zozani, M., Moradi, N., & Ameri, H. (2022). Determination of a cost-effectiveness threshold for cancer interventions in Iran. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.1039589

Salim, M., Dembrower, K., Eklund, M., Lindholm, P., & Strand, F. (2020). Range of radiologist performance in a population-based screening cohort of 1 million digital mammography examinations. *Radiology*, *297*(1), 33–39. https://doi.org/10.1148/radiol.2020192212

Sarmasti, M., Khoshbaten, M., Khalili, F., & Yousefi, M. (2021). Cost-effectiveness of screening Helicobacter pylori for gastric cancer prevention: A systematic review. In *Journal of Gastrointestinal Cancer*. Springer. https://doi.org/10.1007/s12029-021-00726-7

Sauer, A. G., Liu, B., Siegel, R. L., Jemal, A., & Fedewa, S. A. (2018). Comparing cancer screening estimates: behavioral risk factor surveillance system and national health interview survey. *Preventive Medicine*, *106*, 94–100. https://doi.org/10.1016/j.ypmed.2017.10.019

Schöder, H., & Gönen, M. (2007). Screening for cancer with PET and PET/CT: potential and limitations. *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*, *48 Suppl 1*, 4S-18S.

Schwartz, N. R. M., Matrisian, L. M., Shrader, E. E., Feng, Z., Chari, S., & Roth, J. A. (2021). Potential cost-effectiveness of risk-based pancreatic cancer screening in patients with new-onset diabetes. *Journal of the National Comprehensive Cancer Network*, *20*(5), 451–459. https://doi.org/10.6004/jnccn.2020.7798

Shah, K. K. (2017). Is willingness to pay higher for cancer prevention and treatment? *Journal of Cancer Policy*, *11*, 60–64. https://doi.org/10.1016/j.jcpo.2016.09.006

Shah, S. C., Canakis, A., Peek, R. M., & Saumoy, M. (2020). Endoscopy for gastric cancer screening is cost-effective for Asian Americans in the United States. In *Clinical Gastroenterology and Hepatology* (Vol. 18, Issue 13, pp. 3026–3039). W.B. Saunders. https://doi.org/10.1016/j.cgh.2020.07.031

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(1), 7–30. https://doi.org/10.3322/caac.21590

Singhi, A. D., Koay, E. J., Chari, S. T., & Maitra, A. (2019). Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology*, *156*(7), 2024–2040. https://doi.org/10.1053/j.gastro.2019.01.259

Siravegna, G., Marsoni, S., Siena, S., & Bardelli, A. (2017). Integrating liquid biopsies into the management of cancer. *Nature Reviews. Clinical Oncology*, *14*(9), 531–548. https://doi.org/10.1038/nrclinonc.2017.14

Siu, A. L., & U.S. Preventive Services Task Force. (2016). Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*, *164*(4), 279–296. https://doi.org/10.7326/M15-2886

Sivaram, S., Majumdar, G., Perin, D., Nessa, A., Broeders, M., Lynge, E., Saraiya, M., Segnan, N., Sankaranarayanan, R., Rajaraman, P., Trimble, E., Taplin, S., Rath, G. K., & Mehrotra, R. (2018). Population-based cancer screening programmes in low-income and middle-income countries: regional consultation of the International Cancer Screening Network in India. *The Lancet. Oncology*, *19*(2), e113–e122. https://doi.org/10.1016/S1470-2045(18)30003-2

Skedgel, C., Wranik, D., & Hu, M. (2018). The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017. *PharmacoEconomics*, *36*(4), 467–475. https://doi.org/10.1007/s40273-018-0610-0

Smith, K. M., Machalaba, C. C., Seifman, R., Feferholtz, Y., & Karesh, W. B. (2019). Infectious disease and economics: The case for considering multi-sectoral impacts. *One Health (Amsterdam, Netherlands)*, *7*, 100080. https://doi.org/10.1016/j.onehlt.2018.100080

Sroczynski, G., Gogollari, A., Kuehne, F., Hallsson, L. R., Widschwendter, M., Pashayan, N., & Siebert, U. (2020). A systematic review on cost-effectiveness studies evaluating ovarian cancer early detection and prevention strategies. In *Cancer prevention research (Philadelphia, Pa.)* (Vol. 13, Issue 5, pp. 429–442). NLM (Medline). https://doi.org/10.1158/1940-6207.CAPR-19-0506

Statistic Canada. (2018). *Cancer in Canada: Stage at diagnosis*. ttps://www150. statcan.gc.ca/n1/pub/82-003-x/2018012/article/00003-eng. htm

Statistics Canada. (2022). *Number and rates of new cases of primary cancer, by cancer type, age group and sex*. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011101

Stoffel, E. M., McKernin, S. E., & Khorana, A. A. (2019). Evaluating susceptibility to pancreatic cancer: ASCO clinical practice provisional clinical opinion summary. *Journal of Oncology Practice*, *15*(2), 108–111. https://doi.org/10.1200/JOP.18.00629

Sweeney-Magee, M., Gotay, C., Mohammad,) ;, Karim, E., Telford, J., & Dummer, T. (2022). Health promotion and chronic disease prevention in Canada research. *Policy and Practice*, *42*(2). https://doi.org/10.24095/hpcdp.42.2.04

Tafazzoli, A., Ramsey, S. D., Shaul, A., Chavan, A., Ye, W., Kansal, A. R., Ofman, J., & Fendrick, A. M. (2022). The Potential Value-Based Price of a Multi-Cancer Early Detection Genomic Blood Test to Complement Current Single Cancer Screening in the USA. *PharmacoEconomics*, *40*(11), 1107–1117. https://doi.org/10.1007/s40273-022-01181-3

Tammemägi, M. C., Darling, G. E., Schmidt, H., Llovet, D., Buchanan, D. N., Leung, Y., Miller, B., & Rabeneck, L. (2021). Selection of individuals for lung cancer screening based on risk prediction model performance and economic factors – The Ontario experience. *Lung Cancer*, *156*, 31–40. https://doi.org/10.1016/j.lungcan.2021.04.005

Tanner, N. T., Brasher, P. B., Wojciechowski, B., Ward, R., Slatore, C., Gebregziabher, M., & Silvestri, G. A. (2020). Screening adherence in the Veterans Administration Lung Cancer Screening Demonstration Project. *Chest*, *158*(4), 1742–1752. https://doi.org/10.1016/j.chest.2020.04.063

Telford, J. J., Levy, A. R., Sambrook, J. C., Zou, D., & Enns, R. A. (2010). The cost-effectiveness of screening for colorectal cancer. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *182*(12), 1307–1313. https://doi.org/10.1503/cmaj.090845

ten Haaf, K., Tammemägi, M. C., Bondy, S. J., van der Aalst, C. M., Gu, S., McGregor, S. E., Nicholas, G., de Koning, H. J., & Paszat, L. F. (2017). Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: A microsimulation modeling analysis in Ontario, Canada. *PLoS Medicine*, *14*(2). https://doi.org/10.1371/journal.pmed.1002225

Trentham-Dietz, A., Kerlikowske, K., Stout, N. K., Miglioretti, D. L., Schechter, C. B., Ergun, M. A., van den Broek, J. J., Alagoz, O., Sprague, B. L., van Ravesteyn, N. T., Near, A. M., Gangnon, R. E., Hampton, J. M., Chandler, Y., de Koning, H. J., Mandelblatt, J. S., & Tosteson, A. N. A. (2016). Tailoring breast cancer screening intervals by breast density and risk for women aged 50 years or older: Collaborative modeling of screening outcomes. *Annals of Internal Medicine*, *165*(10), 700–712. https://doi.org/10.7326/M16-0476

United Nations, D. of E. and S. A. P. D. (2019). *World Population Prospects 2019: data booklet (ST/ESA/SER.A/424)*.

US Preventive Services Task Force, Bibbins-Domingo, K., Grossman, D. C., Curry, S. J., Davidson, K. W., Epling, J. W., García, F. A. R., Gillman, M. W., Harper, D. M., Kemper, A. R., Krist, A. H., Kurth, A. E., Landefeld, C. S., Mangione, C. M., Owens, D. K., Phillips, W. R., Phipps, M. G., Pignone, M. P., & Siu, A. L. (2016a). Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*, *315*(23), 2564–2575. https://doi.org/10.1001/jama.2016.5989

US Preventive Services Task Force, Bibbins-Domingo, K., Grossman, D. C., Curry, S. J., Davidson, K. W., Epling, J. W., García, F. A. R., Gillman, M. W., Harper, D. M., Kemper, A. R., Krist, A. H., Kurth, A. E., Landefeld, C. S., Mangione, C. M., Owens, D. K., Phillips, W. R., Phipps, M. G., Pignone, M. P., & Siu, A. L. (2016b). Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*, *315*(23), 2564–2575. https://doi.org/10.1001/jama.2016.5989

Vahabi, M., Lofters, A. K., Kopp, A., & Glazier, R. H. (2021). Correlates of non-adherence to breast, cervical, and colorectal cancer screening among screen-eligible women: a population-based cohort study in Ontario, Canada. *Cancer Causes & Control : CCC*, *32*(2), 147–155. https://doi.org/10.1007/s10552-020-01369-y

Vijayaraghavan, A., Efrusy, M. B., Mayrand, M.-H., Santas, C. C., & Goggin, P. (2010). Cost-effectiveness of high-risk human papillomavirus testing for cervical cancer screening in Québec, Canada. *Canadian Journal of Public Health = Revue Canadienne de Sante Publique*, *101*(3), 220–225.

Vogelstein, B., Papadopoulos, N., Velculescu, V. E., Zhou, S., Diaz, L. A., & Kinzler, K. W. (2013). Cancer genome landscapes. *Science (New York, N.Y.)*, *339*(6127), 1546–1558. https://doi.org/10.1126/science.1235122

Wan, J. C. M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J. D., Caldas, C., Pacey, S., Baird, R., & Rosenfeld, N. (2017). Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nature Reviews. Cancer*, *17*(4), 223–238. https://doi.org/10.1038/nrc.2017.7

WHO. (2003). *Making choices in health : WHO guide to cost-effectiveness analysis* (T. Tan-Torres Edejer, R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D. Evans, D. Murray, & C. Murray, Eds.). World Health Organiation.

World Health Organization. (2022). *Cancer*. https://www.who.int/health-topics/cancer#tab=tab_1

Xie, L., Semenciw, R., & Mery, L. (2015). Cancer incidence in Canada: trends and projections (1983-2032). *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice*, *35 Suppl 1*, 2–186.

Yachida, S., White, C. M., Naito, Y., Zhong, Y., Brosnan, J. A., Macgregor-Das, A. M., Morgan, R. A., Saunders, T., Laheru, D. A., Herman, J. M., Hruban, R. H., Klein, A. P., Jones, S., Velculescu, V., Wolfgang, C. L., & Iacobuzio-Donahue, C. A. (2012). Clinical significance of the genetic landscape of pancreatic cancer and implications for identification of potential long-term survivors. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *18*(22), 6339–6347. https://doi.org/10.1158/1078-0432.CCR-12-1215

Yeh, J. M., Ho, W., & Hur, C. (2010). Cost-effectiveness of endoscopic surveillance of gastric ulcers to improve survival. *Gastrointestinal Endoscopy*, *72*(1), 33–43. https://doi.org/10.1016/j.gie.2010.01.047

Yoshinaga, M., Motomura, S., Takeda, H., Yanagisawa, Z., & Ikeda, K. (1995). Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *The American Journal of Gastroenterology*, *90*(7), 1076–1079.

Zhang, X., Li, M., Chen, S., Hu, J., Guo, Q., Liu, R., Zheng, H., Jin, Z., Yuan, Y., Xi, Y., & Hua, B. (2018). Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review. *Gastroenterology*, *155*(2), 347-354.e9. https://doi.org/10.1053/j.gastro.2018.04.026

Appendices

Appendix A List of cancer detected by the DETECT-A test

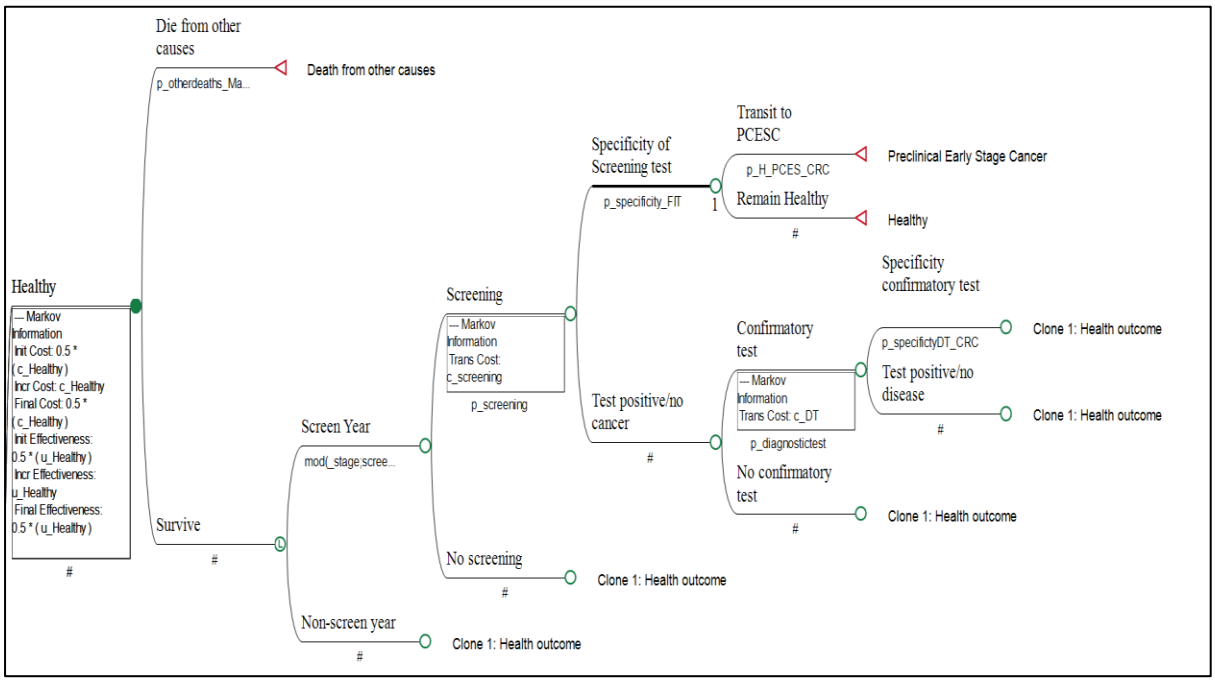
Appendix	Lymphoma
Breast	Ovary
Colorectal	Thyroid
Kidney	Uterine
Lung	Carcinoma of unknown primary location

Appendix B List of cancer detected by the GRAIL-Galleri test

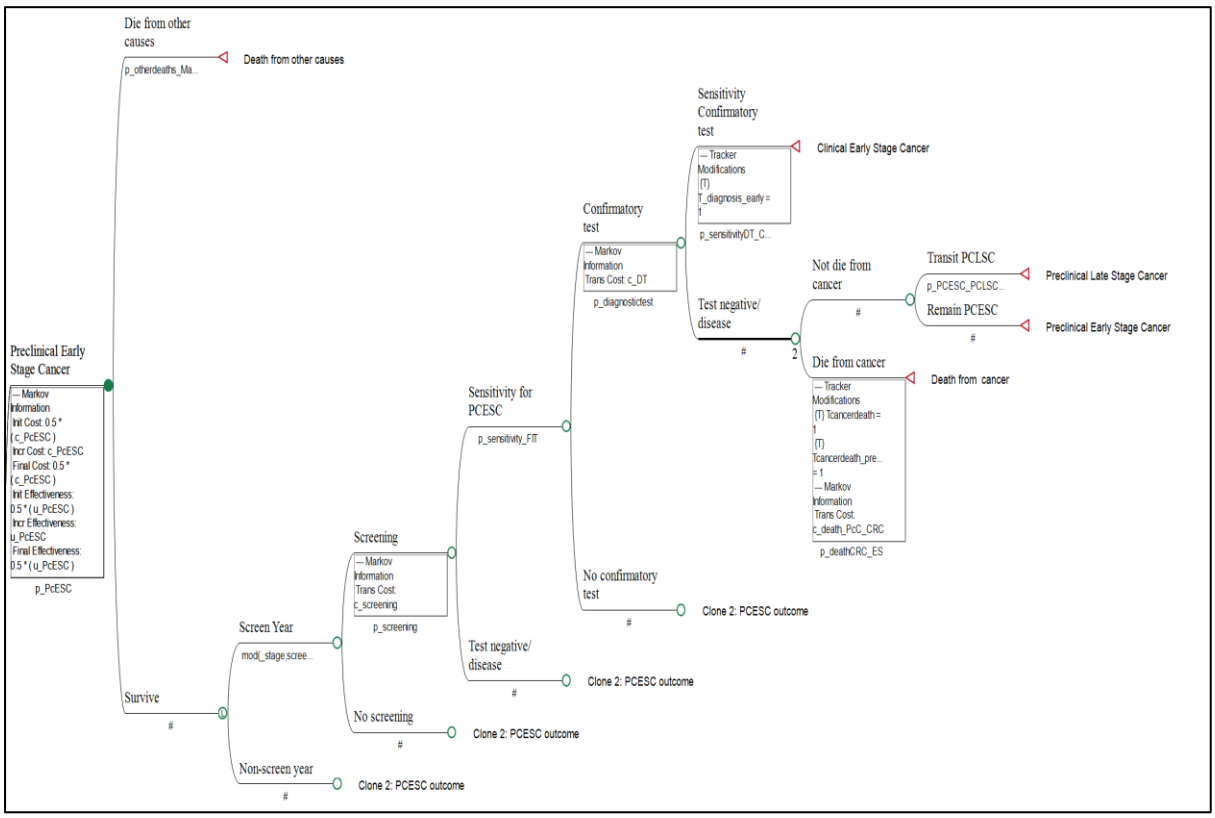
Adrenal Cortical Carcinoma	Colon and Rectum	Melanoma of the Skin	Ovary, Fallopian Tube and Primary Peritoneum	Stomach
Ampulla of Vater	Esophagus and Esophagogastric Junction	Merkel Cell Carcinoma	Pancreas, exocrine	Testis
Anus	Gallbladder	Mesothelioma, Malignant Pleural	Penis	Ureter, Renal Pelvis
Anus	Gastrointestinal Stromal Tumor	Nasal Cavity and Paranasal Sinuses	Plasma Cell Myeloma and Plasma Cell Disorders	Uterus, Carcinoma and Carcinosarcoma
Appendix, Carcinoma	Gestational Trophoblastic Neoplasms	Nasopharynx	Prostate	Uterus, Sarcoma
Bile Ducts, Distal	Kidney	Neuroendocrine Tumors of the Appendix	Small Intestine	Vagina
Bile Ducts, Intrahepatic	Larynx	Neuroendocrine Tumors of the Colon and Rectum	Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs	Vulva
Bladder, Urinary	Leukemia	Neuroendocrine Tumors of the Pancreas	Soft Tissue Sarcoma of the Head and Neck	
Bone	Liver	Oral Cavity	Soft Tissue Sarcoma of the Retroperitoneum	
Breast	Lung	Oropharynx (HPV-Mediated, p16+)	Soft Tissue Sarcoma of the Trunk and Extremities	
Cervix	Lymphoma (Hodgkin and Non-Hodgkin)	Oropharynx (p16-) and Hypopharynx	Soft Tissue Sarcoma Unusual Histologies and Sites	

Appendix C Colorectal arm of state transition model under MCED strategy

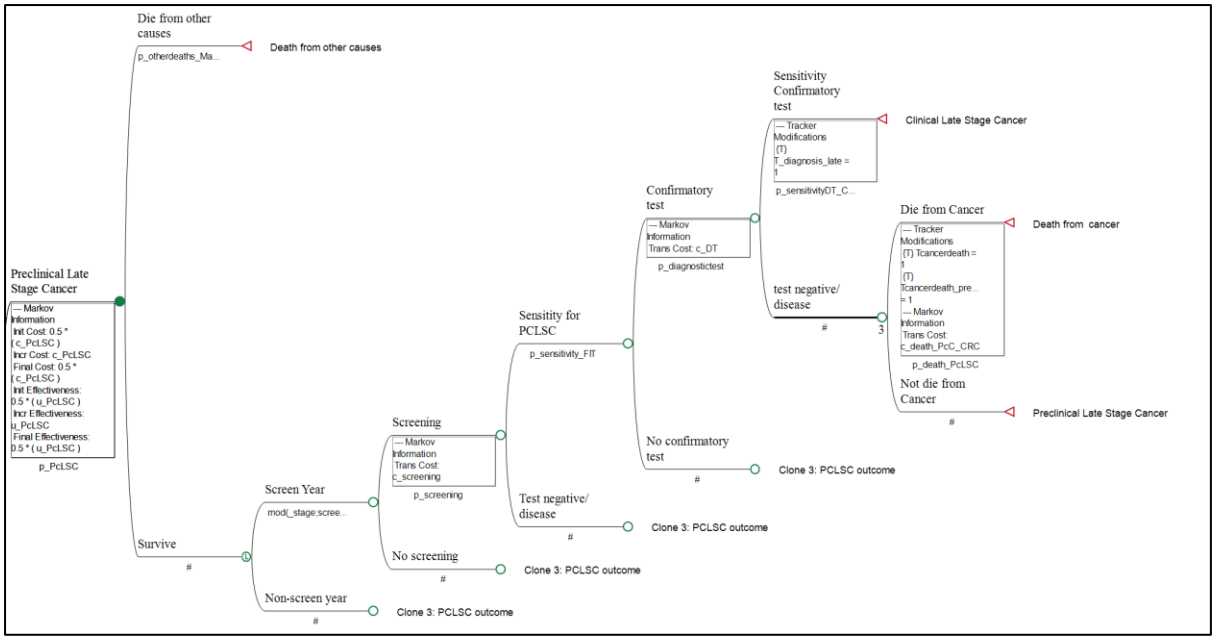
I.



II.



III.


Die from other causes
p_otherdeaths_Ma...
Death from other causes
Sensitivity Confirmatory test
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Clinical Late Stage Cancer
Confirmatory test
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Die from Cancer
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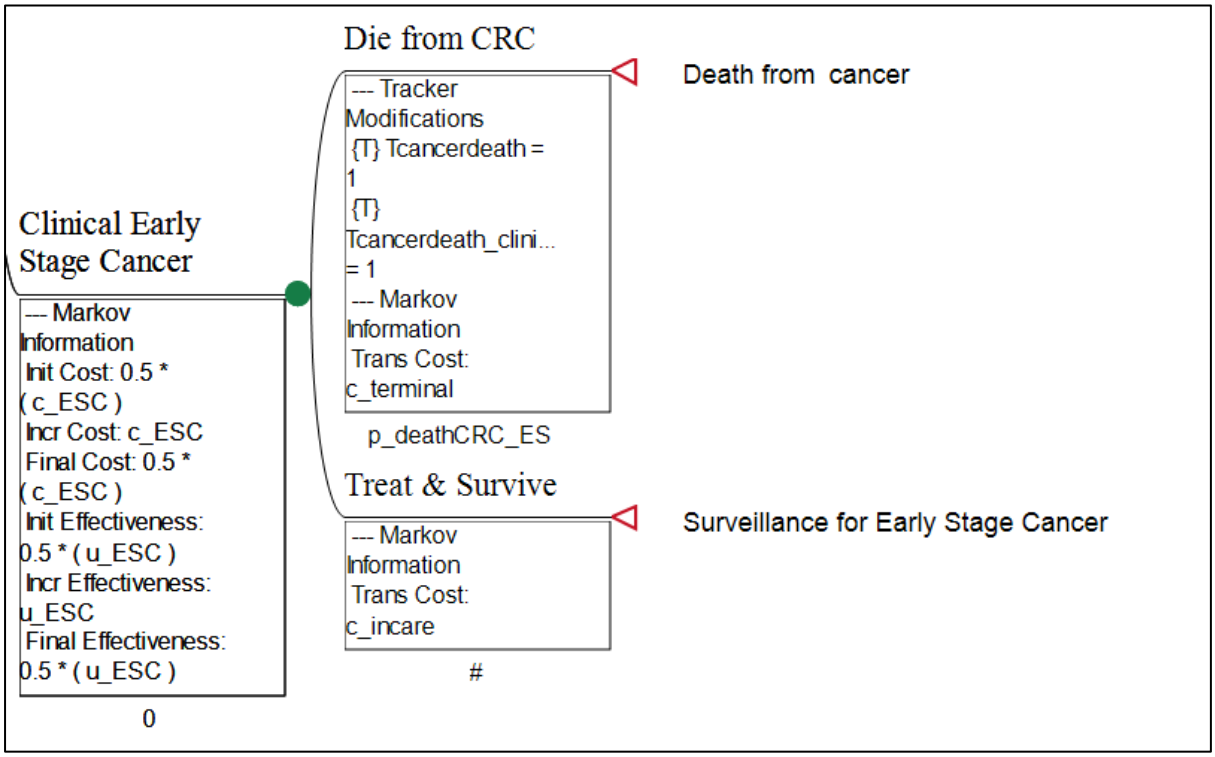
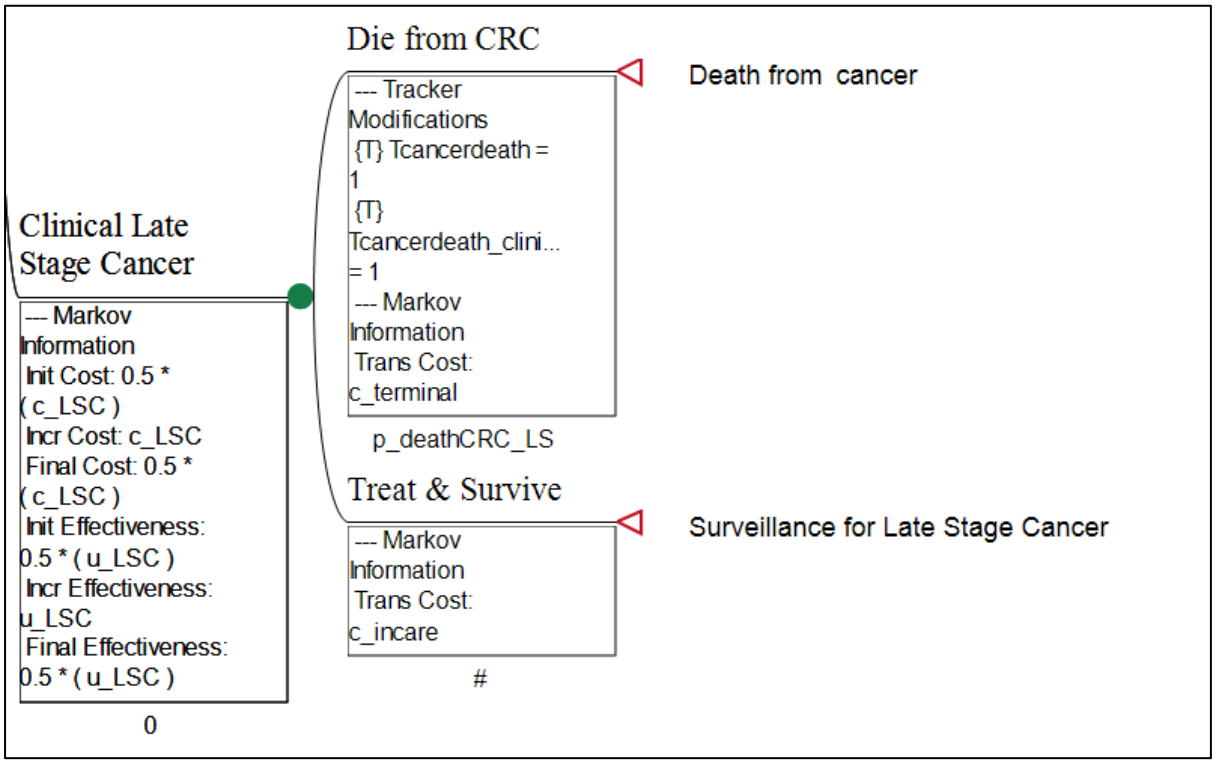
p_death_PcLSC
Death from cancer
Preclinical Late Stage Cancer
--- Markov Information Init Cost: 0.5 * (c_PcLSC) Incr Cost: c_PcLSC Final Cost: 0.5 * (c_PcLSC) Init Effectiveness: 0.5 * (u_PcLSC) Incr Effectiveness: u_PcLSC Final Effectiveness: 0.5 * (u_PcLSC)
p_PcLSC
Sensitity for PCLSC
p_sensitivity_FIT
test negative/ disease
3
Not die from Cancer
Preclinical Late Stage Cancer
Screening
--- Markov Information Trans Cost: c_screening
p_screening
No confirmatory test
Clone 3: PCLSC outcome
Screen Year
mod(_stage,scree...
Test negative/ disease
Clone 3: PCLSC outcome
Survive
No screening
Clone 3: PCLSC outcome
Non-screen year
Clone 3: PCLSC outcome

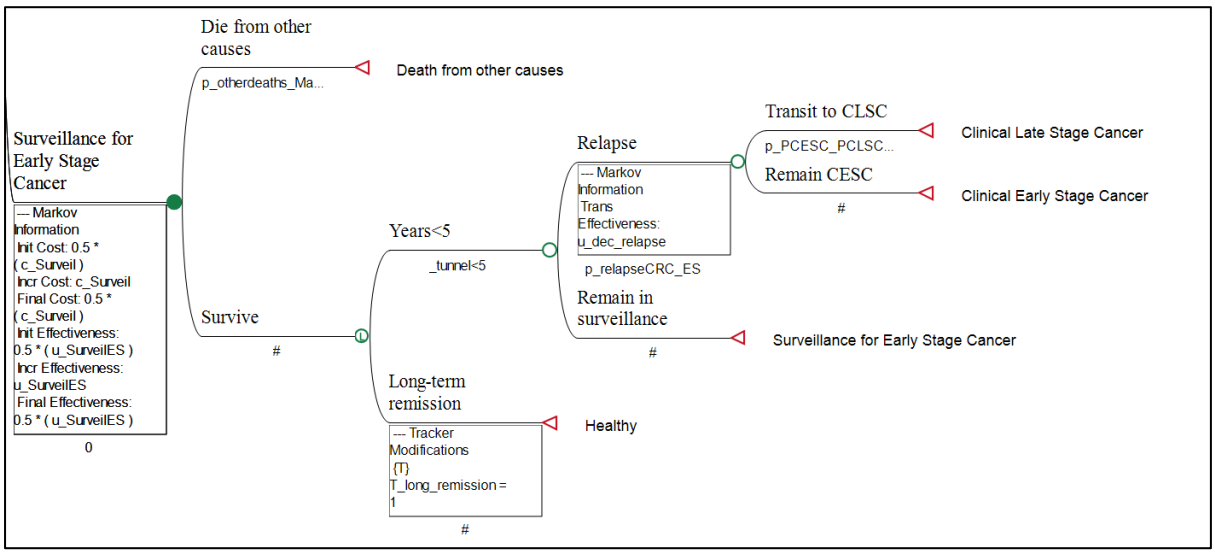
IV.


Die from CRC
--- Tracker Modifications {T} Tcancerdeath = 1 {T} Tcancerdeath_clini... = 1 --- Markov Information Trans Cost: c_terminal
p_deathCRC_ES
Death from cancer
Clinical Early Stage Cancer
--- Markov Information Init Cost: 0.5 * (c_ESC) Incr Cost: c_ESC Final Cost: 0.5 * (c_ESC) Init Effectiveness: 0.5 * (u_ESC) Incr Effectiveness: u_ESC Final Effectiveness: 0.5 * (u_ESC)
0
Treat & Survive
--- Markov Information Trans Cost: c_incare
#
Surveillance for Early Stage Cancer

V.


Die from CRC
Death from cancer
--- Tracker Modifications {T} Tcancerdeath = 1 {T} Tcancerdeath_clini... = 1 --- Markov Information Trans Cost: c_terminal
Clinical Late Stage Cancer
--- Markov Information Init Cost: 0.5 * (c_LSC) Incr Cost: c_LSC Final Cost: 0.5 * (c_LSC) Init Effectiveness: 0.5 * (u_LSC) Incr Effectiveness: u_LSC Final Effectiveness: 0.5 * (u_LSC)
p_deathCRC_LS
Treat & Survive
Surveillance for Late Stage Cancer
--- Markov Information Trans Cost: c_incare
0
#

VI.


Die from other causes
Death from other causes
p_otherdeaths_Ma...
Surveillance for Early Stage Cancer
--- Markov Information Init Cost: 0.5 * (c_Surveil) Incr Cost: c_Surveil Final Cost: 0.5 * (c_Surveil) Init Effectiveness: 0.5 * (u_SurveilES) Incr Effectiveness: u_SurveilES Final Effectiveness: 0.5 * (u_SurveilES)
0
Survive
#
Years<5
_tunnel<5
Relapse
--- Markov Information Trans Effectiveness: u_dec_relapse
p_relapseCRC_ES
Transit to CLSC
p_PCESC_PCLSC...
Clinical Late Stage Cancer
Remain CESC
#
Clinical Early Stage Cancer
Remain in surveillance
#
Surveillance for Early Stage Cancer
Long-term remission
Healthy
--- Tracker Modifications {T} T_long_remission = 1
#

Appendix D Input variables (baseline values and 95% CI or ±25%), female model

Variables	Baseline	Low	High
Mortality			
Preclinical late-stage cancer	1	0.75	1
Breast: early-stage	0.005	0.00375	0.00625
late-stage	0.085	0.06375	0.10625
Colorectal: early-stage	0.038	0.0285	0.0475
late-stage	0.355	0.26625	0.44375
Esophageal: early-stage	0.54	0.405	0.675
late-stage	0.763	0.57225	0.95375
Liver: early-stage	0.402	0.3015	0.5025
late-stage	0.804	0.603	1
Lung: early-stage	0.251	0.18825	0.31375
late-stage	0.761	0.57075	0.95125
Ovarian: early-stage	0.125	0.09375	0.15625
late-stage	0.447	0.33525	0.55875
Pancreatic: early-stage	0.58	0.435	0.725
late-stage	0.915	0.68625	1
Stomach: early-stage	0.239	0.17925	0.29875
late-stage	0.775	0.58125	0.96875
Transition Probabilities			
from Healthy to Preclinical early-stage cancer[1]			
Breast	0.005055	0.004993	0.005118
Colorectal	6.04E-04	5.83E-04	6.26E-04
Esophageal	2.50E-05	2.10E-05	3.10E-05
Liver	1.37E-04	1.27E-04	1.47E-04
Lung	8.89E-04	8.64E-04	9.16E-04
Ovarian	9.30E-05	8.40E-05	1.02E-04
Pancreatic	1.04E-04	9.60E-05	1.14E-04
Stomach	9.90E-05	9.10E-05	1.09E-04
from Preclinical early-stage to Preclinical late-stage cancer[1]			
Breast	0.002062	0.002008	0.002115
Colorectal	9.19E-04	8.80E-04	9.57E-04
Esophageal	7.00E-05	6.00E-05	8.10E-05
Liver	1.53E-04	1.38E-04	1.68E-04
Lung	0.001849	0.001797	0.001903
Ovarian	3.84E-04	3.61E-04	4.09E-04
Pancreatic	5.17E-04	4.89E-04	5.47E-04
Stomach	1.41E-04	1.26E-04	1.57E-04
Prevalence			

Preclinical early-stage			
Breast	0.108777	0.081583	0.135971
Colorectal	0.005305	0.003979	0.006631
Esophageal	0.000165	0.000124	0.000207
Liver	0.000391	0.000293	0.000489
Lung	0.002613	0.001959	0.003266
Ovarian	0.001051	0.000788	0.001314
Pancreatic	0.00017	0.000128	0.000213
Stomach	0.000627	0.00047	0.000784
Preclinical late stage cancer			
Breast	0.006943	0.005207	0.008679
Colorectal	0.015915	0.011936	0.019894
Esophageal	0.000205	0.000153	0.000256
Liver	0.000519	0.000389	0.000648
Lung	0.007838	0.005878	0.009797
Ovarian	0.005519	0.004139	0.006899
Pancreatic	0.00114	0.000855	0.001425
Stomach	0.001023	0.000767	0.001279
Cancer recurrence			
Early-stage			
Breast	0.09	0.0675	0.1125
Colorectal	0.05	0.0375	0.0625
Esophageal	0.18	0.135	0.225
Liver	0.12	0.09	0.15
Lung	0.3	0.225	0.375
Ovarian	0.2	0.15	0.25
Pancreatic	0.38	0.285	0.475
Stomach	0.426	0.3195	0.5325
Late-stage			
Breast	0.92	0.69	1
Colorectal	0.35	0.2625	0.4375
Esophageal	0.48	0.36	0.6
Liver	0.65	0.4875	0.8125
Lung	0.7	0.525	0.875
Ovarian	0.825	0.61875	1
Pancreatic	0.46	0.345	0.575
Stomach	0.338	0.2535	0.4225
Cost[1]			
Diagnostic work-up			
Breast	666.73	121	1,214
Colorectal	1266.3	912	1,618
Esophageal	287	-283	858
Liver	3761	3,173	4,350
Lung	2661	1,214	3,179

Ovarian	1937	1,502	2,373
Pancreatic	2231	1,667	2,795
Stomach	885	278	1,494
Initial care			
Breast	32195	32,179	32,210
Colorectal	15885	15,876	15,891
Esophageal	55455	55,423	55,489
Liver	25130	25,028	25,234
Lung	28058	28,042	28,075
Ovarian	29292	29,273	29,310
Pancreatic	41539	41,501	41,575
Stomach	38922	38,899	38,945
Surveillance			
Breast	6954	6,946	6,962
Colorectal	8763	8,759	8,767
Esophageal	8767	8,714	8,821
Liver	10093	10,019	10,167
Lung	8126	8,116	8,138
Ovarian	5330	5,316	5,343
Pancreatic	11354	11,313	11,397
Stomach	3458	3,424	3,491
Terminal care			
Breast	40456	40,447	40,465
Colorectal	24171	24,163	24,177
Esophageal	67246	67,209	67,284
Liver	36205	36,157	36,254
Lung	46363	46,354	46,372
Ovarian	45071	45,054	45,089
Pancreatic	69316	69,294	69,338
Stomach	68316	68,293	68,341

[1] 95% confidence intervals are provided for these input values. All other intervals are ±25%.

Appendix E Input variables (baseline values and 95% CI or ±25%), male model

Variables	Baseline	Low	High
Mortality			
Preclinical late-stage cancer	1	0.75	1
Colorectal: early-stage	0.058	0.0435	0.0725
late-stage	0.542	0.4065	0.6775
Esophageal: early-stage	0.54	0.405	0.675
late-stage	0.751	0.56325	0.93875
Liver: early-stage	0.359	0.26925	0.44875
late-stage	0.816	0.612	1
Lung: early-stage	0.296	0.222	0.37
late-stage	0.814	0.6105	1
Pancreatic: early-stage	0.58	0.435	0.725
late-stage	0.915	0.68625	1
Stomach: early-stage	0.226	0.1695	0.2825
late-stage	0.763	0.57225	0.95375
Transition Probabilities			
from Healthy to Preclinical early-stage cancer[1]			
Colorectal	8.52E-04	8.25E-04	8.79E-04
Esophageal	9.40E-05	8.50E-05	1.03E-04
Liver	3.94E-04	3.76E-04	4.12E-04
Lung	8.33E-04	8.07E-04	8.60E-04
Pancreatic	1.31E-04	1.21E-04	1.42E-04
Stomach	1.50E-04	1.38E-04	1.62E-04
from Preclinical early-stage to Preclinical late-stage cancer[1]			
Colorectal	0.001321	0.001274	0.00137
Esophageal	3.32E-04	3.10E-04	3.56E-04
Liver	4.63E-04	4.37E-04	4.93E-04
Lung	0.002347	0.002285	0.002409
Pancreatic	6.92E-04	6.59E-04	7.32E-04
Stomach	3.14E-04	2.91E-04	3.38E-04
Prevalence			
Preclinical early-stage			
Colorectal	0.006428	0.004821	0.008034
Esophageal	0.000653	0.00049	0.000816
Liver	0.001084	0.000813	0.001355
Lung	0.002503	0.001877	0.003128
Pancreatic	0.000217	0.000163	0.000271
Stomach	0.000992	0.000744	0.00124

Preclinical late stage cancer			
Colorectal	0.019283	0.014462	0.024103
Esophageal	0.000807	0.000605	0.001009
Liver	0.001436	0.001077	0.001796
Lung	0.007508	0.005631	0.009384
Pancreatic	0.001453	0.00109	0.001816
Stomach	0.001618	0.001214	0.002023
Cancer recurrence			
Early-stage			
Colorectal	0.05	0.0375	0.0625
Esophageal	0.18	0.135	0.225
Liver	0.12	0.09	0.15
Lung	0.3	0.225	0.375
Pancreatic	0.38	0.285	0.475
Stomach	0.426	0.3195	0.5325
Late-stage			
Colorectal	0.35	0.2625	0.4375
Esophageal	0.48	0.36	0.6
Liver	0.65	0.4875	0.8125
Lung	0.7	0.525	0.875
Pancreatic	0.46	0.345	0.575
Stomach	0.338	0.2535	0.4225
Cost[1]			
Diagnostics			
Colorectal	319.73	- 93	808
Esophageal	1063	592	1,544
Liver	4,395	3,778	5,012
Lung	2383	1,895	2,872
Pancreatic	2,460	1,908	3,010
Stomach	1,102	625	1,580
Initial care			
Colorectal	32,679	32,670	32,690
Esophageal	54,037	54,001	54,075
Liver	27,762	27,723	27,799
Lung	29,132	29,123	29,142
Pancreatic	38,973	38,935	39,010
Stomach	41,912	41,864	41,961
Surveillance			
Colorectal	7,080	7,075	7,086
Esophageal	7,138	7,116	7,162
Liver	15,540	15,518	15,562
Lung	7,193	7,184	7,201
Pancreatic	8,185	8,154	8,215

Stomach	4,328	4,310	4,345
Terminal care			
Colorectal	42,130	42,121	42,140
Esophageal	70,660	70,637	70,682
Liver	39,345	39,315	39,376
Lung	51,013	51,007	51,021
Pancreatic	70,398	70,379	70,417
Stomach	69,820	69,804	69,839

[1] 95% confidence intervals are provided for these input values. All other intervals are ±25%.

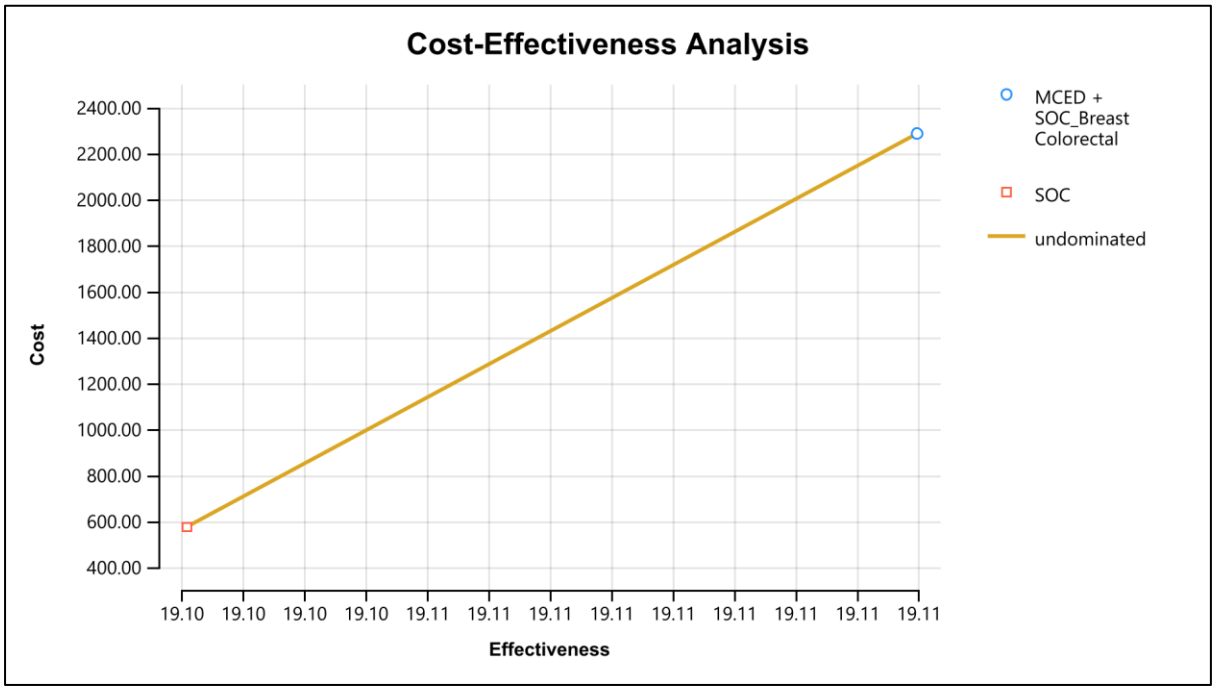
Appendix F Input variables (baseline values and 95% CI or ±25%), both male and female models

Diagnostic Performance			
Sensitivity:	Baseline	Low	High
Fecal Immunochemical Test[1]	0.85	0.6375	1
Screening Mammography	0.76	0.7	0.81
MCED test:			
Esophageal	0.688	0.52	0.79
Liver	0.977	0.88	1
Lung	0.587	0.4	0.68
Ovarian	0.981	0.9	1
Pancreatic	0.72	0.62	0.78
Stomach	0.72	0.6	0.82
Diagnostic tests:			
Diagnostic Mammography[1]	0.878	0.6585	1
Colonoscopy[1]	0.93	0.6975	1
Esophageal	0.909	0.839	0.956
Liver	0.775	0.709	0.829
Lung	0.9007	0.8605	0.9325
Ovarian	0.894	0.769	0.965
Pancreatic	0.95	0.932	0.955
Stomach	0.86	0.77	0.92
Specificity:			
Fecal Immunochemical Test[1]	0.94	0.705	1
Screening Mammography	0.96	0.94	0.97
MCED test	0.9914	0.74355	1
Diagnostic tests:			
Diagnostic Mammography	0.905	0.67875	1
Colonoscopy[1]	1	0.75	1
Esophageal	1	0.75	1
Liver	0.913	0.865	0.945
Lung	1	0.9384	1
Ovarian	0.998	0.998	1
Pancreatic	0.92	0.866	0.957
Stomach	0.93	0.89	0.96
Utility[1]			
Early-stage			
Breast	0.745	0.55875	0.93125
Colorectal	0.845	0.63375	1
Esophageal	0.815	0.61125	1
Liver	0.772	0.579	0.965
Lung	0.835	0.62625	1

Ovarian	0.62	0.465	0.775
Pancreatic	0.772	0.579	0.965
Stomach	0.773	0.57975	0.96625
Late-stage			
Breast	0.3	0.225	0.375
Colorectal	0.4	0.3	0.5
Esophageal	0.405	0.30375	0.50625
Liver	0.404	0.303	0.505
Lung	0.465	0.34875	0.58125
Ovarian	0.45	0.3375	0.5625
Pancreatic	0.404	0.303	0.505
Stomach	0.404	0.303	0.505
Surveillance			
Early-stage	0.8	0.6	1
Late-stage	0.5	0.375	0.625
Healthy	1	0.75	1
Utility decrement	-0.1	-0.075	-0.125
Cost			
Screening			
Fecal Immunochemical test	38.27	29	48
Mammography	314.7	236	393
MCED test	874	656	1,093
FIT + MCED	912.27	684	1,140
Death associated with undiagnosed cancer			
Breast	3338.4	3,084	3,595
Colorectal	3,711.5	3,556	3,868
Esophageal	2,844.4	2,652	3,037
Liver	4,945.2	4,570	5,322
Lung	3,822	3,712	3,933
Ovarian	3,816.8	3,479	4,156
Pancreatic	4,208.1	4,060	4,356
Stomach	3,515.2	3,341	3,691
Uptake[1]			
Diagnostic participation	0.84	0.63	1.0
Screening participation rate	0.75	0.5625	0.9375

[1] ±25% intervals are provided for these input values. All other intervals are 95% confidence intervals.

Appendix G Cost-effectiveness graph for male model



Appendix H Cost-effectiveness graph for female model