
Medical Policy



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***Current Policy Effective Date: 5/1/26**
(See policy history boxes for previous effective dates)

Title: Genetic Testing Multicancer Early Detection Testing (e.g., Galleri)

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. Multicancer early detection tests (MCEDs), also known as 'liquid biopsies' are minimally invasive tests that can simultaneously detect multiple types of cancer by analyzing bodily fluids like blood for biomarkers such as circulating tumor DNA (ctDNA) that are released by cancer cells.

Medical Policy Statement

The use of multicancer early detection (MCED) tests (e.g., Galleri) is **experimental/investigational** for cancer screening. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Inclusionary and Exclusionary Guidelines

NA

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

NA

Other codes (investigational, not medically necessary, etc.):

81479*

81599*

86849*

**Galleri does not have a specific code (per website bill directly to laboratory)*

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Background

Cancer is the second leading cause of death in the United States following heart disease, causing 1 in every 6 deaths. Excluding non-melanoma skin cancers, over 2 million new cancer cases are expected to be diagnosed in the US in 2025 and more than 618,000 people will die from the disease. 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. This review focuses on tests for screening indications.

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 type (e.g., colon cancer).

Cancer screening tests such as ‘liquid biopsies’ that are minimally invasive have been called multicancer early detection (MCED) tests. MCED tests are distinct from traditional cancer screening tests due to two main factors. Firstly, they employ a single blood test rather than x-rays, imaging tests like mammography, or procedures like colonoscopy. Secondly, they simultaneously screen for multiple types of cancer from various organs, including those not checked by existing methods. MCED tests predict the presence of cancer, rather than diagnose it. Depending on the biological signals measured, they may screen for multiple cancer types. Current development focuses on measuring signals in blood plasma, such as changes in DNA/RNA sequences, DNA methylation patterns, DNA fragmentation patterns, protein biomarker levels, and antibodies against cancer cell components. Researchers are

continually developing new technological approaches to expand the range of measurable biological signals, such as those identified by immune cells.

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.

Summary of Evidence

For individuals who are being screened for cancer who receive multicancer early detection (MCED) testing, the relevant published evidence includes a systematic review, and one US-based prospective study. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, quality of life, treatment-related mortality, and treatment-related morbidity. A systematic review of 36 studies on MCED tests highlighted variability in diagnostic accuracy. Evidence was limited, with no completed RCTs. While the tests exhibited high specificity, sensitivity varied depending on study design, population, reference tests, and follow-up duration. Insufficient follow-up for negative results led to high risk of bias across studies. Currently, the Galleri test is the only commercially available MCED test in the United States. One prospective study of the Galleri test reported a positive predictive value of 38% (95% CI, 29 to 48) and specificity and negative predictive value of approximately 99%. The specifics regarding the practical application of the test, including the appropriate at-risk target populations, frequency of testing, and follow-up for positive and negative results, have not been fully described. There is a need for performance characteristics for both the prediction of overall cancer likelihood and the tissue of origin. No clinical utility studies have been published to date, and estimates of changes in cancer-specific mortality, quality of life, functional outcomes, and rates of overdiagnosis and overtreatment remain unknown. The National Health Service (NHS)-Galleri study is a large population-based study of 140,000 participants. The primary end point is a surrogate end point of incidence of stage III and IV cancers. However, the preplanned analysis of the first year of three planned yearly rounds of screening did not trigger the NHS to move forward with the previously planned large-scale adoption of the test. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

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

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 NCI panel on MCED assays also made recommendations regarding periodicity of screening for trials of MCED tests. 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.' It is unclear how the Galleri test would fit into existing clinical pathways for screening; the website FAQs offer the following information

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 Grail, LLC and Jamshidi et al (2022) published (CCGA; NCT02889978) study included assay discovery, development, and refinement for the Galleri MCED test. The CCGA clinical validation substudy of the marketed version of the test will be discussed in the following section on Clinical Validity.

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 NCI panel on MCED assays made recommendations regarding randomized controlled trial (RCT) outcomes for trials of MCED tests. 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.

Duffy et al (2021) reported, shift in stage-specific incidence (stage-shift) has been validated as a surrogate for mortality for screening of breast cancer with mammography and Cuzick et al (2007) published, colorectal cancer with flexible sigmoidoscopy. However, in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial of postmenopausal women without increased familial ovarian cancer risk, Menon et al (2021) reported, 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

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.

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.

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 over diagnosed 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.

Klein et al (2021), Tang et al (2023), Shao et al (2023), Nicholson et al (2023), 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. or symptomatic patients. As such, these do not reflect the intended-use populations, do not provide estimates of performance characteristics in the intended-use-screening population, and will not be reviewed further.

Wade et al (2025) undertook a systematic literature review of the clinical effectiveness evidence on blood-based multi-cancer early detection tests for screening. This was funded by the UK National Institute for Health and Care Research (NIHR) Health Technology Assessment program. . The literature search identified studies on MCED tests targeting individuals aged 50–79 without cancer suspicion. Key outcomes included test accuracy, cancer detection rates (by site and stage), diagnostic resolution time, mortality, harms, quality of life, and satisfaction. Thirty-six studies published through September 2023 met the review inclusion criteria: 1 ongoing RCT, 13 cohort studies, 17 case-control studies, and 5 ongoing cohort/case-control studies. MCED tests claimed to detect 3 to over 50 cancer types. Diagnostic accuracy varied widely among available tests. For US-based tests, Galleri® showed sensitivity 20.8 to 66.3% and specificity 98.4 to 99.5%, while CancerSEEK (now called Cancerguard™ currently undergoing further assessment by Exact Sciences) had sensitivity 27.1 to 62.3% and specificity 98.9 to 99.1%. The sensitivity of several non-US based-tests ranged from 40% to 100%, and specificity 96.4 to 99.9%. Sensitivity for detecting early-stage cancers (stages I-II) was generally lower than for later-stage cancers (stages III-IV). Study selection was complex due to unclear development stages of MCED tests. The evidence was limited, with no completed RCTs and high risk of bias in most studies, primarily due to limited follow-up of negative test results. Only one Galleri study (Schrag et al, 2023 described below) recruited asymptomatic US individuals over 50, but it did not report patient-relevant outcomes like mortality or quality of life. High specificity (>96%) was consistent across MCED tests, while sensitivity varied based on study design, population, reference tests used, and follow-up duration.

Nabavizadeh et al (2025) reports early results from the PATHFINDER II (PF2) prospective, multicenter, interventional study, which evaluated the safety and performance of the Galleri multicancer early detection (MCED) blood test in a large, diverse screening population. (PF2) enrolled 35,878 participants aged 50 years or older with no recent cancer history across the United States and Canada. Among the 23,161 participants with at least 12 months of follow-up and evaluable data, 216 (0.93%) tested positive for a cancer signal. The test demonstrated a high specificity of 99.6% and a positive predictive value of 61.6%. The first cancer signal of origin (CSO) prediction was correct in 91.7% of cases. In a prespecified subgroup of 12 cancers that account for two thirds of U.S. cancer deaths, the tests episode sensitivity was 73.7%; overall sensitivity across all cancers was 40.4%. Of the 329 participants diagnosed with cancer during follow up, 200 were screen detected: 133 by the MCED test (including 114 new

primary cancers and 19 recurrences), 20 by U.S. Preventive Services Task Force (USPSTF) A/B recommended screenings, and 47 by USPSTF level screenings. The MCED detected cancers represented a detection rate of 0.57% and 75.2% of these cancers lack common screening options. While the study provides promising early data on the Galleri MCED test, sponsor driven funding, limited follow up, and potential for selective reporting constitute significant weaknesses that should be considered when interpreting the results. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Guerra et al (2025): This article reviews the emerging field of multicancer early detection tests (MCEDs), often called liquid biopsies, which aim to screen for many cancers simultaneously using blood-based biomarkers such as circulating tumor DNA, RNA, and proteins. It explains how MCEDs work, the role of machine-learning algorithms in identifying a cancer signal of origin (CSO), and the current status of regulatory approval. The United States FDA has not approved the use of any MCED for cancer screening, however, Galleri (Grail) is commercially available. It is not yet known if MCED reduces mortality. There has been a lot of debate about the best end points for MCEDs and other screening tests. The gold standard would be all-cause mortality or cancer-specific mortality. However, the correlation between cancer stage and survival appears to vary by cancer type. Overall, MCEDs hold promise for expanding cancer screening but require robust outcome data before widespread adoption; careful shared decision making and attention to equity and cost are essential. The optimal workup for a positive test as well as who to test, when and how often also remain under investigation.

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 seven US health networks between 2019 and 2020. 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%) of participants. In 2 of those participants, diagnostic assessments began before Galleri test results were reported. 35 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 (IQR, 37 to 219). 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.

Characteristics of the PATHFINDER study 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.

Table 1. Characteristics of Clinical Validity Studies of Galleri Test

Study	Study Population	Design	Setting	Reference Standard
Schrag (2023), PATHFINDER (NCT04241796)	Adults aged 50 years or older without signs or symptoms of cancer	Prospective cohort study using a non- consecutive convenience sample	Oncology and primary care outpatient clinics at seven 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 ^b	Prevalence Of Condition	Clinical Validity (95% Confidence Interval)			
					Sensitivity	Specificity	PPV	NPV
Schrag (2023), PATHFINDER (NCT04241796)	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 (2023), PATHFINDER (NCT04241796)	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	Population ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Schrag (2023), PATHFINDER (NCT04241796)	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.

Neal et al (2022), 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. 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.

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. A systematic review of 36 studies on MCED tests revealed variability in diagnostic accuracy. Evidence was minimal with no completed RCTs. Despite high specificity, sensitivity varied by study design, population, reference tests, and follow-up duration, with insufficient follow-up for negative results contributing to bias across studies. 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, Pancreatic and Prostate (v.2.2026) make the following statement regarding screening with ctDNA tests:

- 'For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA [circulating tumor DNA] 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. For these reasons, ctDNA should not be used, outside of the clinical trial setting, to replace well-established methods of cancer screening (eg, mammography).'

U.S. Preventive Services Task Force Recommendations

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT05159544 ^a	A Prospective, Multicenter, Noninterventional Cohort Study of Multi-Omics Models for Pan-Cancer Screening	60,000	Dec 2024

NCT02889978 ^a	The Circulating Cell-free Genome Atlas Study (CCGA)	15254	Mar 2024
NCT05295017 ^a	LEVANTIS-0093A: GAGomes for Multi-Cancer Early Detection in High-Risk Adults (LEV93A)	1,235	Mar 2026
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	140000	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	35,885	Apr 2028
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	13035	Aug 2030
NCT05673018 ^a	REACH Study: Real-world Evidence to Advance Multi-Cancer Early Detection Health Equity	50,000	Sep 2030
Unpublished			
NCT04213326 ^a	Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing - Ascertaining Serial Cancer Patients to Enable New Diagnostic	6400	Jan 2021
NCT03085888 ^a	The STRIVE Study: Breast Cancer Screening Cohort for the Development of Assays for Early Cancer Detection	99,481	Apr 2024
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	9,057	Oct 2024

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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.

In February 2024, the National Cancer Institute (NCI) launched the Cancer Screening Research Network (CSRN) to evaluate emerging technologies for cancer screening. As part of this initiative, the CSRN began the Vanguard Study, which aims to enroll up to 24,000 participants to evaluate the feasibility and benefits of MCED tests. This study will focus on diverse populations across eight US sites led by the Fred Hutchinson Cancer Center, with

further participation from the US Department of Defense and the Department of Veterans Affairs. Participants will be randomly assigned to a control group or one of two MCED test groups. The control group will have blood drawn without further testing, while the MCED test groups will receive assays - Avantect® from ClearNote Health and Shield™ from Guardant Health - at no cost. The study objectives include assessing participant willingness, adherence to testing, diagnostic follow-up, and evaluating the feasibility of diagnostic processes.

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

Government Regulations

National: NA

LCD: NA

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Circulating Tumor DNA and Circulating Tumor Cells for Selecting targeted therapy for advanced solid Cancers (Liquid Biopsy)
- Urinary Biomarkers for Bladder Cancer
- Serologic Genetic and Molecular Screening for Colorectal Cancer
- Analysis of Human DNA (i.e., ColoGuard®) and FIT-RNA (i.e., Colosense®) in Stool Samples as a Technique for Colorectal Cancer Screening

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through December 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/24	2/20/24		Joint policy established (jf) Vendor Managed: NA Ref added: 3,15,19,20
5/1/25	2/18/25		Routine Maintenance (jf) Vendor Managed: NA Ref added: 15,19,20
5/1/26	2/17/26		Routine Maintenance (jf) Vendor Managed: NA Ref Added: 5,15,28 Literature Review: Grail Formatting changes made: ○ Sections rearranged for better flow ○ Added new header on page 1 of medical policy ○ Description and Background separated ○ References placed in alphabetical order and superscripts removed

Next Review Date: 1st Qtr, 2027

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE

POLICY: GENETIC TESTING MULTICANCER EARLY DETECTION TESTING (E.G., GALLERI)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	See Government Regulations section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.