

<b>2.04.158</b>		<b>Multicancer Early Detection Testing</b>	
<b>Original Policy Date:</b>	September 1, 2023	<b>Effective Date:</b>	September 1, 2023
<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 12

## Policy Statement

- i. The use of multicancer early detection (MCED) tests (e.g., Galleri) is considered **investigational** for cancer screening.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

The review will focus on MCED tests that are available in the US. The Galleri test is the only commercially available MCED test in the US at this time. This review will not include tests that screen for only 1 cancer (e.g., colon).

While advocates of the test might claim the simplicity of a blood test will improve compliance over existing cancer screening tests and offer screening for cancers that currently do not have recognized screening tests available, no evidence exists to support these claims or to estimate the potential harms of false positives.

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

## Description

Many cancers appear to have a better prognosis if diagnosed early in their natural history. This has led to efforts to detect preclinical cancers in asymptomatic individuals through screening. Cancer screening tests such as 'liquid biopsies' that are minimally invasive and can simultaneously detect multiple types of cancer have been called multicancer early detection (MCED) tests.

## Related Policies

- Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance
- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- Serologic Genetic and Molecular Screening for Colorectal Cancer
- Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

No MCED tests have been approved or cleared by the U.S. Food and Drug Administration (FDA). GRAIL, Inc. announced in 2019 that its MCED test (Galleri®) had been granted breakthrough device designation by the FDA.<sup>3</sup>

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Galleri is available under the auspices of the Clinical Laboratory Improvement Amendments.

Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

## Rationale

### Background

Cancer is the second leading cause of death in the US following heart disease. Cancer is the cause of death in 1 of every 5 deaths in the US. In the US, more than 1.7 million new cases of cancer were reported in 2019, and almost 600,000 people died of cancer.<sup>1</sup>

Many cancers appear to have a better prognosis if diagnosed early in their natural history. This has led to efforts to detect preclinical cancers in asymptomatic persons through screening. However, screening tests have associated benefits and harms that must be considered when evaluating whether a test should be used in a population.

Early detection of cancer has 2 components: early diagnosis and screening. Early diagnosis is the early identification of cancer in *symptomatic* individuals with the aim of reducing the proportion of individuals diagnosed at a late stage. Screening is the identification of preclinical cancer or precursor lesions in apparently healthy, *asymptomatic* populations by tests that can be applied rapidly and widely in the target population.<sup>2</sup> This review focuses on tests for screening indications.

Cancer screening tests such as 'liquid biopsies' that are minimally invasive and can simultaneously detect multiple types of cancer have been called multicancer early detection (MCED) tests.

### Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA

(Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

## Multicancer Early Detection Screening of Asymptomatic Populations

### Clinical Context and Test Purpose

The purpose of multicancer early detection (MCED) testing in individuals being screened for cancer is to inform a decision about whether to refer the individual for further screening or diagnostic testing. Different cancers are vastly heterogeneous in their natural histories, invasiveness of diagnostic work-up, prognoses, and responses to treatment, and therefore have distinct screening recommendations. Population-based cancer screening is currently recommended for a few select cancers.

To evaluate an MCED test, an explication of how the test would be integrated into current screening and diagnostic pathways is needed. Positive screening tests set off a chain of cascading events that can lead to benefit or harm. This cascade varies depending on whether the MCED is positioned as a triage, replacement, or add-on<sup>4</sup> for existing screening and diagnostic tools, periodicity of the MCED test, as well as invasiveness and effectiveness of diagnostic work-up and treatments.

To demonstrate that a screening test is useful:

1. A screening test should find *clinically significant* disease earlier in the natural history of the disease;
2. An intervention must be available to alter the natural history of the disease in a manner that is expected to improve the net health outcome.

The following PICO was used to select literature to inform this review.

### **Populations**

The relevant population of interest are individuals who are being screened for cancer. Screening is the identification of pre-clinical cancer or precursor lesions in apparently healthy, asymptomatic populations.

A person's risk of developing cancer depends on risk factors related to genetics, demographics, environmental or other exposures and the interaction between these risk factors. Several risk factors are associated with an increased risk of cancer in general (e.g., older age, family history, smoking, diet, obesity, physical activity, exposure to certain viruses, hormones or radiation).<sup>5</sup> Additional risk factors are specific to cancer type (e.g., sunlight exposure and skin cancer, radon exposure and lung cancer, occupational chemical exposures and respiratory cancers, viral exposures (e.g., cervical or liver cancer)).

Cancer survival rates are lower for Black individuals than for White individuals for almost every cancer type. The survival disparity is partially explained by the later stage at diagnosis for Black individuals; however, Black individuals also have lower survival within specific stages for most cancers<sup>6</sup>.

The National Cancer Institute convened a panel of experts in 2021 to discuss initial design concepts for trials evaluating MCED assays for cancer screening.<sup>7</sup> The panel suggested that trials should target the general population in the age range of 50 to 75 years.

### **Interventions**

The tests being considered are MCED tests. This review will not discuss tests that are used to screen for 1 cancer.

Several MCED tests are in development. Most MCED tests being developed are 'liquid biopsies' that detect altered DNA from cancer-causing genes that has been shed into circulation, called circulating-tumor DNA (ctDNA). ctDNA is only a small proportion of the total circulating-free DNA (cfDNA), particularly in patients with early-stage cancer.

Screening is not usually a single event. Screening tests may be applied repeatedly over time with a specified frequency. The screening interval or periodicity is normally determined by the growth rate of a cancer; for example, in average-risk adults of appropriate ages, breast cancer screening is performed approximately every 1 to 2 years whereas colon cancer screening is performed approximately every 5 to 10 years. The National Cancer Institute panel on MCED assays also made recommendations regarding periodicity of screening for trials of MCED tests.<sup>7</sup> The panel proposed trials should consist of annual screening for 3 to 5 years.

Many of the MCED tests in development predict the overall likelihood of cancer and the tissue of origin.

Standardized diagnostic pathways for each of the cancers included in an MCED test are needed, including specification of follow-up of positive and negative test results.

### **Galleri**

According to the manufacturer's website, the Galleri<sup>®</sup> MCED test is 'a qualitative, next-generation sequencing-based, in vitro diagnostic test intended for the detection of DNA methylation patterns using cell-free DNA (cfDNA) isolated from human peripheral whole blood.'<sup>8</sup> It is unclear how the Galleri test would fit into existing clinical pathways for screening; the website FAQs offer the following information:<sup>8</sup>

- 'Galleri can benefit patients with an elevated risk of cancer due to age, such as those aged 50 or older.'
- 'With Galleri, annual screening provides the opportunity to detect more cancers early. It is up to the patient's healthcare provider to determine the appropriate screening interval based on the individual's underlying risk factors.'
- 'The results of the Galleri test must be confirmed by diagnostic tests in accordance with standard medical practice.'
- 'Individuals should be advised to continue participating in all recommended cancer screening options at appropriate intervals.'
- 'When a cancer signal is detected, even after a negative diagnostic evaluation of the Cancer Signal Origin(s), the likelihood that the individual has cancer remains elevated and may warrant further evaluation.'

The Circulating Cell-free Genome Atlas (CCGA; NCT02889978) study included assay discovery, development, and refinement for the Galleri MCED test.<sup>9,10</sup> The CCGA clinical validation substudy of the marketed version of the test will be discussed in the following section on Clinical Validity.

### **Comparators**

The comparator of interest is standard of care cancer screenings. The U.S. Preventive Services Task Force (USPSTF) supports screening for breast, cervical, colorectal, and lung cancers.

### **Outcomes**

The National Cancer Institute panel on MCED assays made recommendations regarding randomized controlled trial (RCT) outcomes for trials of MCED tests.<sup>7</sup> The panel concluded that the primary outcome of trials should be either cancer mortality (all cancers) or cancer mortality from the subset of cancers included in each assay. Key secondary efficacy outcomes identified by the panel were all-cause mortality and incidence of advanced stage disease. Key safety outcomes identified by the

panel were false-positives, invasive procedures, serious adverse events, and overdiagnosis. The panel proposed trials should include follow-up of at least 7 years.

### Potential Benefits

The primary benefit of screening for cancer is the potential to diagnose cancer at an earlier stage or detect precursor lesions that can be treated with less aggressive or more effective treatment, thereby theoretically improving the length or quality of life. Thus, cancer-specific mortality and quality of life are the primary outcomes of interest for assessing benefit. However, mortality is a demanding outcome that requires long follow-up times and a large number of participants in order to produce reliable and precise estimates.

Longitudinal examination of the population-based, age-standardized stage distribution of all cancers may give early information on the likelihood of a survival benefit. However, it is possible for screening to increase the proportion of early-stage cancers that are detected without reducing the absolute incidence of advanced cancer because of overdiagnosis.

Shift in stage-specific incidence (stage-shift) has been validated as a surrogate for mortality for screening of breast cancer with mammography<sup>11</sup> and colorectal cancer with flexible sigmoidoscopy.<sup>12</sup> However, in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial of postmenopausal women without increased familial ovarian cancer risk, while annual screening with biomarker CA125 and transvaginal ultrasound scans did reduce stage III or IV disease incidence compared to no screening, it did not improve survival with a median follow-up of over 16 years<sup>13</sup>. Owens et al developed a mathematical model for the relationship between stage shift and disease-specific mortality and compared results to those from published screening trials. The authors concluded that the expected reduction in mortality given a specific stage-shift will likely vary substantially across cancer types and that stage-shift is unlikely to be a reliable basis for inference about mortality reduction for many cancer types.<sup>14</sup>

As such, stage-shift is not a validated surrogate for cancer-specific mortality across a wide range of cancers.

Stage-shift could also be related to health outcomes of interest other than mortality, such as functional or quality of life outcomes, by affecting intensity or timing of future treatment for recurrence or metastasis. Use of stage-shift as a surrogate for other health outcomes requires validation.

### Potential Harms

Population-based screening is applied to asymptomatic people without signs of disease. The prevalence of any given cancer is generally low. Therefore the majority of those screened for a particular cancer are not destined to develop clinically significant cancer that needs treatment and therefore do not benefit from screening. However, all persons screened are at risk of harm from either the screening test or the cascade of events following from a positive screening test.

### Direct Harms

For many screening tests, there are relatively few direct medical harms of the actual screening tests. For example, screening tests that rely on blood draws are associated with minor discomfort.

### Downstream Harms

The majority of harms from cancer screening come from downstream cascading events. The harms may arise from the diagnostic work-up of false positive screens, from diagnosis and treatment of overdiagnosed cancers, and from false negative screens for those cancers where screens are already part of standard care.

The harms from the diagnostic work-up of false positives depends on the false positive rate and on the nature of the work-up.

The false positive rate per screening test may be low, but given that many screening strategies include repeated screening tests over many years or a lifetime, the absolute number of people with complications as a result of a false-positive diagnostic work-up can be considerable. In addition, in the context of a test for multiple cancers, false positives can occur across several diseases.

Overdiagnosis of cancer that would not have become burdensome during an individual's lifetime leads to unnecessary treatments along with their associated risks.

False-negative test results of a new cancer screening test also have the potential to cause harm. For those cancers that already have established screening recommendations as part of standard care (e.g., breast, prostate), the new cancer screening test might alter individuals' adherence to existing recommendations which could lead to missed early diagnoses.

Performance characteristics should be provided for the overall population and stratified by demographic characteristics, stage, grade, and by cancer categorized by median time to recurrence or metastasis (e.g., less than 2 years versus 2 to 4 years versus greater than 4 years).

### **Cumulative risk**

The periodicity of the screening test affects the overall rate of true and false positive results of the screening strategy. A screening strategy in which a test is performed frequently has several opportunities to detect a preclinical cancer. However, it also has a higher cumulative risk of at least 1 false positive test.

The 'prevalent screen' is the first time a screening test is applied. In the prevalent screen, cases of cancer will have been present for varying lengths of time. The subsequent screens are called 'incident screens'. During incident screens, most cases found will have had their onset between rounds of screening, although some will have been missed by the previous screens (false negatives). The yield of a single screening test is higher for the prevalent screen but the incident screenings are more likely to detect aggressive cancer.

Performance characteristics of the MCED test are needed for a single use of the test and cumulatively over repeated use corresponding to the proposed periodicity of the test.

### **Study Selection Criteria**

The review will focus on MCED tests that are available in the US. The Galleri test is the only commercially available MCED test in the US at this time.

For the evaluation of clinical validity of the Galleri test, studies that meet the following eligibility criteria will be considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Participant/sample clinical characteristics were described; participants represent intended-use;
- Participant/sample selection criteria were described.

Published studies have used populations consisting of patients with an established diagnosis of cancer and control populations of healthy individuals.<sup>15,16,17</sup> As such, these do not reflect the intended-use populations, do not provide estimates of performance characteristics in the intended-use population, and will not be reviewed further.

### **Clinically Valid**

No studies met the study selection criteria.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCT).

### **No RCTs have been published.**

An RCT (NHS-Galleri; NCT05611632) is underway in the United Kingdom, conducted within the National Health Service (NHS), to test whether Galleri can reduce the number of late-stage cancers.<sup>18</sup> The trial has enrolled over 140,000 people, from the general population of England ages 50 to 77 years who did not have or were not being investigated for cancer. Participants were randomized to have their blood tested using Galleri or to the control group who will have their blood stored. Blood is being collected up to 3 times annually. Follow-up is underway. The study registration indicates that estimated study completion date is in 2026.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. The evidence is insufficient to demonstrate test performance so no inferences can be made about clinical utility through a chain of evidence.

### **Section Summary: Multicancer Early Detection Screening of Asymptomatic Populations**

The Galleri test is the only commercially available MCED test in the US at this time. Specifics of how the test should be used in practice, including the appropriate at-risk target populations, frequency of testing, and follow-up of positive and negative test results, have not been fully described. Available estimates of clinical validity are from a case-control study and likely overestimate performance characteristics for the target population. Results from the PATHFINDER study have been presented at a conference and summarized in a press release but have not been published in full. Performance characteristics, including sensitivity, specificity and predictive values, for the prediction of risk of cancer and for tissue of origin should be provided for the overall intended-use population and stratified by demographic characteristics, stage, grade, and by cancer. Performance characteristics are needed for a single use of the test and cumulatively over repeated use corresponding to the proposed periodicity of the test.

There are no studies demonstrating clinical utility of the Galleri test. An RCT testing whether Galleri can reduce the number of late-stage cancers is underway in the UK. No data are available on cancer-related mortality, quality of life or functional outcomes, or rates of overdiagnosis and overtreatment.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### National Comprehensive Cancer Network

NCCN Guidelines on Genetic/Familial High-risk Assessment: Breast, Ovarian, and Pancreatic (v.3.2023) make the following statement regarding screening with ctDNA tests:<sup>19</sup>

- 'For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined. The psychological impact of ctDNA testing remains unknown.'

### U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force (USPSTF) recommendations for MCED testing have been identified.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02889978 <sup>a</sup>	The Circulating Cell-free Genome Atlas Study (CCGA)	15254	Mar 2024
NCT03085888 <sup>a</sup>	The STRIVE Study: Breast Cancer Screening Cohort for the Development of Assays for Early Cancer Detection	99481	May 2025
NCT05611632 <sup>a</sup>	A Randomized, Controlled Trial to Assess the Clinical Utility of a Multi-cancer Early Detection (MCED) Test for Population Screening in the United Kingdom (UK) When Added to Standard of Care	140000	Feb 2026
NCT03934866 <sup>a</sup>	The SUMMIT Study: Cancer Screening Study With or Without Low Dose Lung CT to Validate a Multi-cancer Early Detection Test	13035	Aug 2030
<i>Unpublished</i>			
NCT04213326 <sup>a</sup>	Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing - Ascertaining Serial Cancer Patients to Enable New Diagnostic	6400	Jan 2021
NCT04241796 <sup>a</sup>	The PATHFINDER Study: Assessment of the Implementation of an Investigational Multi-Cancer Early Detection Test Into Clinical Practice	6662	Jan 2022

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## Documentation for Clinical Review

- No records required

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	None	
HCPCS	None	

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/01/2023	New policy.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT	
BEFORE	AFTER
<p><b>New Policy</b></p> <p><b>Policy Statement:</b> N/A</p>	<p><b>Multicancer Early Detection Testing 2.04.158</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. The use of multicancer early detection (MCED) tests (e.g., Galleri) is considered <b>investigational</b> for cancer screening.</li> </ul>