

2.04.158		Multicancer Early Detection Testing	
Original Policy Date:	September 1, 2023	Effective Date:	August 1, 2024
Section:	2.0 Medicine	Page:	Page 1 of 14

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.

Coding
See the [Codes table](#) for details.

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

- Serologic Genetic and Molecular Screening for Colorectal Cancer

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). Several tests, including Galleri® (GRAIL), CanScan™ (Geneseeq), OverC™ Multi-Cancer Detection Blood Test (Burning Rock) have been granted breakthrough device designation by the FDA.

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.¹

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.² 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-on³ 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).⁴ 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 and 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.⁵

The National Cancer Institute convened a panel of experts in 2021 to discuss initial design concepts for trials evaluating MCED assays for cancer screening.⁶ 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.⁶ 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[®] 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.'⁷ It is unclear how the Galleri test would fit into existing clinical pathways for screening; the website FAQs offer the following information:⁷

- "The Galleri test is recommended for use in adults with an elevated risk for cancer, such as those aged 50 or older."
- "Modeled data suggests that adding Galleri to annual wellness visits can improve the chances of finding cancer early. It is up to the patient's healthcare provider to determine the appropriate screening interval based on the individual's underlying risk factors."
- "When the Galleri test detects a cancer signal, results must be confirmed by diagnostic evaluation recommended by qualified health care professionals in accordance with standard medical practice."
- "The use of the Galleri test should not replace, supersede, or otherwise alter the use or frequency of standard of care cancer screening or detection modalities."
- "In the event that a diagnostic evaluation after a "Cancer Signal Detected" result does not confirm cancer, patients may be eligible for a complimentary Galleri retest within 3-6 months after the original test result."

The Circulating Cell-free Genome Atlas (CCGA; NCT02889978) study included assay discovery, development, and refinement for the Galleri MCED test.^{8,9} 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.⁶ 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 mammography¹⁰ and colorectal cancer with flexible sigmoidoscopy.¹¹ 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.¹² 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.¹³

Feng et al (2023) conducted a meta-analysis included 41 randomized clinical trials of cancer screening and reported that incidence of late-stage cancer may be a reasonable alternative outcome to cancer-specific mortality for some cancer types, but not for others.¹⁴

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 of the Galleri test (CCGA and SYMPLIFY), have used populations consisting of patients with an established diagnosis of cancer and control populations of healthy individuals^{15,16,17}, or symptomatic patients.¹⁸ As such, these do not reflect the intended-use screening populations, do not

provide estimates of performance characteristics in the intended-use- screening population, and will not be reviewed further.

Clinically Valid

Characteristics of clinical validity studies are shown in Table 1. Study results are shown in Table 2. Evaluation of study limitations in relevance and study design and conduct is shown in Tables 3 and 4.

Schrag et al (2023) reported results of the PATHFINDER prospective study of the Galleri test. PATHFINDER enrolled 6662 adults aged 50 years or older without signs or symptoms of cancer from oncology and primary care outpatient clinics at 7 US health networks between 2019 and 2020.¹⁹ A total of 6621 participants had analyzable results and were included in the analysis; 64% of participants were women and 92% were White. The reference standard was a cancer diagnosis established by pathological, laboratory, or radiographic confirmation. Diagnostic assessments were coordinated by, and at the discretion of, the participant's doctor. Participants were followed for 12 months. A cancer signal was detected by the Galleri test in 92 (1.4%) participants. In 2 of those participants, diagnostic assessments began before Galleri test results were reported. Thirty-five of the participants with a positive Galleri test were diagnosed with cancer; 57 of the participants with a positive Galleri test had no cancer diagnosis. The median time to diagnostic resolution was 79 days (interquartile range [IQR], 37 to 219). A total of 76 of the 90 participants with positive Galleri test results had laboratory tests, 83 (92%) had at least one imaging test, 44 (53%) had more than 1 imaging study, and 44 (49%) had at least one procedure. Within 12 months of enrollment, 122 cancers were diagnosed in 121 participants: 35 (29%) detected by Galleri; 38 (31%) detected through other screening tests; 48 (40%) clinically detected. Overall positive predictive value (PPV) was 35/92 (38%; 95% CI, 29 to 48). Negative predictive value (NPV) was 6235/6321(99%; 95% CI, 98 to 99). Specificity was 6235/6290 (99%; 95% CI, 99 to 99). Sensitivity was not reported in the publication but is 35/121 (29%; 95% CI, 21 to 38) based on the values provided. A correct first or second prediction of tissue of origin was returned for 33 (97%) of 34 true positives.

Table 1. Characteristics of Clinical Validity Studies of Galleri Test

Study	Study Population	Design	Setting	Reference Standard
Schrag et al (2023), PATHFINDER (NCT04241796) ¹⁹ .	Adults \geq 50 years of age without signs or symptoms of cancer	Prospective cohort study using a non-consecutive convenience sample	Oncology and primary care outpatient clinics at 7 US health networks	Pathological, laboratory, or radiographic confirmation

Table 2. Results of Clinical Validity Studies of Galleri Test

Study	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity (95% Confidence Interval)			
					Sensitivity	Specificity	PPV	NPV
Schrag et al (2023), PATHFINDER (NCT04241796) ¹⁹ .	6662	6621	Not 'analyzable'; were excluded but definition was not provided. Additionally 2 patients whose diagnostic assessments began before MCED test results were reported were excluded from some but not all calculations	121 / 6621 (1.8%)	29% (21 to 38) ^a	99% (99 to 99)	38% (29 to 48)	99% (98 to 99)

^a Not provided in the publication; calculated based on reported values

Table 3. Relevance Limitations of Clinical Validity Studies of Galleri Test

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Schrag et al (2023), PATHFINDER (NCT04241796) ¹⁹ .	5. Study population lacks diversity			1. Does not report health outcomes	1. 12 months of follow-up

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity; 6. Other

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest; 4. Other.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose; 4. Other.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests); 5. Other.

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined); 2. Other.

Table 4. Study Design and Conduct Limitations of Clinical Validity Studies of Galleri Test

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Schrag (2023), PATHFINDER (NCT04241796) ¹⁹ .	2. Convenience sample; not consecutive				1. No description of why samples were not 'analyzable'	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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.²⁰ 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. One prospective study is available providing estimates of clinical validity ; reported PPV was 38% (95% CI, 29 to 48) while specificity and NPV were approximately 99%. 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. 2024) make the following statement regarding screening with ctDNA tests:²¹

- '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 5. In addition to the studies listed below, a study entitled 'Multi-Cancer Early Detection - Real-World Evidence Program in the Medicare Population' with registration number NCT05673018 was announced, but subsequently the registration fields in clinicaltrials.gov were changed to 'Redacted' and continue to be unavailable as of April 16, 2024.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT05227261 ^a	Assessment of a Novel Blood Test in Early Detection of the Five Common Cancers Based on the Investigation of the Circulating Tumour DNA	10,000	Dec 2023
NCT05159544 ^a	A Prospective, Multicenter, Noninterventional Cohort Study of Multi-Omics Models for Pan-Cancer Screening	60,000	Jan 2024
NCT02889978 ^a	The Circulating Cell-free Genome Atlas Study (CCGA)	15,254	Mar 2024
NCT05295017 ^a	LEVANTIS-0093A: GAGomes for Multi-Cancer Early Detection in High-Risk Adults (LEV93A)	1256	Mar 2025
NCT03085888 ^a	The STRIVE Study: Breast Cancer Screening Cohort for the Development of Assays for Early Cancer Detection	99,481	May 2025
NCT05611632 ^a	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	140,000	Feb 2026
NCT05205967 ^a	REFLECTION: Real World Evidence for Learnings in Early Cancer Detection, a Clinical Practice Learning Program for Galleri [®]	17,000	Aug 2026
NCT06011694 ^a	A Prospective, Multicenter Cohort Study of the Multi-omics Liquid Biopsy MCED Test MERCURY in an Average Risk Chinese Population	15,000	May 2027
NCT05155605	The PATHFINDER 2 Study: Evaluating the Safety and Performance of the GRAIL Multi-Cancer Early Detection Test in an Eligible Screening Population	35,000	Dec 2027
NCT05227534	A Prospective Multi-cancer Early-detection and interVENTional Study in Asymptomatic Individuals: PREVENT	12,500	Dec 2028
NCT03934866 ^a	The SUMMIT Study: Cancer Screening Study With or Without Low Dose Lung CT to Validate a Multi-cancer Early Detection Test	13,035	Aug 2030
<i>Unpublished</i>			
NCT04213326 ^a	Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing - Ascertaining Serial Cancer Patients to Enable New Diagnostic	6400	Jan 2021
NCT04817306 ^a	A Prospective, Multicenter Study on Development and Validation of the Performance of a cfDNA Methylation-based Model for Early Cancer Detection (Pan-cancer Early Detection projeCT, PREDICT Study)	14,026	Mar 2023
NCT04822792	Pan-cancer Early-stage Detection by Liquid Biopsy in Peripheral Blood: a Multi-center, Prospective Observational Study	11,879	June 2023

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019). <https://www.cdc.gov/cancer/dataviz>. Accessed April 16, 2024.
2. World Health Organization. Screening and early detection. <https://www.who.int/europe/news-room/fact-sheets/item/cancer-screening-and-early-detection-of-cancer>. Accessed April 16, 2024.
3. Bossuyt PM, Irwig L, Craig J, et al. Comparative accuracy: assessing new tests against existing diagnostic pathways. *BMJ*. May 06 2006; 332(7549): 1089-92. PMID 16675820
4. Cancer.Net Editorial Board. Understanding Cancer Risk. 2018; <https://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/understanding-cancer-risk>. Accessed April 16, 2024.
5. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA Cancer J Clin*. Jan 2022; 72(1): 7-33. PMID 35020204
6. Minasian LM, Pinsky P, Katki HA, et al. Study design considerations for trials to evaluate multicancer early detection assays for clinical utility. *J Natl Cancer Inst*. Mar 09 2023; 115(3): 250-257. PMID 36458902
7. GRAIL, LLC. Frequently asked questions for healthcare providers interested in ordering the Galleri test. <https://www.galleri.com/hcp/support/provider-faqs>. Accessed April 16, 2024.
8. Jamshidi A, Liu MC, Klein EA, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. *Cancer Cell*. Dec 12 2022; 40(12): 1537-1549.e12. PMID 36400018
9. Liu MC, Oxnard GR, Klein EA, et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol*. Jun 2020; 31(6): 745-759. PMID 33506766
10. 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*. Jul 27 2021; 59(8): 1353-1361. PMID 33856748
11. Cuzick J, Cafferty FH, Edwards R, et al. Surrogate endpoints for cancer screening trials: general principles and an illustration using the UK Flexible Sigmoidoscopy Screening Trial. *J Med Screen*. 2007; 14(4): 178-85. PMID 18078562
12. Menon U, Gentry-Maharaj A, Burnell M, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet*. Jun 05 2021; 397(10290): 2182-2193. PMID 33991479
13. Owens L, Gulati R, Etzioni R. Stage Shift as an Endpoint in Cancer Screening Trials: Implications for Evaluating Multicancer Early Detection Tests. *Cancer Epidemiol Biomarkers Prev*. Jul 01 2022; 31(7): 1298-1304. PMID 35477176
14. Feng X, Zahed H, Onwuka J, et al. Cancer Stage Compared With Mortality as End Points in Randomized Clinical Trials of Cancer Screening: A Systematic Review and Meta-Analysis. *JAMA*. Jun 11 2024; 331(22): 1910-1917. PMID 38583868
15. 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*. Sep 2021; 32(9): 1167-1177. PMID 34176681
16. Tang WHW, Yimer H, Tummala M, et al. Performance of a targeted methylation-based multi-cancer early detection test by race and ethnicity. *Prev Med*. Feb 2023; 167: 107384. PMID 36495927
17. Shao SH, Allen B, Clement J, et al. Multi-cancer early detection test sensitivity for cancers with and without current population-level screening options. *Tumori*. Jun 2023; 109(3): 335-341. PMID 36316952
18. Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *Lancet Oncol*. Jul 2023; 24(7): 733-743. PMID 37352875

19. Schrag D, Beer TM, McDonnell CH, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *Lancet*. Oct 07 2023; 402(10409): 1251-1260. PMID 37805216
20. Neal RD, Johnson P, Clarke CA, et al. Cell-Free DNA-Based Multi-Cancer Early Detection Test in an Asymptomatic Screening Population (NHS-Galleri): Design of a Pragmatic, Prospective Randomised Controlled Trial. *Cancers (Basel)*. Oct 01 2022; 14(19). PMID 36230741
21. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed April 16, 2024.

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.
08/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

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.

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

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 (No changes)	
BEFORE	AFTER
<p>Multicancer Early Detection Testing 2.04.158</p> <p>Policy Statement:</p> <ul style="list-style-type: none"> I. The use of multicancer early detection (MCED) tests (e.g., Galleri) is considered investigational for cancer screening. 	<p>Multicancer Early Detection Testing 2.04.158</p> <p>Policy Statement:</p> <ul style="list-style-type: none"> I. The use of multicancer early detection (MCED) tests (e.g., Galleri) is considered investigational for cancer screening.