

CADTH Horizon Scan

Emerging Multi- Cancer Early Detection Technologies

Authors: Sinwan Basharat, Jennifer Horton

ISSN: 2563-6596

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Table of Contents

Key Messages	6
Multi-Cancer Early Detection Technologies Could Transform Cancer Screening	6
How It Works	6
Who Might Benefit?	8
Availability and Cost	9
What Is the Evidence?	9
Galleri Test Performance	9
CancerSEEK Test Performance	10
Issues to Consider	11
Real-World Measures of Test Performance.....	11
Complex Benefits and Harms of Screening.....	11
Disruptiveness to Health Systems	12
Related Developments	13
Looking Ahead	13
References	14

List of Tables

Table 1: Ongoing Clinical Studies With the Galleri Test (GRAIL Inc.)..... 10

List of Figures

Figure 1: Circulating Tumour DNA in the Bloodstream May Have a Distinct Molecular Signature That Could Indicate the Presence of Cancer 7

Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies; these technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada. This report is not an endorsement or assessment of any test or technology.
- This Horizon Scan summarizes the available information regarding the emerging technology of liquid biopsy–based, multi-cancer early detection tests for cancer screening. This Horizon Scan focuses specifically on the [Galleri](#) (GRAIL Inc.) and [CancerSEEK](#) (Exact Sciences) tests, which are further along in the development cycle and are being assessed in different international clinical studies.
- Multi-cancer early detection technologies aim to provide a new approach to complement traditional cancer screening programs. These tests examine genetic signals within blood samples with next-generation sequencing and computational algorithms to assess the presence and type of different cancers. Research to date has focused on describing results from training and validation studies that have provided initial estimates of test performance and modelling studies estimating the potential impact on cancer incidence.
- This Horizon Scan also highlights some issues for health care decision-makers to consider about the technology relating to real-world test performance, the potential benefits and harms of screening with multi-cancer early detection tests, and the disruptiveness to health systems they could pose. Ongoing review of clinical trials and the emerging evidence base can help inform health systems in Canada about their potential role within cancer-control initiatives.

Multi-Cancer Early Detection Technologies Could Transform Cancer Screening

Emerging health technologies that use liquid biopsies for the early detection of cancer may offer a new approach to complement traditional cancer screening programs. These tests may help reduce some of the barriers associated with standard screening tests and expand the scope of screening beyond individual cancers.¹ Two specific technologies, namely the [Galleri Test](#) (GRAIL Inc.)² and [CancerSEEK](#) (Exact Sciences),³ are emerging multi-cancer early detection (also termed pan-cancer) tests that use next-generation sequencing, computational algorithms with artificial intelligence, and molecular analysis of blood samples to identify early signals of different cancers. Within the wider context of emerging molecular and genomic testing technologies, these multi-cancer early detection tests could be disruptive to the Canadian health care landscape because they could transform the existing model of cancer screening, in which 1 screening test detects for a single cancer type.

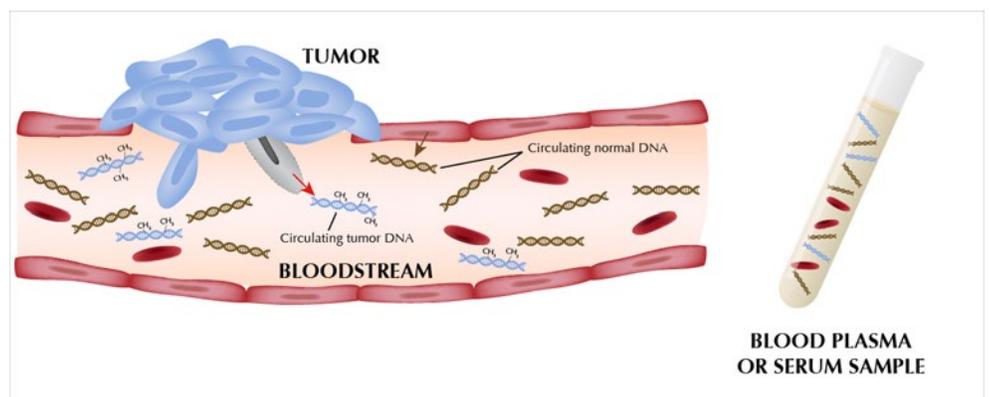
How It Works

Unlike traditional screening tests that examine individual tissues or organs, multi-cancer early detection tests examine molecular signals within blood that could indicate the presence of different cancer types.⁴ Specifically, these tests examine cell-free DNA (cfDNA) which is

released by cells from across the body into the bloodstream and other bodily fluids. Analysis of cfDNA is an emerging area of interest for cancer screening, diagnosis, and management because many cancerous cells are known to release elevated levels of cfDNA and may provide an accessible and non-invasive approach to obtain critical information about the cancer.^{5,6} Among people with cancer, an estimated 0.5% of cfDNA may be from the tumour; however, the amount of DNA shed can vary based on the size of the tumour and different pathological features of the cancer.^{7,8} Although the relative proportion of cfDNA in blood originating from the cancer (called *circulating tumour* [ctDNA]) is relatively small compared with DNA from other tissues and cells of the body, ctDNA can have a distinct molecular signature compared with DNA shed from healthy cells.⁴ These differences may include mutations, copy number variations, and epigenetic changes (i.e., changes in DNA that affect how genes are read) that could serve as biomarkers for ctDNA.^{7,9} Multi-cancer early detection tests analyze DNA to identify mutations and/or other molecular markers that could indicate the presence of cancer (Figure 1). In addition to identifying ctDNA from the pool of cfDNA, the tests also aim to obtain information about the cancer's type, origin, and other characteristics that could be relevant for treatments or prognosis. Both the Galleri and CancerSEEK tests operate based on this biological underpinning, although by analyzing different molecular markers and using distinct computational methods.

The Galleri Test uses DNA sequencing that specifically examines more than 100,000 genomic regions that can be differentially methylated (a methyl chemical structure attached to DNA).¹⁰ Methylation is a form of an epigenetic modification that can affect how genes are read, and it is known to play an important role in the development and progression of many cancers.^{9,11} Among different cancers and cell types, certain genomic regions can be associated with either increased or decreased methylation and serve as biomarkers for detecting cancer, informing treatment decisions, monitoring residual disease activity after treatment, and providing an early signal for recurrence.¹¹ The key benefits of examining methylation patterns is that it offers a wide range of potential regions to analyze compared with a limited set of mutations. Some of these targets may be detectable at early stages of the cancer and may provide a reliable signal despite the relatively small proportion of ctDNA in the blood.^{7,10,12} Ongoing development and validation of analysis algorithms aim to continually improve test performance.¹³

Figure 1: Circulating Tumour DNA in the Bloodstream May Have a Distinct Molecular Signature That Could Indicate the Presence of Cancer



Source: Created by Claire Davis; reprinted with permission from Huntsman Cancer Institute at the University of Utah.

The CancerSEEK test takes an alternative approach by examining a fewer number of genomic regions and looking for specific mutations, but it has an additional analytical component that examines proteins associated with certain cancers.¹⁴ Increased levels of certain proteins may provide an early indication of some cancers as the proteins may be linked with abnormal cell or tissue growth.¹⁵ Initial calibrations of the test aimed to optimize the number of genomic regions and proteins that could help identify early-stage tumours in 8 common cancer types with high accuracy but not increase the risk of producing false-positive results. Based on the calibration, the test assays the presence of mutations within 16 genes (more than 1,900 distinct genomic positions) and the levels of 8 proteins that could help identify early-stage tumours.¹⁴ Machine-learning algorithms are also used to improve the test's detection capabilities but are not necessary for conducting the analysis.¹⁶

Who Might Benefit?

Cancers are the leading cause of mortality, attributing to more than 80,000 deaths in Canada each year.¹⁷ Early detection of cancer is a strategic health priority in Canada and internationally, and can occur through either improving and expanding screening (i.e., testing people who do not show symptoms) or improving diagnostic pathways.^{18,19} Although guidelines from the Canadian Task Force on Preventive Health Care recommend that standard screening be offered for breast, cervical, colorectal, lung, prostate, and ovarian cancers, most provincial and territorial jurisdictions across Canada have standard screening programs limited to breast,²⁰ cervical,²¹ and colorectal²² cancers.

Multi-cancer early detection tests, if shown to be accurate, reliable, and feasible, may help complement existing screening programs and potentially diagnose more cases of cancer.²³ They may also enable early detection of cancer types for which there are no screening tests available. For example, pancreatic cancer does not have a screening test, yet is among the 5 leading causes of cancer-related deaths in Canada.²⁴ More than half of cancer deaths are attributed to cancers that do not have screening tests.^{24,25} Individual screening tests for each of these cancers would likely not be feasible at a population level given their relatively lower incidence, but multi-cancer early detection technologies may be more feasible. If earlier detection is associated with better outcomes and particularly reduced mortality, potentially thousands of people in Canada may benefit each year.^{1,7,26}

People can also face different barriers with traditional screening related to screening access, health education, and discomfort with certain tests (pain, fear of pain, or general unease).²⁷⁻²⁹ These barriers can often intersect with social determinants of health and can reduce the uptake of well-established screening programs.²⁷⁻³² Because multi-cancer early detection technologies rely on blood samples, their simplicity may offer several advantages for screening that could potentially improve accessibility, reduce test discomfort, and reach a greater number of people when complemented with traditional screening tests.²⁵ A qualitative study assessing the preferences of people diagnosed with cancer reported that a majority of people (90%) would prefer liquid biopsy testing compared with tissue biopsies, if given a choice.³³ However, improving cancer screening participation, regardless of specific tests, requires appropriate engagement, considerations for equity, endorsement from health care professionals, and other approaches to help encourage uptake.^{34,35}

Availability and Cost

Neither the Galleri or CancerSEEK tests are authorized for routine clinical use in Canada or the US, but both tests received the FDA's Breakthrough Device Designation in 2019, signalling an expedited process for authorization if either manufacturer submits an application.^{7,36} As of June 2021, the Galleri Test is available with a prescription as a clinical laboratory-based test (limited to the remit of complex testing) in the US at a cost of US\$949.^{2,25} People in England may receive the test as part of a national clinical trial enrolling eligible participants in 9 areas of the country through their general family practice.³⁷

What Is the Evidence?

Assessing screening tests and screening programs is a complex process that includes assessing test sensitivity (the ability to correctly identify people with the condition), specificity (the ability to correctly identify people without the condition), predictive values (positive predictive value refers to the likelihood or odds of a person with a positive result actually having the condition), and implications of how test results may affect individuals and health system outcomes.^{38,39} This Horizon Scan did not aim to review the breadth of evidence relating to the benefits or harms of multi-cancer early detection tests nor critically appraise the studies summarized. Rather, the Horizon Scan provides a summary of some of the published studies about these emerging tests. Note that published studies to date have been largely funded and conducted by test manufacturers.

Galleri Test Performance

The Galleri Test is being studied as part of the [Circulating Cell-free Genome Atlas \(CCGA\)](#)⁴⁰ study, a prospective multi-site, non-randomized study with 15,254 participants. The study includes participants both with and without a clinical diagnosis of cancer who are followed for up to 5 years. Blood samples from participants are analyzed with the Galleri Test along with additional tests as part of routine cancer care or other screening programs to train computation algorithms, validate the tests, and assess test performance. Various findings from substudies have been published while additional analyses are ongoing.

Following the initial discovery stage, a training and validation study analyzed test performance using blood samples of participants with and without cancer.¹² The study was double-blinded and included samples from more than 50 different cancer types of which 12 were high-signal cancer types (pre-specified from an earlier substudy to provide sufficient signal). For the 12 high-signal cancer types, test sensitivity was reported to be 76.4% for stage I to stage IV.¹² However, sensitivity varied based on cancer stage, with the highest sensitivity reported for stage IV (92%) and the lowest for stage I (39%) samples.¹² Sensitivity for all 50 cancer types was reported to be lower: 54.9% for stage I to stage IV.¹² Specificity was reported to be 99.3% with a less than 1% false-positive rate.¹²

A subsequent study further refining the analytical models of the Galleri Test reported similar rates of sensitivity and specificity, but also extrapolated results to estimate that the positive predictive value may be 44.4% for people between the ages 50 years and 79 years of age living in the US.¹³ However, the authors of the study cautioned that more accurate measures of positive predictive values are being assessed in ongoing studies.¹³ Among true positive

cases of cancer, the study reported that the test was able to correctly predict the origin of cancer for 88.7% of samples; that is, it was able to detect not only the presence of cancer, but also the cancer type for 88.7% of samples.¹³

Ongoing Studies

Additional studies for the Galleri Test are also under way, some of which are presented in Table 1. These studies are continuing to validate test performance in different populations, assess safety, examine the role the test may play within a health system’s routine screening program, while collecting more rigorous evidence in a randomized trial.

CancerSEEK Test Performance

The CancerSEEK test has been assessed in a proof of concept study¹⁴ and in a prospective intervention study.¹⁶ The first study used the test on blood samples from 1,005 people with a new diagnosis of 8 common cancer types (stage I to stage III only) who had not yet received chemotherapy and a comparison group of 812 people with no known history of cancer or other listed conditions.¹⁴ The study reported a median test sensitivity for the 8 cancer types to be 70%, with considerable variation between different cancer types and stages.¹⁴ The highest sensitivity was reported for ovarian cancers (98%) and the lowest was reported for breast cancer (33%).¹⁴ Specificity was reported to be greater than 99%.¹⁴ The authors noted that the true test performance of CancerSEEK is likely to be lower because in a population setting of cancer screening there would likely be fewer people with advanced disease as in the study sample.¹⁴

Table 1: Ongoing Clinical Studies With the Galleri Test (GRAIL Inc.)

Name and location	Study type	Participants	Aims
SUMMIT Study: A Cancer Screening Study (SUMMIT) NCT03934866 UK	Prospective, cohort April 2019 to August 2030	People 55 to 77 years of age with high risk of lung cancer N = 130,000 participants (enrolled)	<ul style="list-style-type: none"> • Validate multi-cancer early detection test performance • Assess the performance of low-dose computed tomography screening.
PATHFINDER 2: A Multi-Cancer Early Detection Study NCT05155605 US	Prospective, cohort December 2021 to September 2025	People 50 years of age or older N = 10,000 (targeted)	<ul style="list-style-type: none"> • Assess safety and performance of multi-cancer early detection among people eligible for routine cancer screening as per guidelines.
REFLECTION: A Clinical Practice Learning Program for Galleri NCT05205967 US	Prospective, cohort August 2021 to August 2028	People 18 years of age or older N = 35,000 (targeted)	<ul style="list-style-type: none"> • Understand the performance of the test in clinical settings and the impact on patients and health care providers, including health care utilization, patient and provider satisfaction and acceptance, and adherence to routine cancer screening tests.
NHS-Galleri Trial ISRCTN91431511 UK	Randomized controlled trial July 2021 to February 2026	People 50 to 77 years of age N = 140,000 (1:1 control-intervention, targeted)	<ul style="list-style-type: none"> • Assess whether the multi-cancer early detection test can identify cancer earlier when combined with routine screening within the NHS’s system of care.

The subsequent prospective intervention study aimed to assess the test in a setting and population that may be more similar to routine cancer screening. The study enrolled women between ages 65 years and 75 years, with no history of cancer, who were likely to undergo standard screening.¹⁶ All participants were tested at baseline, and individuals who had a positive signal received a second confirmation test. Following clinical review, participants with a positive confirmation test were invited to take a full-body diagnostic PET-CT scan to identify if they may have cancer.

In the study, 9,911 people took the first blood test, of whom 127 were evaluated by imaging after a second confirmation test and clinical review.¹⁶ The test helped identify 26 people with cancer; an additional 70 people were identified to have cancer through other diagnostic or routine screening tests during the study period (people did not overlap in either group).¹⁶ Sensitivity for the test (based on 2 samples: baseline and confirmation) was reported to be 27.1% and specificity was reported to be 98.9% for the 8 cancer types assessed by CancerSEEK.¹⁶ The study helped show that, in routine care, the tests may be able to identify additional cases of cancer that may not have been identified through standard screening alone. At least 1 prospective, cohort study (called [ASCEND](#)⁴¹) is under way with a newer version of the CancerSEEK test, and its parent company is continuing to develop their liquid biopsy-based, multi-cancer early detection technology.⁴²

Issues to Consider

Real-World Measures of Test Performance

Although measures of test sensitivity in observational studies provide an estimate about test performance, in real-world application of screening at a population level, positive predictive values (impacted by the prevalence of a condition) are a key measure that informs how well a positive test result can predict the likelihood of cancer.^{26,38} As research is within early stages, and estimates of positive predictive values may not be reliable, it is important to be cautious because low positive predictive values could lead to an increase in unnecessary follow-up tests and may not be suitable for general screening use.²⁶ Furthermore, a limitation of tests that rely on ctDNA is that there may not be enough ctDNA to produce a strong detectable signal at early stages of many cancers, hence why both tests have reported varying test sensitivities at different stages of cancer.^{7,8,43} The reported sensitivity of these emerging technologies are lower than established screening tests.¹ Authors of studies for both the Galleri and CancerSEEK tests have also acknowledged that sensitivity and specificity rates may be further reduced in settings where the majority of people are asymptomatic or not likely to have any clinical concerns.^{13,16}

Complex Benefits and Harms of Screening

Screening is a complex health intervention that needs careful consideration of the breadth of potential benefits and harms for individuals and health systems.³⁸ In particular, for multi-cancer early detection technologies that examine the presence of multiple cancers (which are all unique conditions), a detailed review of these technologies requires a complex analysis of the benefits and harms for those multiple conditions.⁴⁴

One quantitative framework for assessing these technologies has proposed a model that incorporates the numbers of cancers detected along with the rates of follow-up testing, impact on clinical outcomes, and impact on mortality.⁴⁴ These metrics are important because there may be an assumption that early detection will invariably lead to improved clinical outcomes.¹⁰ However, unless early detection is coupled with effective therapies or improved disease management, there is uncertainty about the additional benefit early detection can provide for all cancers.⁴⁴⁻⁴⁶ The first randomized controlled trial of the Galleri Test will help to better assess the longer-term clinical outcomes of screening in a real-world setting.⁴⁷ Some researchers have advocated for the NHS-Galleri trial to assess the effect of multi-cancer early detection on all-cause mortality and that may be a more informative measure for clinical effectiveness.^{8,48}

Another modelling study estimated that if multi-cancer early detection tests were made available in the US and the UK to people between the ages of 50 years and 79 years, the tests may help increase the rate of cancer detection by more than 50% when accompanied with routine screening programs.²³ However, as with any screening program, it could lead to additional people undergoing unnecessary follow-up testing, overdiagnosis (detecting cancers that would not lead to harm), and psychological stress and anxiety about whether a person has cancer.^{7,26,45} Although existing research studies report the rates of false-positive results for the Galleri and CancerSEEK tests to be less than 1% (which is lower than other routine screening tests), at a population level for widely used tests, this rate could translate to thousands of people undergoing unnecessary follow-up tests.^{1,23} For routine cancer screening programs, there is mixed evidence about how false-positive results influence people's participation in future screenings, which is also important to consider for multi-cancer early detection technologies.^{49,50}

Disruptiveness to Health Systems

Multi-cancer early detection technologies operate within a different paradigm compared with the traditional model of screening a single cancer with a single test. Instead, they use a model of 1 test for multiple cancers and, if implemented, would require a substantially different approach to cancer screening because multiple health professionals would need to review the results and determine the appropriate follow-up investigations.¹ If more cancer cases are detected, there are uncertainties and concerns about whether health systems would be able to cope with the need for additional tests, such as imaging and biopsies, to confirm diagnoses.⁴⁶ Moreover, because the prevalence of individual cancers among a population of average-risk people is relatively low, health systems would need to consider the most-appropriate eligibility criteria and testing frequency to minimize harms of testing.⁴⁶ Finally, these genomic technologies rely on computational algorithms that use machine learning and artificial intelligence to determine the likelihood of cancer; therefore, ensuring that training and validation datasets are representative of diverse population groups is critical for health equity.⁵¹ Underrepresentation of certain groups of people is a known barrier within genomic medicine, and genetic tests intended for cancer screening should be assessed for their applicability to diverse groups, otherwise it could exacerbate disparities in health services.⁵²

Related Developments

The Galleri and CancerSEEK tests are further along the development cycle and have been assessed in more studies, but other liquid biopsy–based multi-cancer early detection technologies are also in development. Some of the identified experimental tests include [PanSeer](#) (Singlera Genomics Inc., US), [CancerRadar](#) (EarlyDiagnostics, US), and [Adela](#) (Adela Inc., US and Canada). All 3 of these tests use some form of methylation-based analysis and machine-learning algorithms to identify signals in blood for multiple cancers.^{53,54}

Looking Ahead

Multi-cancer early detection technologies represent an emerging health technology that could disrupt traditional models of cancer screening. By potentially using a single, non-invasive, and relatively convenient blood test to assess the presence of multiple types of cancer, it may be possible to detect more cancers at an earlier stage when accompanied with established screening programs. However, the technology is in its initial stages of development, and the majority of research, largely funded by test developers, has described results of training and validation studies. A randomized controlled trial being conducted by the NHS in England in partnership with 1 test developer (GRAIL Inc.) will help inform the clinical effectiveness of the test to detect cancer in a real-world setting. It will also help reveal if and how the test could be used alongside routine screening programs, while taking into consideration issues related to feasibility, acceptability, and health system impact. Engaging people likely to undergo liquid biopsy–based screening, patients, caregivers, and people facing barriers to existing screening programs will be critical to understand issues related to implementation and health equity. Overall, screening is a complex health intervention that requires a detailed analysis of potential harms and benefits. Should health systems in Canada explore the role of the technology within cancer-control initiatives, a cautious approach that examines the full range of impacts on individuals and health systems and would be required.

References

- Hackshaw A, Clarke CA, Hartman AR. New genomic technologies for multi-cancer early detection: Rethinking the scope of cancer screening. *Cancer Cell*. 2022;40(2):109-113. [PubMed](#)
- The Galleri test. 2022; <https://www.galleri.com/the-galleri-test/>. Accessed Feb 24, 2022.
- Multi-Cancer Early Detection (MCED). <https://www.exactsciences.com/Pipeline-and-Data/Multi-Cancer-Early-Detection>. Accessed Feb 24, 2022.
- Bronkhorst AJ, Ungerer V, Holdenrieder S. Early detection of cancer using circulating tumor DNA: biological, physiological and analytical considerations. *Crit Rev Clin Lab Sci*. 2019;1-17. [PubMed](#)
- Yan YY, Guo QR, Wang FH, et al. Cell-Free DNA: Hope and Potential Application in Cancer. *Front Cell Dev Biol*. 2021;9:639233. [PubMed](#)
- Cisneros-Villanueva M, Hidalgo-Perez L, Rios-Romero M, et al. Cell-free DNA analysis in current cancer clinical trials: a review. *Br J Cancer*. 2022;126(3):391-400. [PubMed](#)
- Duffy MJ, Diamandis EP, Crown J. Circulating tumor DNA (ctDNA) as a pan-cancer screening test: is it finally on the horizon? *Clin Chem Lab Med*. 2021;59(8):1353-1361. [PubMed](#)
- Pons-Belda OD, Fernandez-Uriarte A, Diamandis EP. Can Circulating Tumor DNA Support a Successful Screening Test for Early Cancer Detection? The Grail Paradigm. *Diagnostics (Basel)*. 2021;11(12):23. [PubMed](#)
- Lianidou E. Detection and relevance of epigenetic markers on ctDNA: recent advances and future outlook. *Mol Oncol*. 2021;15(6):1683-1700. [PubMed](#)
- Ofman JJ, Hall MP, Aravanis AM. GRAIL and the quest for earlier multi-cancer detection. *Nature Sponsor Feature*. 2020. <https://www.nature.com/articles/d42473-020-00079-y>. Accessed Feb 24, 2022.
- Locke WJ, Guanzone D, Ma C, et al. DNA Methylation Cancer Biomarkers: Translation to the Clinic. *Front Genet*. 2019;10:1150. [PubMed](#)
- Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV, Consortium C. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol*. 2020;31(6):745-759. [PubMed](#)
- Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32(9):1167-1177. [PubMed](#)
- Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018;359(6378):926-930. [PubMed](#)
- Landegren U, Hammond M. Cancer diagnostics based on plasma protein biomarkers: hard times but great expectations. *Mol Oncol*. 2021;15(6):1715-1726. [PubMed](#)
- Lennon AM, Buchanan AH, Kinde I, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science*. 2020;369(6499):03.
- Statistics Canada. Leading causes of death, total population, by age group. 2022; <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401>. Accessed Feb 24, 2022.
- Crosby D, Lyons N, Greenwood E, et al. A roadmap for the early detection and diagnosis of cancer. *The Lancet Oncology*. 2020;21(11):1397-1399. [PubMed](#)
- Canadian Strategy for Cancer Control (2019-2029). Toronto (ON): Canadian Partnership Against Cancer; 2019: <https://www.partnershipagainstcancer.ca/cancer-strategy/>. Accessed Feb 24, 2022.
- Breast Screening in Canada: 2019/2020 Environmental Scan. Toronto (ON): Canadian Partnership Against Cancer; 2021: <https://s22457.pcdn.co/wp-content/uploads/2021/01/breast-cancer-screening-environmental-scan-2019-2020-Jan132021-EN.pdf>. Accessed Feb 24, 2022.
- Cervical Screening in Canada: 2019/2020 Environmental Scan. Toronto (ON): Canadian Partnership Against Cancer; 2020: <https://www.partnershipagainstcancer.ca/topics/cervical-cancer-screening-scan-2019-2020/>. Accessed Feb 3, 2022.
- Colorectal Screening in Canada: 2019/2020 Environmental Scan. Toronto (ON): Canadian Partnership Against Cancer; 2020: <https://s22457.pcdn.co/wp-content/uploads/2021/01/colorectal-cancer-screening-environmental-scan-2019-2020-Jan132021-EN.pdf>. Accessed Feb 24, 2022.
- Hackshaw A, Cohen SS, Reichert H, Kansal AR, Chung KC, Ofman JJ. Estimating the population health impact of a multi-cancer early detection genomic blood test to complement existing screening in the US and UK. *Br J Cancer*. 2021;125(10):1432-1442. [PubMed](#)
- Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada. Canadian Cancer Statistics 2021. Toronto (ON): Canadian Cancer Society; 2021: <https://cdn.cancer.ca/-/media/files/research/cancer-statistics/2021-statistics/2021-pdf-en-final.pdf>. Accessed Feb 24, 2022.
- Beer TM. Examining developments in multicancer early detection: highlights of new clinical data from recent conferences. *Am J Manag Care*. 2021;27(19 Suppl):S347-S355. [PubMed](#)
- Fiala C, Diamandis EP. Can a Broad Molecular Screen Based on Circulating Tumor DNA Aid in Early Cancer Detection? *J Appl Lab Med*. 2020;5(6):1372-1377. [PubMed](#)
- Gabel P, Larsen MB, Nielsen PB, Svendstrup DB, Andersen B. Satisfaction, discomfort, obligations, and concerns in population-based breast cancer screening: cross-sectional study in a Danish population. *BMC Health Serv Res*. 2017;17(1):489. [PubMed](#)
- Wang H, Roy S, Kim J, Farazi PA, Siahpush M, Su D. Barriers of colorectal cancer screening in rural USA: a systematic review. *Rural Remote Health*. 2019;19(3):5181. [PubMed](#)

29. Equity-Focused Interventions to Increase Colorectal Cancer Screening: Program Pack. Toronto, ON: Canadian partnership Against Cancer; 2021: <https://www.partnershipagainstcancer.ca/topics/equity-colorectal-cancer-screening/>. Accessed Feb 24, 2022.
30. Lofters AK, Schuler A, Slater M, et al. Using self-reported data on the social determinants of health in primary care to identify cancer screening disparities: opportunities and challenges. *BMC Fam Pract*. 2017;18(1):31. [PubMed](#)
31. Sayani A, Vahabi M, O'Brien MA, et al. Advancing health equity in cancer care: The lived experiences of poverty and access to lung cancer screening. *PLoS One*. 2021;16(5):e0251264. [PubMed](#)
32. Ferreira CS, Rodrigues J, Moreira S, Ribeiro F, Longatto-Filho A. Breast cancer screening adherence rates and barriers of implementation in ethnic, cultural and religious minorities: A systematic review. *Mol Clin Oncol*. 2021;15(1):139. [PubMed](#)
33. Lee MJ, Hueniken K, Kuehne N, et al. Cancer Patient-Reported Preferences and Knowledge for Liquid Biopsies and Blood Biomarkers at a Comprehensive Cancer Center. *Cancer Manag Res*. 2020;12:1163-1173. [PubMed](#)
34. Feldman J, Davie S, Kiran T. Measuring and improving cervical, breast, and colorectal cancer screening rates in a multi-site urban practice in Toronto, Canada. *BMJ Qual Improv Rep*. 2017;6(1). [PubMed](#)
35. Duffy SW, Myles JP, Maroni R, Mohammad A. Rapid review of evaluation of interventions to improve participation in cancer screening services. *J Med Screen*. 2017;24(3):127-145. [PubMed](#)
36. Medical Device Network. Grail gets FDA breakthrough designation for multi-cancer test. 2019; <https://www.medicaldevice-network.com/news/grail-test-fda-breakthrough-status/>. Accessed Feb 15, 2022.
37. NHS. NHS launches world first trial for new cancer test. 2021; <https://www.england.nhs.uk/2021/09/nhs-launches-world-first-trial-for-new-cancer-test/>. Accessed Feb 24, 2022.
38. WHO Regional Office for Europe. Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm. 2020. <https://www.euro.who.int/en/publications/abstracts/screening-programmes-a-short-guide-increase-effectiveness-maximize-benefits-and-minimize-harm-2020>. Accessed Feb 24, 2022.
39. Crandon S. Sensitivity and specificity explained: A Cochrane UK Trainees blog. 2019; <https://uk.cochrane.org/news/sensitivity-and-specificity-explained-cochrane-uk-trainees-blog>. Accessed March 20, 2022.
40. Grail LLC. NCT02889978: The Circulating Cell-free Genome Atlas Study (CCGA) *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2021: <https://clinicaltrials.gov/ct2/show/NCT02889978>. Accessed Feb 24, 2022.
41. Thrive Earlier Detection Corp. NCT04213326: Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing (ASCEND). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2021: <https://clinicaltrials.gov/ct2/show/study/NCT04213326>. Accessed March 10, 2022.
42. Exact Sciences. *Making earlier cancer detection a routine part of medical care*. 2022. https://s22.q4cdn.com/877809405/files/doc_presentations/2022/02/Latest-2022-corp-presentation.pdf.
43. Fiala C, Diamandis EP. A multi-cancer detection test: focus on the positive predictive value. *Ann Oncol*. 2020;31(9):1267-1268. [PubMed](#)
44. Jiao B, Gulati R, Katki HA, Castle PE, Etzioni R. A Quantitative Framework to Study Potential Benefits and Harms of Multi-Cancer Early Detection Testing. *Cancer Epidemiol Biomarkers Prev*. 2022;31(1):38-44. [PubMed](#)
45. Olivier T, Gill J, Prasad V. Multi-Cancer Screening Tests: Communicating About Risks Should be Prioritized. *Am J Med*. 2021;14:14. [PubMed](#)
46. Putcha G, Gutierrez A, Skates S. Multicancer Screening: One Size Does Not Fit All. *JCO precis*. 2021;5:574-576.
47. Hackshaw A, Berg CD. An efficient randomised trial design for multi-cancer screening blood tests: nested enhanced mortality outcomes of screening trial. *Lancet Oncol*. 2021;22(10):1360-1362. [PubMed](#)
48. Carr D, Kent DM, Welch HG. All-cause mortality as the primary endpoint for the GRAIL/National Health Service England multi-cancer screening trial. *J Med Screen*. 2021;9691413211059638. [PubMed](#)
49. Shen Y, Winget M, Yuan Y. The impact of false positive breast cancer screening mammograms on screening retention: A retrospective population cohort study in Alberta, Canada. *Can J Public Health*. 2018;108(5-6):e539-e545. [PubMed](#)
50. Taksler GB, Keating NL, Rothberg MB. Implications of false-positive results for future cancer screenings. *Cancer*. 2018;124(11):2390-2398. [PubMed](#)
51. Jooma S, Hahn MJ, Hindorff LA, Bonham VL. Defining and Achieving Health Equity in Genomic Medicine. *Ethn Dis*. 2019;29(Suppl 1):173-178. [PubMed](#)
52. Cooke Bailey JN, Bush WS, Crawford DC. Editorial: The Importance of Diversity in Precision Medicine Research. *Front Genet*. 2020;11:875. [PubMed](#)
53. Chen X, Gole J, Gore A, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nat Commun*. 2020;11(1):3475. [PubMed](#)
54. Burgener JM, Zou J, Zhao Z, et al. Tumor-Naive Multimodal Profiling of Circulating Tumor DNA in Head and Neck Squamous Cell Carcinoma. *Clin Cancer Res*. 2021;27(15):4230-4244. [PubMed](#)