GRAIL

GALLERI MULTI-CANCER EARLY DETECTION TEST

SPONSOR EXECUTIVE SUMMARY

MOLECULAR AND CLINICAL GENETICS PANEL

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LIST OF ABBREVIATIONS

Abbreviations	Definition
AE	Adverse Event
BCC	Basal Cell Carcinoma
CCGA	Circulating Cell-free Genome Atlas
cfDNA	Cell-free Deoxyribonucleic Acid
CI	Confidence Interval
CSO	Cancer Signal Origin (also called tissue of origin)
CSO-S	Cancer Signal Origin - Supplemental
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration
HPV	Human Papillomavirus
IDE	Investigational Device Exemption
MCED	Multi-Cancer Early Detection
MCED-V2	Version 2 of the GRAIL Multi-Cancer Early Detection test
NA	Not Applicable
NCRAS	National Cancer Registration and Analysis Service
NGS	Next-Generation Sequencing
NHS	National Health Service
NPA	Negative Percent Agreement
NPV	Negative Predictive Value
PET-CT	Positron Emission Tomography-Computed Tomography
PMA	Premarket Approval
PPA	Positive Percent Agreement
PPV	Positive Predictive Value
PSA	Prostate-Specific Antigen
QC	Quality Control
SCC	Squamous Cell Carcinoma (of the Skin)
SEER	Surveillance, Epidemiology, and End Results Program
STAI	State-Trait Anxiety Inventory
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force

1 SYNOPSIS

1.1 Introduction

GRAIL is seeking approval of Galleri®,[1] a next-generation sequencing (NGS)-based *in vitro* diagnostic test intended for the early detection of multiple types of cancer in adults aged 50 years or older. The test is also intended for the prediction of Cancer Signal Origin (CSO) in individuals with a Cancer Signal Detected test result.

Existing cancer screening tests recommended by the United States Preventive Services Task Force (USPSTF) reduce morbidity and mortality when used at recommended intervals; however, most cancer deaths occur from cancers without recommended screening options or when recommended screening guidelines are not followed.

Currently, many cancers are diagnosed only after symptoms develop, often at advanced stages when treatment options are limited and outcomes are worse. As a result, a substantial unmet need exists for screening approaches capable of detecting most types of cancers, including cancer types not addressed by guideline-recommended screening programs, to enable earlier diagnosis and effective treatment.

The Galleri multi-cancer early detection (MCED) test is a non-invasive, blood-based cancer screening test that detects multiple cancer types based on a shared cancer signal and predicts the cancer signal origin to streamline the diagnostic work-up. Galleri is intended to be used in addition to, and not as a replacement for, guideline-recommended cancer screening tests. When Galleri is used in addition to guideline-recommended cancer screening, the overall cancer screening program becomes more effective and efficient (Hackshaw et al., 2021).

The clinical development program for Galleri includes more than 385,000 participants across studies (including ~165,000 participants from PATHFINDER 2 and NHS-Galleri that informed the safety and effectiveness of Galleri) supporting test development, validation, and evaluation in large screening-eligible populations, including interventional and randomized studies. These studies consistently showed a robust performance profile of a high positive predictive value (PPV), high specificity, accurate CSO prediction, and clinically meaningful episode sensitivity across cancer types, including higher episode sensitivity in the cancer types contributing to the most cancer deaths, compared with episode sensitivity for all cancers combined. The prospective, interventional studies also consistently demonstrated a strong safety profile, with no adverse device effects and few study-related adverse events (AEs), which were primarily phlebotomy-related and transient. By enabling early detection across multiple cancer types, particularly aggressive cancers that require urgent diagnosis and treatment, and with a low false-positive rate that prioritizes safety, Galleri has a

[1] Throughout this document, “Galleri” refers to the premarket approval (PMA) version of the GRAIL multi-cancer early detection (MCED) test. Earlier versions of the test are referred to as “MCED-V2” (version 2) or “MCED-V1” (version 1).

favorable benefit-risk profile and has the potential to provide a clinically meaningful public health benefit by reducing the burden of cancer.

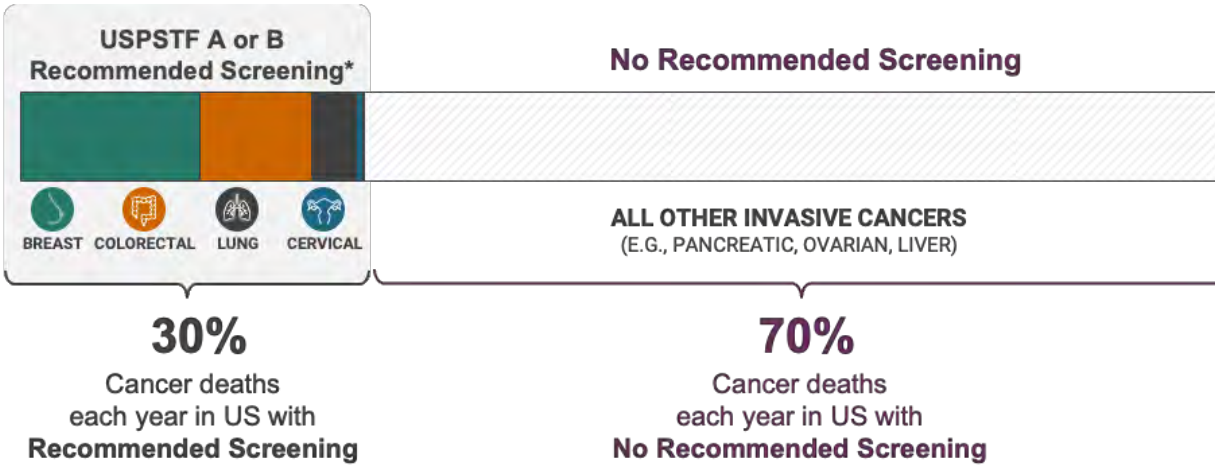
1.2 Background and Unmet Need

Cancer is a leading cause of morbidity and mortality in the United States, with approximately 2.1 million new cases and more than 600,000 deaths estimated in 2026 (Siegel et al., 2026). The lifetime risk of a cancer diagnosis for any individual is high, approaching 40% for both men and women in the United States (US) (Siegel et al., 2026). The overall cancer burden is growing with the aging of the population, and a 38% increase in new cancers is expected by 2050 (Ferlay, 2024).

Early detection is a bedrock of cancer control, enabling curative-intent treatment that reduces cancer morbidity and mortality. Each four-week delay in receipt of cancer treatment is associated with approximately a 4%–20% increase in cancer mortality, depending on cancer type and treatment (Hanna et al., 2020). Conversely, screen-detected cancers are unlikely to be diagnosed via emergency department presentation, which is associated with substantial increases in mortality (Elliss-Brookes et al., 2012; Thompson et al., 2026). Recent advances in cancer treatment, especially before distant metastasis, further underscore the importance of early detection (Sherman et al., 2025).

Our current approach to cancer detection relies heavily on patients seeking medical care for symptoms, leading to later stage at diagnosis, poorer prognosis, and substantially greater treatment burden and cost. While cancer screening programs are established and successful at detecting cancer in asymptomatic persons, they target only five cancer types – breast, cervical, colorectal, and lung in high-risk smokers (USPSTF Grade A or B recommendation) – as well as prostate (Grade C). These programs play a critical role in reducing morbidity and mortality due to these cancer types but address only a fraction of the overall cancer burden, as only 14% of all cancers are detected via USPSTF Grade A- or B-recommended screening programs (NORC, 2022), meaning that 86% of all newly diagnosed cancers are not. Figure 1 shows that 70% of the cancer death burden is due to types without guideline-recommended screening options, and this percentage climbs to approximately 87% of cancer deaths when factoring in the suboptimal utilization of lung and other recommended screening (Ofman et al., 2025).

Figure 1: Cancer Deaths for Cancer Types with USPSTF Screening Recommendations vs Cancer Types Without Screening Options



*Prostate cancer screening is recommended on an individual basis.
Source: Ofman et al., 2025

For cancer types without guideline-recommended screening options, the most common modes of cancer detection include emergency department presentation, incidental detection, or primary care referral based on signs, symptoms, or physician "gut feeling," which incorporates subjectivity and experience (Danckert et al., 2021; Elliss-Brookes et al., 2012; Smith et al., 2020; Thompson et al., 2024; Yao et al., 2023; Zhou et al., 2017). These standard routes to diagnosis highlight the fact that for most cancers, there is no available option for detection of asymptomatic cancers, which tend to be earlier-stage at diagnosis (Koo et al., 2020) and, hence, more likely to be eligible for curative-intent therapy. In other words, based on the current healthcare system, the ability to detect asymptomatic unscreened cancers is negligible, or essentially 0% sensitivity, for cancer types that lack guideline-recommended screening.

As an MCED test, Galleri represents a paradigm shift in cancer screening and has been developed to address the growing need to detect a higher proportion of the overall cancer burden at stages when those cancers can be treated with curative-intent therapy. For example, an MCED test with even 20% sensitivity would detect more cancers than a (hypothetical) colorectal cancer screening test with 100% sensitivity. Galleri detects a systemic cancer signal shared by many clinically meaningful cancer types from a single blood draw. By targeting a high specificity, strong PPV, and accurate CSO prediction, Galleri has a high cancer detection rate with minimal risks from unnecessary diagnostic work-ups. Galleri thereby complements and enhances the current program of guideline-recommended screening for five cancer types by increasing the cancer types that can be detected through screening.

Existing guideline-recommended tests have been designed to favor sensitivity over specificity for the targeted cancer type. Prioritizing sensitivity, however, may be associated with lower specificity (high false-positive rate) and lower PPV. Table 1

includes performance metrics for guideline-recommended cancer screening tests and usual care for detection of all cancer.

Table 1: Test Performance for Guideline-Recommended Cancer Screening Tests and Usual Care for All Cancer Types

Cancer Type	Screening Approach	Sensitivity (%)	Specificity (%)	PPV (%)
Breast	Mammography	87.4–87.6%	90.2–92.2%	5.2–6.9%[1]
Cervical	Cytology / HPV Test	95.2%	85.5%	0.1–0.8%[2]
Colorectal	Colonoscopy	*Reference Standard*		
	Stool DNA	93.9%	90.6%	3.4%[3]
	Fecal immunochemical test	74%	94%	3.2%[4]
Lung	Low-dose CT	80.3–93.3%	76.4–78.6%	6.9%[5]
Prostate	PSA-based screening	73.2%	85.4%	22–27%[6]
All types	Signs and symptoms	40.3% for symptomatic cancer 0% for asymptomatic cancer	87.8% for symptomatic cancer N/A for asymptomatic cancer	< 5–10% for symptomatic cancer 0% for asymptomatic cancer
	Physician “gut feeling”	40% for suspected cancer 0% for unsuspected cancer	85% for suspected cancer N/A for unsuspected cancer	3% for suspected cancer if population cancer prevalence > 1.15% 0% for unsuspected cancer

CT: computed tomography; HPV: human papillomavirus; N/A: not applicable; PPV: positive predictive value; PSA: prostate-specific antigen
[1] Lee et al., 2023
[2] Kim et al., 2018
[3] Pickhardt, 2016
[4] Ding et al., 2022
[5] Jonas et al., 2021
[6] Grubb et al., 2008

Galleri was designed to enable population-scale screening with a high cancer detection rate for clinically actionable disease (avoiding overdiagnosis), while maintaining a low false-positive rate and high PPV to minimize unnecessary diagnostic procedures. Therefore, when evaluating Galleri test performance, study results should be interpreted in the context of Galleri’s intended use to screen for multiple types of cancers.

Conventional guideline-recommended screening tests address one cancer at a time, such that each test has an independent and additive false-positive rate (Table 1). Therefore, adding several new single-cancer early detection tests to the existing program of guideline-recommended screening tests would drastically increase its cumulative false-positive rate, triggering marked increases in unnecessary diagnostic investigations and associated costs for cancer-free people (Madhavan et al., 2025).

In contrast, adding an MCED test with a very low single false-positive rate across all cancer types would maintain nearly the same cumulative false-positive rate as currently exists for guideline-recommended screening tests, resulting in substantially safer and more efficient cancer screening program for the population at large.

1.3 Product Overview

Galleri is a qualitative, NGS-based *in vitro* diagnostic test intended to detect cancer-specific methylation patterns in cell-free DNA (cfDNA) isolated from peripheral whole blood. Galleri is intended for screening for the early detection of multiple types of cancer in adults aged 50 years or older. The test is also intended for the prediction of CSO in individuals with a Cancer Signal Detected test result to help guide diagnostic work-up.

A test result of Cancer Signal Detected, which includes a predicted CSO and, if appropriate, a predicted supplemental CSO (CSO-S), may indicate the presence of an invasive solid tumor or hematologic malignancy and should be followed by a diagnostic work-up recommended by a qualified healthcare professional. A test result of No Cancer Signal Detected does not rule out the presence of cancer. In either case, individuals should continue with guideline-recommended single-cancer screening tests.

Galleri detects cancers based on cfDNA shed into the bloodstream, conveying a shared cancer signal based on methylation patterns that are a known “hallmark” of cancer (Hanahan & Weinberg, 2000; Hanahan & Weinberg, 2011). While it has been shown that the methylation-based cancer signal detected by Galleri is generalizable to hundreds of histologically distinct cancer types, methylation patterns are also tissue-specific, allowing the test to identify the most likely tissue or organ associated with the cancer signal. Importantly, this CSO prediction capability helps guide physicians in the diagnostic evaluation following a positive test result.

The Galleri PMA submission, which presents prespecified analyses focused on safety and effectiveness, includes 12 months of follow-up data from two large interventional studies conducted under US Food and Drug Administration (FDA)-approved investigational device exemptions (IDE). PATHFINDER 2, the largest interventional study of an MCED test ever conducted in the US, provided 12-month follow-up data from approximately 25,000 participants. NHS-Galleri, a randomized, controlled clinical study conducted in England, included data from the prevalent screening round (first year) for approximately 140,000 participants.

In the PATHFINDER 2 and NHS-Galleri studies, results were returned using version 2 of the GRAIL MCED test (MCED-V2). The Galleri test that was submitted for premarket approval (the PMA device) is an improved version of MCED-V2, with updates intended to further optimize safety, usability, and scalability for population-level screening.

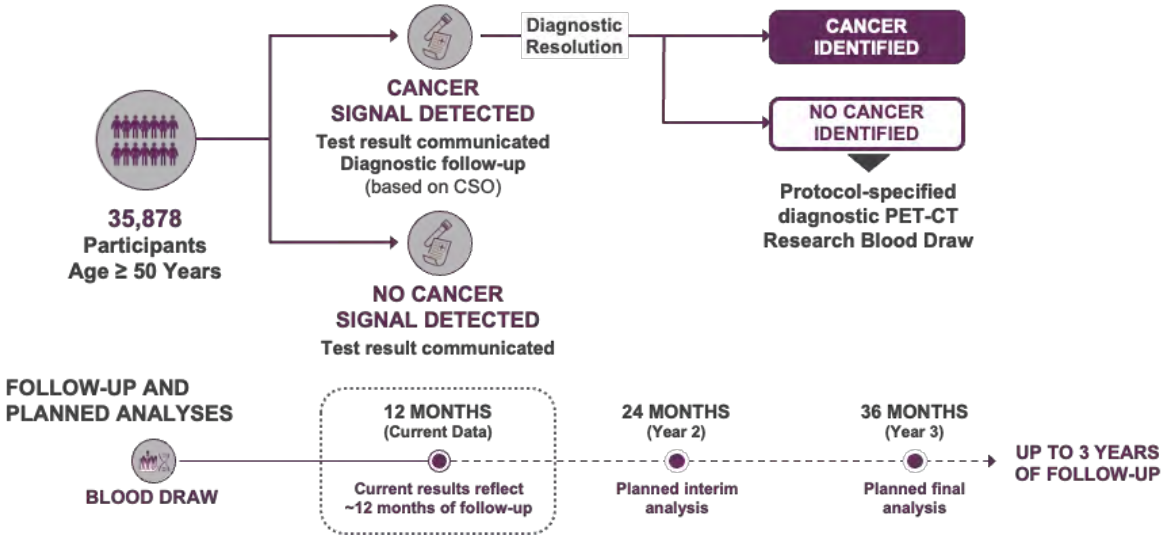
Because of these updates, a pre-specified analysis was conducted in discussion with FDA to assess performance of Galleri in PATHFINDER 2 and NHS-Galleri. In this analysis, Galleri was run on a subset of frozen samples banked from the clinical studies. This subset included all samples from participants with a positive MCED-V2 test result,

all samples from participants who were diagnosed with cancer within 12 months of the blood draw, and a stratified random sampling of participants who were not diagnosed with cancer and had MCED-V2 negative results. Galleri test performance was then estimated using weighted analyses so that the results represent the full study populations. Safety endpoints were assessed using MCED-V2 data, consistent with the approach discussed with FDA.

1.3.1 PATHFINDER 2 Effectiveness Results

PATHFINDER 2 is a prospective, interventional study in individuals 50 years of age or older across 31 sites in the US and one site in Canada (Figure 2). Following enrollment, participants underwent a study-specific blood draw, and samples were processed with the MCED-V2 test. Participants who received a Cancer Signal Detected result underwent diagnostic evaluation guided by the CSO prediction(s). If diagnostic resolution was not achieved after this targeted evaluation, a diagnostic positron emission tomography-computed tomography scan (PET-CT) was performed. Participants with a No Cancer Signal Detected result were informed that a cancer signal was not identified. Importantly, participants were reminded not to interpret this negative result as the absence of cancer, and were instructed to continue with routine clinical care, including recommended cancer screening. All participants are being actively followed for 3 years to assess cancer outcomes and monitor adherence to recommended screening.

Figure 2: PATHFINDER 2 Study Design Schematic



PATHFINDER 2 enrolled a large and diverse participant population representative of the intended-use population (see Section 5.2.1). At the time of the PMA analysis, 25,578 consented participants had 12 months of follow-up time. Baseline characteristics were largely consistent with the intended-use population distribution of known risk factors for cancer (see Section 5.2.1). Galleri test performance results are summarized

in Table 2, demonstrating Galleri's high PPV, very low false-positive rate, and clinically meaningful episode sensitivity.

Table 2: PATHFINDER 2: Galleri Test Performance Measures for Cancer Detection

	Cancer Diagnosis Within 12 Months (N=303)	No Cancer Diagnosis Within 12 Months (Weighted N*=21,115)	Total (Weighted N*=21,418)	
Galleri Cancer Signal Detected	106	32	138	**PPV=77.0%** (65.8%, 85.4%)
Galleri No Cancer Signal Detected	197	21,084	21,281	**NPV=99.07%** (98.93%, 99.20%)
	Episode Sensitivity=35.0% (29.8%, 40.5%)	**Specificity=99.85%** (99.75%, 99.91%)		

NPV, negative predictive value; PPV, positive predictive value.
*Weights were calculated for participants with no cancer diagnosis and MCED-V2 no cancer signal detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected. CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity); and logistic regression with robust sandwich variance for weighted measures (specificity, PPV, and NPV).

The cancer detection rate was 0.49%. Adding Galleri to USPSTF Grade A/B/C-recommended screening tripled the number of cancers detected by screening, and Galleri increased the number of cancers detected by screening by seven-fold when added to USPSTF Grade A/B-recommended screening (details in Section 5.4.1 and Figure 7).

Prespecified analyses of 12 cancer types responsible for two-thirds of US cancer deaths and 6 aggressive cancers with low 5-year survival demonstrated higher episode sensitivity in these subgroups (Table 3). Greater episode sensitivity for these cancer types than for all cancer types combined (especially less-aggressive or indolent cancer types) is biologically expected, as more aggressive cancers tend to shed more cfDNA into the bloodstream (Hasenleithner & Speicher, 2022). Test performance results by cancer type are provided in Section 7.

Table 3: PATHFINDER 2: Galleri 12-Month Episode Sensitivity in Prespecified Cancer Type Subgroups

	Episode Sensitivity		
	n/N	%	95% CI
12 cancers responsible for two-thirds of US cancer deaths[1]	73/119	61.3%	52.4%-69.6%
6 aggressive cancers with low 5-year survival in US[2]	32/53	60.4%	46.9%-72.4%
Cancers without common screening options[3]	79/167	47.3%	39.9%-54.9%

1 Anus, bladder/urothelial tract, colon/rectum, esophagus, head and neck, liver/intrahepatic bile duct, lung, lymphoid lineage, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, plasma cell lineage, and stomach
2 Esophagus, liver/intrahepatic bile duct, lung, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, and stomach
3 Anus, bladder/urothelial tract, bone/soft tissue sarcoma, esophagus, head and neck, kidney, liver/intrahepatic bile duct, lung, myeloid lineage, lymphoid lineage, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, plasma cell lineage, skin, stomach, thyroid, uterus, and "other"

Among cancers detected by Galleri in PATHFINDER 2, 49% were diagnosed at stage I or stage II, and 69% were diagnosed at stages I–III (details in Section 5.4.1). Overall, 82% of Galleri-detected stages I–III cancers and 38% of Galleri-detected stage IV cancers were managed with curative intent (defined as treatment undertaken with the goal of cure), providing direct evidence of clinical actionability. Together, these findings suggest that the majority of true-positive cancers were clinically actionable and amenable to treatment with curative intent.

Galleri CSO prediction was highly accurate, enabling efficient diagnostic resolution. Among participants with true-positive results, the CSO prediction accurately identified the location of the cancer in 94.3% (95% confidence interval (CI): 88.2%, 97.4%) of cases (details in Section 5.4.3). Based upon MCED-V2 results that were returned to participants, the high accuracy of CSO predictions helped guide efficient diagnostic evaluation. The median time to diagnostic resolution (defined as the number of days from communication of a positive test result until the date of the last diagnostic evaluation used to determine the presence or absence of cancer) was 46 days among all participants and 36 days among participants with true-positive results. Among participants with a false-positive result, the median time to diagnostic resolution was 75 days. For context, a claims-based analysis of more than 450,000 insured patients with cancer in the US reported a median time to diagnosis of 118 days (Gitlin et al., 2023)[2]. The diagnostic resolution timeline established for MCED-V2 is directly applicable to Galleri, supported by the high degree of concordance in CSO predictions between the two test versions as described in Section 3.4.4 below.

In PATHFINDER 2, Galleri met all prespecified study success criteria for specificity, episode sensitivity across all cancer types, and CSO prediction accuracy among true-

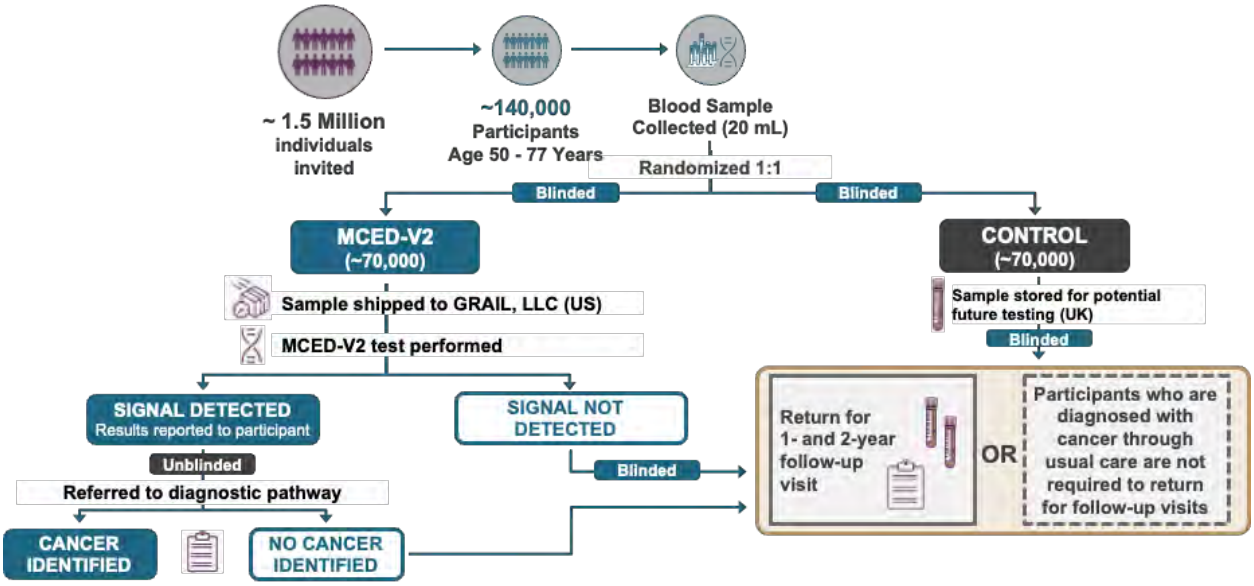
[2] The index date in this study was set to the date of an office visit occurring fewer than 4 weeks prior to the first diagnostic test date *or* on the first diagnostic test date if no office visit was recorded.

positive participants. Together, these findings support the use of Galleri as an adjunct to guideline-recommended cancer screening in the intended-use population.

1.3.2 NHS-Galleri Effectiveness Results

NHS-Galleri is a prospective randomized controlled trial of 142,826 consented participants aged 50–77 years in England (Figure 3). Participants were randomized to either an intervention arm, in which blood samples were analyzed using MCED-V2 or a control arm, in which samples were stored for potential future research. Participants who received a Cancer Signal Detected result were referred through the National Health Service (NHS) urgent cancer referral pathway for diagnostic evaluation, meaning all subsequent workup and treatment occurred outside of the trial. All participants were followed for three screening rounds; the first round of data (the prevalent screening round), which corresponds to the single round of screening in PATHFINDER 2, is included in the Galleri PMA.

Figure 3: NHS-Galleri: Study Design Schematic



A total of 142,250 (99.9%) participants were randomized in the study, with 71,122 in the intervention arm and 71,128 in the control arm. Demographics and baseline clinical characteristics were well-balanced between the randomized arms and were largely consistent with the intended-use population distribution of known risk factors for cancer (see Section 6.2 for details) (Swanton et al., 2022).

Galleri test performance results in the NHS-Galleri intervention arm are summarized in Table 4, demonstrating high PPV, a very low false-positive rate, and clinically meaningful episode sensitivity.

Table 4: NHS-Galleri: Galleri Test Performance Results (Prevalent Screening Round)

	Cancer Diagnosis Within 12 Months (N=820)	No Cancer Diagnosis Within 12 Months (Weighted N*=49,919)	Total (Weighted N*=50,739)	
Galleri Cancer Signal Detected	259	132	391	**PPV = 66.2%** (56.7%, 74.6%)
Galleri No Cancer Signal Detected	561	49,786	50,347	**NPV = 98.89%** (98.78%, 98.98%)
	Episode Sensitivity = 31.6% (28.5%, 34.8%)	**Specificity = 99.74%** (99.61%, 99.82%)		

NPV, negative predictive value; PPV, positive predictive value.
*Weights were calculated for participants with no cancer diagnosis and MCED-V2 no cancer signal detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected.
CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity); logistic regression with robust sandwich variance for weighted measures (specificity, PPV, and NPV).

Galleri's cancer detection rate was 0.51%, corresponding to a six-fold increase in the number of cancers detected by screening when Galleri was added to NHS screening programs (details in Section 6.4.1 and Figure 10).

Episode sensitivity was greater in the prespecified cancer subgroups of 12 cancers responsible for two-thirds of US cancer deaths and 6 aggressive cancers with low 5-year survival (details in Section 6.4.2). Test performance results by cancer type are provided in Section 7.

Galleri's CSO prediction accuracy was high: 91.9% for CSO prediction, and 93.1% when including both CSO and CSO-S predictions (details in Section 6.4.3). Among participants with true-positive results, 68.7% were diagnosed at stages I–III (details in Section 6.4.1).

Based on the results of NHS-Galleri PMA analysis, Galleri met all prespecified study success criteria, including specificity, episode sensitivity across all cancer types, and CSO prediction accuracy among true-positive participants. Together, these results provide additional prospective evidence supporting Galleri's use as an adjunct to guideline-recommended cancer screening.

1.3.3 Summary of Effectiveness

Effectiveness results across PATHFINDER 2 and NHS-Galleri were consistent and supportive of the safety and effectiveness of Galleri (Table 5). Across these two large studies through 12 months of follow-up, Galleri's cancer detection rate was 0.49% in PATHFINDER 2 and 0.51% in NHS-Galleri, corresponding to a 3- to 7-fold increase in

the number of cancers detected by screening when added to national guideline-recommended screening programs. Galleri demonstrated a high PPV; 66%–77% of participants with a Cancer Signal Detected result were diagnosed with cancer within 12 months. The false-positive rate was extremely low, ranging from 0.15%–0.26%, which corresponds to approximately one false positive result among every 500 individuals tested. Episode sensitivity ranged from 32%–35% across the two studies and was higher in the 12 pre-specified cancers responsible for approximately two-thirds of cancer deaths in the US. Importantly, CSO prediction was highly accurate, ranging from 92%–94%.

Table 5: PATHFINDER 2 and NHS-Galleri: Summary of Galleri Test Performance Results

	PATHFINDER 2 N=21,418[1]	NHS-Galleri N=50,739[1]
Cancer Detection Rate	0.49% (0.41 – 0.60%)	0.51% (0.45 – 0.58%)
PPV	77.0% (65.8 – 85.4%)	66.2% (56.7 – 74.6%)
False-Positive Rate	0.15% (0.09 – 0.25%)	0.26%[2] (0.18 – 0.39%)
Episode Sensitivity (12 Months)[3]	35.0% (29.8 – 40.5%)	31.6% (28.5 – 34.8%)
Episode Sensitivity (12 Months) 12 cancers responsible for two-thirds of US cancer deaths	61.3% (52.4 – 69.6%)	52.1% (46.9 – 57.2%)
CSO Prediction Accuracy	94.3% (88.2 – 97.4%)	91.9% (87.9 – 94.6%)

[1] Weighted
[2] NHS-Galleri does not capture recurrences which contributes to apparent increase in False-Positive Rate compared with PATHFINDER 2
[3] MCED-detected cancers/all cancers diagnosed over a 12-month period

1.4 Safety

The PATHFINDER 2 and NHS-Galleri clinical studies have demonstrated a favorable safety profile of Galleri, based on data generated using MCED-V2 (investigational device). The infrequent risks associated with the screening test are mitigated through labeling, comprehensive provider and patient education, and clinical support pathways for patients and their healthcare providers.

Across >165,000 participants, no device-related serious AEs were observed. Otherwise, serious AEs were uncommon and transient, and resolved without sequelae. Most of the study-related AEs were related to the phlebotomy procedure. Risks related to venipuncture are well established. Psychological stress is another risk associated with screening tests or any form of diagnostic testing. State anxiety was found to be elevated

temporarily following a Cancer Signal Detected result but returned to baseline within 12 months. These findings are consistent with patterns of psychological distress observed in association with guideline-recommended cancer screening tests (Kim et al., 2022).

Galleri has an extremely low false-positive rate of less than 0.3%, minimizing the risk of complications from unnecessary diagnostic procedures. The risks from a false-negative result are mitigated through product labeling, which recommends that patients continue with guideline-recommended screening and that new symptoms be evaluated promptly.

1.4.1 *PATHFINDER 2 Safety Results*

In PATHFINDER 2, the primary safety analysis evaluated the number and type of invasive procedures performed in participants who underwent diagnostic evaluation (described in Appendix 10.1) following an MCED-V2 Cancer Signal Detected result.

The proportion of participants who underwent an invasive procedure during diagnostic evaluation was 91% among participants with cancer and 48% among participants without cancer (Table 6). Surgical procedures were more common among participants diagnosed with cancer (15.7%) than those without cancer (4.4%). All four participants who underwent surgery without a cancer diagnosis were found to have benign neoplasms that warranted surgical intervention.

Table 6: PATHFINDER 2: Invasive Diagnostic Procedures

	Cancer Signal Detected			
	Cancer Diagnosis N=128		No Cancer Diagnosis N=90	
Participants with Events, % n				
Invasive procedure	90.6%	116	47.8%	43
Surgical	15.6%	20	4.4%	4
Non-surgical	80.5%	103	46.7%	42
Endoscopy[1]	36.7%	47	36.7%	33
Biopsy[2]	53.1%	68	11.1%	10
No invasive procedure	9.4%	12	52.2%	47

1 e.g., bronchoscopy, colonoscopy, cystoscopy
2 e.g., incisional or excisional biopsy, core needle biopsy, fine needle aspiration biopsy

Diagnostic evaluations performed following a Cancer Signal Detected result were consistent with the CSO-specific recommendations provided in the study protocol for 87% of participants. Among participants who were not diagnosed with cancer, most did not undergo an invasive procedure, and among those who did, most invasive procedures performed were endoscopies, as appropriate for their CSO.

Overall, 0.6% of all 25,114 participants in the safety analysis population underwent at least one invasive procedure following a Cancer Signal Detected test result.

AEs occurring during the time of diagnostic evaluation were uncommon. Of the 53 participants who experienced a study-related AE, 75% had non-serious events in the setting of phlebotomy. Nine participants experienced a total of 10 AEs during the time of diagnostic evaluation; of these, 5 were related to study activities. Overall, less than 1% of consented study participants experienced an AE during the 12-month follow-up period. In addition, there were no adverse device effects.

Effects on participant-reported state anxiety were modest and transient. Results from the State-Trait Anxiety Inventory-6 (STAI-6) showed that participant-reported state anxiety increased in participants who had a Cancer Signal Detected test results and returned to baseline levels by 12 months, consistent with what has been reported for other guideline-based screening modalities (Kim et al., 2022) (see details in Section 5.6.2).

Finally, no negative impact was observed on utilization of guideline-recommended cancer screenings. In PATHFINDER 2, screening utilization at 12 months was similar to baseline levels, indicating that use of the test did not reduce adherence to established screening programs (details in Section 5.6.1).

1.4.2 *NHS-Galleri Safety Results*

In NHS-Galleri, among 142,826 participants (including 576 who were not randomized), 569 study procedure/device-related AEs were reported. Of these AEs, 547 were classified as study-procedure-related (i.e., occurring up to the point of referral into the NHS), 20 were classified as device-related (i.e., occurring after the point of referral), and 2 were classified as both study procedure- and device-related (i.e., occurring during both time periods). The vast majority of these AEs were related to routine phlebotomy procedures. None of the study-procedure- or device-related AEs were assessed as serious (see details in Section 6.5).

Based on STAI-6 results administered to participants who had a Cancer Signal Detected test result, participant-reported state anxiety was modestly and transiently elevated, and decreased 12 months post-test, consistent with observations for other guideline-based screening tests (Kim et al., 2022) (see details in Section 6.4.4).

Participant-reported intention to adhere to guideline-recommended cancer screening was maintained or improved between baseline and year 1 (details in Section 6.4.5).

1.5 Benefit-Risk Summary

For MCED tests, episode sensitivity (as measured in prospective cohorts) is the performance measure presented to show effectiveness because true cancer status, including disease stage, at the time of the MCED test is unknown for individuals with cancer not detected by the MCED test and, thus, test sensitivity (as measured in individuals with known cancer status at the time of the test) cannot be assessed. PPV, false-positive rate, CSO prediction accuracy, and cancer detection rate are other critical measures of test performance to assess in prospective studies in the intended-use

population. Safety outcomes, such as anxiety and AEs, also require rigorous, prospective measurement in the intended-use setting.

Across two large studies totaling more than 165,000 participants, Galleri substantially increased the total number of cancers detected by screening, predominantly at stages with the opportunity for curative-intent treatment. Consistently in both studies, Galleri exhibited a high PPV, a very low false-positive rate, clinically meaningful episode sensitivity, and highly accurate CSO prediction, which facilitated efficient diagnostic resolution. Test performance metrics were especially strong in clinically actionable cancer type subgroups that include aggressive cancers requiring immediate treatment, highlighting the unmet need that Galleri is well-suited to address. Cancer types that lack common screening options – including rare cancer types, which collectively account for ~25% of incident cancers in the US (ACS, 2026) – comprised 75% of Galleri-positive cancers in PATHFINDER 2 and 62% of those in NHS-Galleri. In cancer types with existing guideline-recommended screening options, Galleri-detected interval breast cancers and interval colorectal cancers among PATHFINDER 2 participants who were eligible for and up to date with guideline-recommended screening for these cancer types, as well as lung cancers in participants who were ineligible for guideline-recommended lung cancer screening (Section 5.4.2). These data show that Galleri detects a meaningful number of cancers both in individuals who are eligible and those who are ineligible for guideline-recommended cancer screening tests. Thus, when Galleri is added to guideline-recommended cancer screening tests, Galleri offers broader coverage for detecting multiple types of cancers, including those with current screening options.

Galleri demonstrated a highly favorable safety profile. Study-related AEs were uncommon and unrelated to the device; participant-reported anxiety was modest and transient; and the test did not reduce adherence to guideline-recommended cancer screening. The low false-positive rate and high CSO prediction accuracy facilitated efficient targeted diagnostic evaluation and minimized unnecessary diagnostic procedures.

Prior long-term follow-up studies of users of MCED-V2 (investigational device; not the Galleri PMA device) showed that the risk of overdiagnosis is limited by the biology of the cfDNA test analyte. Specifically, individuals with a Cancer Signal Detected test result had cancers that exhibited more aggressive clinical behavior in terms of survival than those with No Cancer Signal Detected (i.e., test-positive cancers did not resemble overdiagnosed cancers) (Mahal et al., 2024; Patel et al., 2023; Swanton et al., 2026). Detected cancers also exhibited long-term outcomes that were consistent with stage-specific outcomes in the general US population (i.e., cancers detected by the test before distant metastasis were generally amenable to curative-intent treatment).

The risk of false-negative test results is mitigated by the fact that approximately 80% of the cancers not detected by Galleri in PATHFINDER 2 have guideline-recommended

cancer screening options and/or were detected at stage I based on incidental findings or signs/symptoms.

Based on these findings, Galleri meets the criteria recommended by the 2023 FDA Molecular and Clinical Genetics Panel Multi-Cancer Detection Panel described in Table 7.

Table 7: Galleri Meets 2023 Molecular and Clinical Genetics Panel's Recommendations for Multi-Cancer Detection Tests

	2023 Panel Recommendations	Galleri's Performance
✅	Detect multiple, clinically significant cancers, particularly those that lack recommended screening options	Galleri detects a shared cancer signal across a diverse range of cancer types, most of which have no available screening options, yet collectively account for most cancer deaths in the US. Galleri's performance across all cancers and unscreened cancers is strong. Episode sensitivity was >60% in PATHFINDER 2 and >50% in NHS-Galleri for key prespecified subgroups such as the 12 cancers accounting for two-thirds of US cancer deaths.[1] For cancers without common screening options,[2] episode sensitivity was 47.3% in PATHFINDER 2 and 40.6% in NHS-Galleri. As an adjunct to guideline-recommended screening, Galleri has the potential to significantly increase the number of screen-detected cancers at stages amenable to curative-intent treatment (82% of PATHFINDER 2 participants with Galleri-detected stages I-III cancers were treated with curative-intent treatment[3]).
✅	Provide tissue-of-origin (in this document called CSO) information to guide effective diagnostic evaluation	Galleri's CSO prediction is highly accurate (91.9%-94.3%) to guide targeted diagnostic work-up. Specifically, the median time to diagnostic resolution in PATHFINDER 2 was 46 days (interquartile range: 29-93 days).
✅	Demonstrate high PPV and very low false-positive rate to minimize unnecessary work-ups	Galleri has a high PPV of 66%-77% and an extremely low false positive rate of 0.15%-0.26%, minimizing unnecessary diagnostic procedures. Safety-relevant endpoints tied to high PPV and low false positive rate provide reassurance for healthcare providers and patients that a positive test result translates into a high likelihood of cancer, and low risk of unnecessary diagnostic investigations due to false positive results.
✅	Additive to, and not a replacement for, guideline-recommended single-cancer screenings	Galleri substantially increased the number of cancers detected by screening when added to guideline-recommended screening programs. Trial data demonstrated no decline in participant adherence to breast, cervical, colorectal, or lung cancer screenings at 12 months. Additionally, adherence to mammography screening up to 24 months after a negative MCED-V2 test has also been demonstrated using real-world evidence.

[1] 12 cancers responsible for two-thirds of US cancer deaths: anus; bladder or urothelial tract; colon or rectum; esophagus; head and neck; liver or intrahepatic bile duct; lung; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; and stomach

[2] Cancers without common screening options: anus; bladder or urothelial tract; bone or soft tissue sarcoma; esophagus; head and neck; kidney; liver or intrahepatic bile duct; lung; myeloid lineage; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; skin; stomach; thyroid; uterus; and "other"
[3] Curative-intent treatment was defined in PATHFINDER 2 as "treatment undertaken with goal of cure."

The totality of clinical test performance and safety evidence provides strong assurance of safety and effectiveness with a favorable benefit-risk profile for Galleri when used in addition to guideline-recommended screening tests. By increasing the number of cancers detected that are clinically actionable, especially aggressive cancer types that require prompt diagnosis and treatment, and providing accurate CSO prediction to guide efficient diagnostic evaluation, Galleri has the potential to substantially enhance comprehensive cancer screening and reduce the burden of cancer at the population level.

2 Background on Cancer and Screening

Summary

- Cancer is a leading cause of morbidity and mortality in the US, with ~2 million new cases and > 600,000 deaths annually.
- Advancing age is the single most important factor increasing absolute risk of cancer.
- The USPSTF currently provides Grade A or B screening recommendations for only 4 cancer types – breast, cervical, colorectal, and (for a high-risk subset) lung – and adds prostate cancer with a Grade C recommendation.
- For cancers without guideline-recommended screening options, detection typically occurs only after the onset of signs or symptoms, leading to later stage at diagnosis, poorer prognosis, and substantially greater treatment burden and cost.
- More than 70% of US cancer-related deaths arise from cancers without population-based screening recommendations.
- Across the full spectrum of cancer types, earlier stage at diagnosis translates to better long-term outcomes, including lower cancer-specific mortality and reduced morbidity.
- Galleri is a safe and effective test capable of detecting multiple cancer types at earlier stages and guiding efficient diagnostic work-up, when used in addition to the current cancer screening program.

2.1 Overview of Cancer and its Impact on Public Health

Despite meaningful progress in cancer control in the US, including prevention, screening, and treatment (Goddard et al., 2025), in 2026, an estimated 2,114,850 individuals will be newly diagnosed with cancer, and 626,140 will die of cancer (Siegel et al., 2026). In fact, cancer is the second leading cause of death in the US (Ahmad et al., 2024). Due to the aging of the population, the overall burden of new cancers is expected to increase by 38% by 2050 (Ferlay, 2024).

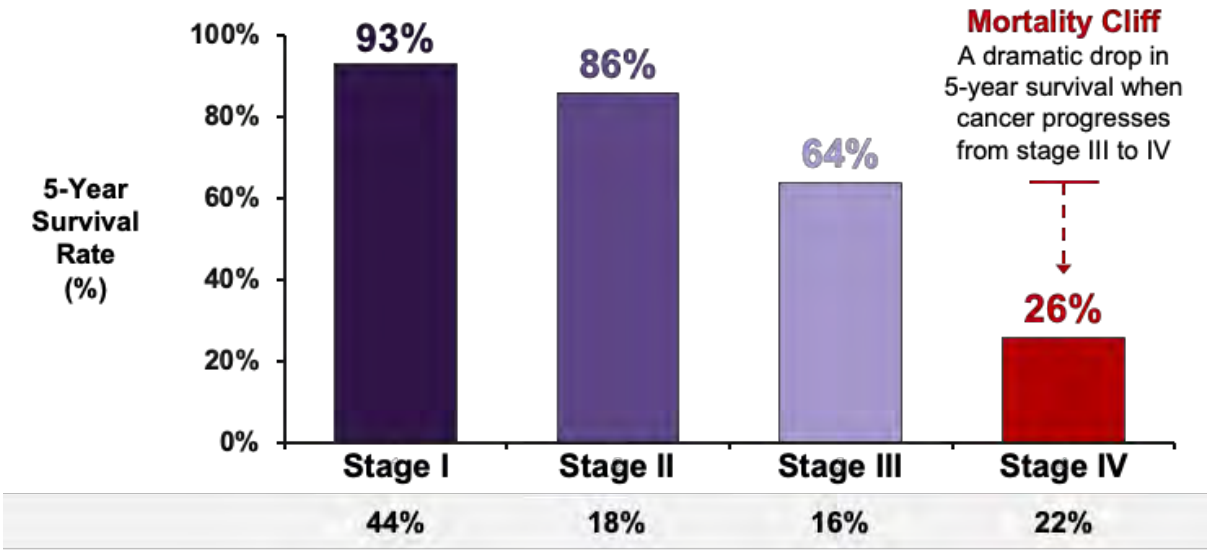
Advancing age is the single most important factor influencing the overall absolute risk of cancer, with cancer incidence increasing exponentially with age. Among adults aged 50 years and older, lifetime risk of cancer is approximately 1 in 3, and nearly 90% of all cancer diagnoses occur in this age group (ACS, 2026; Siegel et al., 2026).

2.1.1 Importance of Screening and Early Detection to Patient Morbidity and Mortality

Extent of cancer spread or stage at the time of diagnosis is a key determinant of morbidity, successful treatment and survival. Recent US Surveillance, Epidemiology,

and End Results (SEER) statistics for cancer-specific survival by stage at diagnosis show that patients diagnosed before cancer has distantly metastasized (stage IV), who have the greatest opportunity for curative-intent treatment, have substantially better survival (i.e., they avoid the survival "cliff" observed between stages III and IV). Cancers diagnosed at stage IV account for 18% of all cancer diagnoses but 48% of all cancer deaths (Clarke et al., 2020). These numbers emphasize that reduction in stage IV incidence may have a major impact on reducing cancer deaths by enabling curative-intent therapy, which has advanced substantially in recent years for cancers without distant metastasis.

Figure 4: US SEER Data: 5-Year Survival by Cancer Stage at Diagnosis in 2016–2017, Followed Through 2023



Source: SEER, 2026

As discussed in Section 1.2 above, cancer screening programs that have a USPSTF Grade A/B recommendation and are broadly utilized in the general population are available for only four cancer types – breast, cervical, colorectal, and lung (for a high-risk subset) – with a Grade C recommendation for prostate. Contemporary implementation and utilization of USPSTF Grade A/B-recommended screening programs is estimated to address 14% of incident cancers and 13% of cancer deaths nationally (NORC, 2022; Ofman et al., 2025), leaving most of the overall cancer burden unaddressed by screening and subject to diagnosis after distant metastasis. Even an individual who utilizes all guideline-recommended screening still has substantial residual risk of cancer morbidity and death, especially from cancers not covered by these programs. At each stage, screen-detected cancers have better outcomes than non-screen-detected cancers (Gill et al., 2014; Harowicz et al., 2026; Tickle et al., 2026), potentially in part through avoidance of emergency presentation (Thompson et al., 2026).

Cancers diagnosed outside of conventional screening programs, including interval cancers (i.e., cancers with guideline-recommended screening options that are diagnosed after a negative routine screening test and before the next scheduled screening test), are predominantly detected only after patients seek medical care for signs and symptoms (Danckert et al., 2021; Elliss-Brookes et al., 2012), which are more likely to occur when cancer has spread regionally or distantly. Moreover, many signs and symptoms of cancer are nonspecific (e.g., weight loss, fatigue), potentially causing a “diagnostic odyssey” or other challenges to timely diagnosis and initiation of treatment (Koo et al., 2018; Zakkak et al., 2024). Thus, in the absence of screening programs to detect cancer among individuals without clinical suspicion of cancer, diagnosis of cancer is more likely to occur after the disease has spread more extensively, with longer time and complexity in diagnostic resolution and, by extension, longer time to the initiation of potentially lifesaving treatments.

MCED represents a paradigm shift in cancer screening by detecting from a simple blood draw a systemic cancer signal shared by a variety of cancers. This MCED approach offers a higher overall cancer detection rate and a lower false positive rate than single-cancer screening approaches, thereby complementing the current and effective program of guideline-recommended screening. Efficient diagnostic work-up is enabled by a strong PPV and a predicted CSO derived from the cancer signal. MCED tests, including Galleri, thereby address our growing public health imperative to detect more of the overall cancer burden earlier and more expediently, when it can be treated with curative-intent therapy.

3 GALLERI PRODUCT DESCRIPTION

Summary

- Galleri is intended for adults aged 50 years or older, in whom almost 90% of all cancer diagnoses in the US occur.
- The test is based on DNA sequencing of cfDNA from blood. Specifically, the test surveys methylation status at specific genomic locations using hybridization capture applied to bisulfite converted DNA.
- Cancers that shed cfDNA tend to be more aggressive. Galleri detects a cancer-specific DNA-based methylation signal shared across multiple cancer types that enables multiple cancers to be screened at high specificity.
- For samples with a Cancer Signal Detected result, the device predicts an anatomical localization called Cancer Signal Origin (CSO), along with a supplemental Cancer Signal Origin information (CSO-S) that provides biological context, if appropriate.
- Evidence across distinct, iterative development studies shows that Galleri can detect and predict the anatomic location of a broad range of cancer types that shed cfDNA into the bloodstream.

3.1 Galleri Proposed Intended Use

The Galleri® test is a qualitative, next-generation sequencing (NGS)-based in vitro diagnostic test intended to detect cancer-specific methylation patterns in cell-free DNA isolated from peripheral whole blood. Galleri is intended for screening for the early detection of multiple types of cancer, in adults aged 50 years or older. The test is also intended for the prediction of Cancer Signal Origin in individuals with a Cancer Signal Detected test result.

A test result of Cancer Signal Detected, including a predicted Cancer Signal Origin, may indicate the presence of an invasive solid tumor or hematologic malignancy and should be followed by a diagnostic work-up recommended by qualified healthcare professionals. A test result of No Cancer Signal Detected does not rule out the presence of cancer, and individuals should continue with guideline-recommended single-cancer screening tests.

This test is performed at GRAIL, Inc. Prescription use only.

3.2 Overview of Galleri Device Development

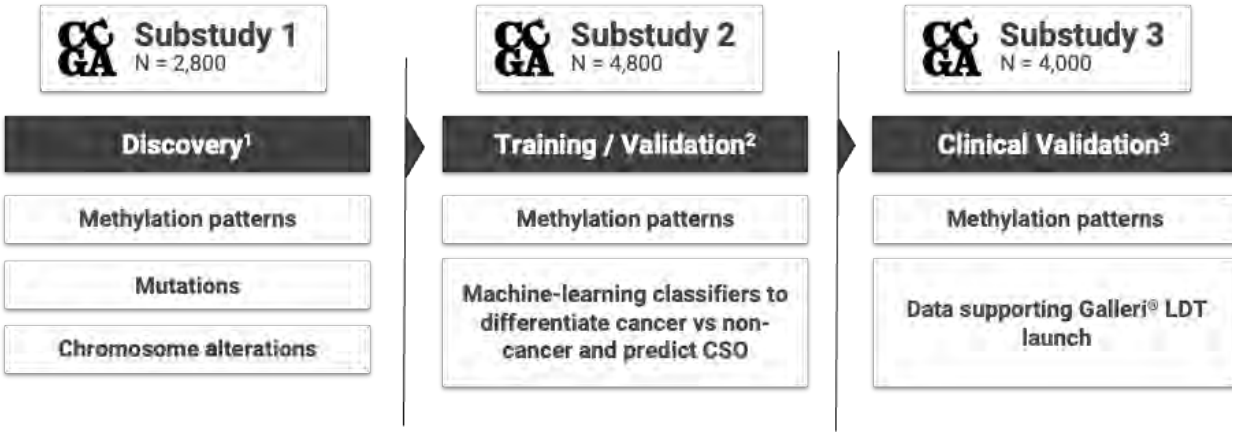
The scientific foundation that led to the development of the Galleri test is based on a 2015 study that investigated the incidental detection of occult malignancies in pregnant women whose noninvasive prenatal testing results were discordant with the fetal karyotype (Bianchi et al., 2015). Follow-up investigation revealed that the assay, which

sequences plasma cfDNA for clinical prenatal aneuploidy screening, had unintentionally detected cfDNA from undiagnosed maternal cancers. Importantly, abnormal aneuploidy signal was observed for multiple different cancer types, which suggested that cfDNA could potentially be used to detect multiple cancers from a single test. Indeed, loss of genomic integrity is viewed as an enabling phenotype of the hallmarks of cancer (Hanahan & Weinberg, 2000). Shared genomic hallmarks of cancer and the integrative property of blood make cfDNA a multi-cancer analyte.

The Galleri test was developed as a blood-based population-screening test for the detection of multiple cancers from shared genomic hallmarks of cancer in cfDNA. To minimize the burden of false positives, Galleri was designed to generate a single assessment for the presence of cancer with a very high specificity (i.e., a very low false-positive rate), and to provide a highly accurate localization of the CSO within the body to facilitate the evaluation of a cancer signal detected result (Jamshidi et al., 2022). This very low false-positive rate and high CSO prediction accuracy, along with clinically meaningful sensitivity and cancer detection rate, combine to improve screening program efficiency and are collectively designed to yield a favorable benefit-to-risk ratio. GRAIL followed a rigorous development process starting with distinct discovery, development, and validation studies using case-control designs (Klein et al., 2021) (Figure 5).

Several genomic hallmarks of cancer exist, including mutations, copy number alterations, and epigenetic changes. To develop the Galleri test with very high specificity, multi-cancer detection capability, and very high CSO prediction accuracy, several biomarkers were assessed systematically in the Circulating Cell-free Genome Atlas (CCGA) study (Jamshidi et al., 2022; Klein et al., 2021; Liu et al., 2020) (Figure 5). Cancer-specific methylation patterns were identified as having the best combination of highest test sensitivity, CSO prediction accuracy, and amenity to population-scale testing. Subsequent CCGA sub-studies that used distinct patient sets were used to develop a targeted methylation assay and validate test performance characteristics.

Figure 5: CCGA: Case-Control Studies in Advance of Interventional Studies*



*These studies used earlier versions of the GRAIL MCED test.
1. Jamshidi et al., 2022
2. Liu et al., 2020
3. Klein et al., 2021

3.3 Galleri Mechanism of Action via Detection of Aberrantly Methylated cfDNA

The Galleri test employs machine learning to assess cancer-relevant methylation patterns across a large number of genomic locations in cfDNA. Specifically, the current version of Galleri captures and aggregates data from millions of methylated DNA fragments using tens of thousands of continuous-valued features that capture methylation patterns across regions. The decision to return cancer signal detection is generated by a machine-learning-based algorithm. The algorithm includes two key classifications: one classifier uses features from cfDNA to determine whether a cancer signal is present. If a cancer signal is detected, another classifier is used to localize the cancer signal to an anatomic location (e.g., the CSO), and in some cases, to provide conditional additional biological context to supplement the CSO (CSO-S).

The cancer signal detection algorithm detects cancer-specific aberrant methylation patterns that are shared across hundreds of histologically distinct cancer types. Aberrant methylation patterns arise early in cancer development, with pre-cancerous lesions and invasive malignant cancers sharing DNA methylation abnormalities (Bararia et al., 2020; Feinberg & Tycko, 2004; Koch et al., 2018; Thomsen et al., 2019; Timp et al., 2014). Aberrant DNA methylation has also been proposed to drive oncogenesis and metastasis (Vogelstein et al., 2013). Given its commonality across cancer types, epigenetic reprogramming that occurs via aberrant DNA methylation is considered a hallmark of cancer (Hanahan & Weinberg, 2000; Hanahan & Weinberg, 2011).

The CSO algorithm analyzes methylation patterns for signals specific to primary organ of the cancer, cell lineage, and oncogenic origin. DNA methylation patterns are established during development in a cell-type-specific manner (Kohli & Zhang, 2013) and are mitotically heritable, enabling epigenetic memory (Almouzni & Cedar, 2016; Li & Zhang, 2014). Therefore, DNA methylation patterns define cell lineage, differentiation,

and embryologic origin (Loyfer et al., 2023). These information-rich patterns can be observed in differentially methylated regions of purified cells that can be used as the basis for predicting the likely cell of origin. Even though the methylated DNA shed from cancers is distinct from corresponding cells in normal tissue, sufficient information in the DNA patterns remains to predict the CSO and CSO-S in many MCED-detected cancers.

By integrating information from thousands of regions, Galleri detects robust methylation patterns that support cancer signal detection and CSO prediction.

3.4 Galleri Device Overview

3.4.1 Test Workflow

Galleri utilizes a multi-step automated workflow that includes the following steps:

1. **Prescription Order and Blood Collection**: After a licensed healthcare provider orders the test for a patient, whole blood is collected into two Streck® cfDNA blood collection tubes and shipped to the GRAIL Clinical Laboratory.
2. **Blood Specimen Receipt and Quality Control (QC)**: Upon arrival at GRAIL, all specimens are inspected and identified to ensure traceability throughout the testing and analysis process. A minimum of 3 mL of whole blood must be received to proceed with plasma isolation and downstream processing.
3. **Plasma Isolation and Hemolysis QC**: Whole blood specimens are processed in the GRAIL Clinical Laboratory within 7 days of collection. Plasma is isolated from both tubes of whole blood and is evaluated for hemolysis. Severely hemolyzed samples are rejected from further processing.
4. **Plasma cfDNA Isolation, cfDNA Quantification & Normalization**: cfDNA is extracted from plasma and quantified.
5. **Optimized Bisulfite Conversion**: This step captures the methylation states of the cfDNA in the DNA sequence by converting unmethylated cytosines to uracil while preserving methylated cytosines as cytosine. This chemical treatment enables the detection of methylation patterns, which are essential for identifying cancer-specific signals.
6. **Library Workflow**: Library workflow prepares nucleic acid fragments so they can be read and analyzed by a sequencing platform. Bisulfite-treated nucleic acid is denatured and converted into NGS libraries, which are then multiplexed and sequenced.
7. **Bioinformatics Pipeline, Batch QC, and Classification Results**: Sequencing data that meet the quality specifications are processed by a regulated software subsystem that performs three major functions: bioinformatics pipeline, batch QC, and classification results. Pipelines prepare sequencing data, generate classifier outputs, and surveil for sample swaps, contamination events, alongside verifying sample identity.

8. **Data Review**: After classification and Batch QC are complete, trained laboratory personnel review the resulting data to verify that the test results are eligible for release. Samples that do not meet QC criteria or have unresolved deviations are placed on hold until further investigation and resolution by qualified staff. All review and disposition activities are conducted under established laboratory quality system procedures.
9. **Test Report Generation**: Once a test result has been determined to be valid and reportable following sample and batch-level QC review, the test report is generated, which includes:
    a. Cancer Signal status ("Cancer Signal Detected" or "No Cancer Signal Detected")
    b. CSO prediction, if a cancer signal is detected
    c. CSO-S prediction, if a cancer signal is detected and if the CSO-S is applicable to the predicted CSO.

3.4.2 Cancer Signal Classifier

The Cancer Signal Classifier determines whether the sample is positive ("Cancer Signal Detected") or negative ("No Cancer Signal Detected") for a cancer-relevant methylation signal.

3.4.3 CSO Classifier

For samples with a Cancer Signal Detected result, the CSO classifier predicts from methylation the most likely origin of the cancer signal. CSO predictions are not diagnostic labels, but tools to guide diagnostic work-up. The CSO architecture is based on methylation signatures and work-up groupings aligned with likely diagnostic testing pathways. Diagnostic considerations based on the CSO prediction are provided as guidance to clinicians after a Cancer Signal Detected result (Appendix 10.5). Galleri reports a single CSO prediction per positive result, selected from 18 anatomical categories:

- Anus
- Bladder, Urothelial Tract
- Bone and Soft Tissue
- Breast
- Cervix
- Colon, Rectum
- Head and Neck
- Hematopoietic and Lymphoid Organs
- Kidney
- Liver, Intrahepatic Bile Duct
- Lung
- Melanocyte-containing Tissues/Skin

- Ovary
- Pancreas, Gallbladder, Extrahepatic Bile Duct
- Prostate
- Stomach, Esophagus
- Thyroid
- Uterus.

For a subset of Cancer Signal Detected results, the CSO-S classifier provides additional biological context of the detected signal (e.g., cellular lineage, histologic type, or viral integration), also predicted from methylation. CSO-S is reported as additional information on the test result report and includes 7 biological categories:

- Human Papillomavirus (HPV)-Associated Methylation Signal
- Squamous Cell Signal of Head and Neck, Lung and Esophagus
- Neuroendocrine Signal
- Female Reproductive Tract Signal
- Lymphoid Lineage
- Myeloid Lineage
- Plasma Cell Lineage.

The CSO-S prediction is returned in approximately 40% of Cancer Signal Detected cases and only when consistent with the reported CSO prediction, ensuring that results remain clinically interpretable.

3.4.4 Description of MCED-V2 and Galleri

Galleri was developed to provide a safe and effective blood-based MCED test using a shared cancer signal followed by CSO prediction. In a screening population, the test is intended to increase cancer detection as an adjunct to current guideline-recommended screening tests, while minimizing the harms of false positives, false negatives, and overdiagnosis.

Galleri has been improved upon over several versions based on learnings from real-world use and clinician feedback. Specifically, Galleri evolved from proof-of-concept (MCED-V1) to clinical evaluation (MCED-V2) and ultimately to the PMA device (Galleri), with iterative refinements increasing targeted specificity to >99.7% and streamlining CSO predictions. Galleri was developed to build on the MCED-V2 test with the intention of further enhancing product safety in the hands of physicians and patients, with the understanding that MCED is a new paradigm in cancer screening and that a diversity of doctors and health systems may use the test. Consequently, the Galleri classifier was trained against a more representative development dataset across participant age, sex, racial/ethnic background, cancer types, and health conditions. The Galleri classifier's development dataset was independent of PATHFINDER 2 and NHS-Galleri studies, and these tests were locked prior to assessing the performance of either test version. Galleri was also optimized to a fully automated laboratory workflow to significantly increase throughput and operational efficiency.

Despite the improvements, Galleri and MCED-V2 are highly similar. Both test versions utilize hybridization capture technology to capture specific methylation states in the human genome. The probe panel for both tests are overlapping, with Galleri's being slightly smaller, focusing on the most informative targets for cancer signal detection. While MCED-V2 was semi-automated, Galleri is fully automated. Finally, both tests provide a CSO prediction, although MCED-V2 returned up to two CSO predictions and Galleri returns a single CSO prediction. As shown in

Table 8, the majority of the CSO labels overlap between the two tests. The concordance results can be found in Appendix 10.4.

Table 8: CSO Labels in MCED-V2 and Galleri

MCED-V2	Galleri*
Anus	Anus
Bladder, Urothelial tract	Bladder, Urothelial tract
Lymphoid lineage	Hematopoietic and Lymphoid organs
Myeloid lineage	
Plasma cell lineage	
Bone and Soft tissue	Bone and Soft tissue
Breast	Breast
Cervix	Cervix
Colon, Rectum	Colon, Rectum
Head and Neck	Head and Neck
Kidney	Kidney (excluding renal pelvis)
Liver, Bile duct	Liver, Bile duct
Lung	Lung
Neuroendocrine cells of lung or other organs	Now provided as a CSO-S* for selected CSOs
Ovary	Ovary
Pancreas, Gallbladder	Pancreas, Gallbladder
Prostate	Prostate
Melanocytic lineage	Melanocyte-containing tissues/Skin
Stomach, Esophagus	Stomach, Esophagus
Thyroid gland	Thyroid
Uterus	Uterus

*See Section 3.4.3 for CSO-S labels.

3.4.5 Analytical Validation

GRAIL conducted analytical validation studies to establish analytical performance characteristics and demonstrate that the Galleri test is suitable for its intended use. The suite of analytical studies and their designs were informed by relevant FDA and Clinical & Laboratory Standards Institute guidelines and Agency interactions and involved a cumulative total of >15,000 sample evaluations. Studies included evaluation of limit of detection, repeatability and reproducibility, precision, analytical specificity (endogenous and exogenous interfering substances), cross-contamination and carry-over, robustness, cfDNA input guardbanding (input titration), and reagent and intermediate sample stability. The studies followed predefined testing protocols and performance objectives, and all study objectives were met.

4 DEVELOPMENT HISTORY

Summary

- Galleri received Breakthrough Designation from the FDA in 2018.
- In addition to the PATHFINDER 2 and NHS-Galleri studies, the clinical development program for Galleri includes CCGA, a longitudinal case-control study of 15,254 participants in the US and Canada; and PATHFINDER 1, a prospective, interventional study of 6,662 participants in the US.
- CCGA and PATHFINDER 1 supported the development of Galleri and demonstrated robust, stable, and replicable performance of earlier versions of the test, although their results are not directly relevant to the safety and effectiveness of Galleri.

4.1 Regulatory Milestones

Key regulatory interactions across more than 8 years of engagement between GRAIL and the FDA are summarized in Table 9. GRAIL and FDA have interacted over multiple pre-submissions, teleconferences, and face-to-face meetings on the analytical and clinical validation data required.

Table 9: Key Regulatory Interactions During Galleri Development

Interaction	Date
Breakthrough Designation granted	August 2018
PATHFINDER IDE approved	November 2019
PMA Module 1 submitted	April 2021
PATHFINDER 2 IDE approved	September 2021
PMA Module 2 submitted	January 2022
NHS-Galleri IDE approved	November 2022
PMA Module 3 submitted	July 2023
PMA Module 4 submitted	December 2024
PMA Module 5 submitted	December 2025
Final module of PMA submitted	January 2026

4.2 Clinical Development Program

The clinical development program for Galleri includes multiple studies supporting test development, validation, and implementation. The initial version of the GRAIL MCED test (MCED-V1) was developed and validated in CCGA, a 15,254-participant case-control study of cases with known cancer and controls without cancer. PATHFINDER 1 then evaluated MCED-V1 and MCED-V2 in an IDE-approved prospective, interventional study involving 6,662 participants without known cancer. The CCGA and PATHFINDER 1 studies supported the development of Galleri, but do not provide data directly relevant to the safety and effectiveness of Galleri.

Briefly, the CCGA study was a longitudinal, multicenter clinical study in the US and Canada that enrolled 8,584 participants with a recent diagnosis of cancer and 6,670 without a recent diagnosis of cancer (Liu et al., 2020). The first CCGA analysis (CCGA1) compared several cfDNA-based approaches for MCED test development, and identified whole-genome methylation in cfDNA as the exhibiting the best performance based on the highest test sensitivity at a fixed > 98% test specificity, along with a low limit of detection, broad feasibility, and, separately, the highest CSO prediction accuracy among the tested features (Jamshidi et al., 2022). The second CCGA classification analysis (CCGA2) was designed to develop and validate the targeted methylation cfDNA assay (MCED-V1) that served as the basis for the development of the classifier that distinguishes cancer from non-cancer and predicts the CSO (MCED-V2) (Liu et al., 2020). The third CCGA classification analysis (CCGA3) was used to assess the performance of the MCED-V2 version of the Galleri test, to lay the foundation for subsequent prospective clinical studies of test performance and safety (Klein et al., 2021).

The PATHFINDER 1 study was an IDE-approved, prospective, interventional study of 6,662 US participants without clinical suspicion of cancer who received an investigational multi-cancer early detection test (MCED-V1) (Schrag et al., 2023). Later, blood samples were reanalyzed with an updated version of the test (MCED-V2) to evaluate the performance of MCED-V2. The primary objective of the PATHFINDER 1 study was to assess the extent of diagnostic testing required to achieve diagnostic resolution following a Cancer Signal Detected MCED-V1 test result. The secondary objective was to evaluate test performance. Results confirmed the viable implementation of MCED screening for cancer in the intended-use population (Schrag et al., 2023).

The primary evidence for the Galleri PMA comes from the results from the IDE-approved PATHFINDER 2 and NHS-Galleri studies (details in Sections 5 and 6, respectively). PATHFINDER 2 enrolled 35,878 participants and is the largest interventional study of an MCED test ever conducted in the US. NHS-Galleri is a randomized, controlled clinical trial that enrolled 142,826 participants in England. As discussed with FDA, the PMA submission includes a prespecified analysis focused on Galleri test performance and safety, based on 12 months of follow-up data from approximately 25,000 participants in PATHFINDER 2, and data from the prevalent screening round (first year) of NHS-Galleri.

5 PATHFINDER 2

Summary

- PATHFINDER 2 enrolled a diverse and representative group of participants, supporting the generalizability of these findings to the US intended-use population.
- In PATHFINDER 2, Galleri demonstrated high PPV, a very low false-positive rate, clinically meaningful episode sensitivity, highly accurate CSO prediction, and efficient time to diagnostic resolution.
    - Galleri episode sensitivity for cancers responsible for two-thirds of US cancer deaths was 61.3%, and overall episode sensitivity was 35.0%.
    - Specificity was 99.85%, PPV was 77.0%, and CSO prediction accuracy was 94.3%.
    - Galleri testing approximately tripled the number of cancers detected by screening when added to USPSTF Grade A/B/C-recommended screening, and increased the number by seven-fold when added to USPSTF Grade A/B screening.
    - More than two-thirds of cancers were stages I-III at diagnosis. Of these, 82% received treatment with curative intent.
- Study-related AEs were uncommon, changes in participant-reported state anxiety were modest and transient, and the test did not reduce adherence to guideline-recommended cancer screening.
- The low false-positive rate and accurate CSO prediction facilitated targeted diagnostic evaluation and minimized unnecessary diagnostic procedures.
    - Median time to diagnostic resolution was 46 days (36 days for true positives and 75 days for false positives), substantially faster than that observed among insured US cancer patients.
    - Invasive procedures were performed primarily in patients ultimately diagnosed with cancer.
- All prespecified study success criteria were exceeded, including episode sensitivity across all cancer types (35.0%), specificity (99.85%), and CSO prediction accuracy (94.3%).

5.1 Study Design

PATHFINDER 2 is an IDE-approved, prospective, interventional study using MCED-V2 (investigational device) in which participants aged 50 years or older without clinical suspicion for cancer were enrolled at 31 healthcare sites in the US and one site in Canada (Nabavizadeh et al., 2026). The primary objectives of the study were to

evaluate the safety and the performance of Galleri in a large, diverse intended-use screening population.

Following informed consent, up to four tubes of blood were collected from study participants, plasma samples were tested with the MCED-V2 test version, and results were returned to clinical site study investigators. Plasma samples remaining after MCED-V2 testing were frozen and stored for future use. A subset of the frozen plasma samples was selected for testing with the Galleri test to evaluate test performance (see Section 5.3 for additional details).

In cases with a Cancer Signal Detected (positive) test result, a targeted diagnostic work-up was coordinated by the study medical team at the enrolling sites. Up to two CSO predictions could be returned with MCED-V2. The site study medical teams were strongly encouraged to evaluate participants for cancer based on the first CSO prediction using the CSO-based diagnostic evaluations described in the study protocol (see Appendix 10.1). If no cancer was identified based on the first CSO prediction, then site study medical teams were asked to evaluate the participant for the second CSO prediction, if one was reported.

For participants for whom diagnostic resolution of cancer was not achieved through CSO-guided targeted work-up and PET-CT was not used as part of diagnostic evaluation, a diagnostic PET-CT was requested to assess cancer status. For participants for whom diagnostic resolution of cancer diagnosis was achieved, clinical information including but not limited to cancer type, pathology, imaging, and clinical stage at diagnosis was collected. Clinical stage at initial diagnosis was used as the preferred method to compare across cancers, since not all individuals with cancer undergo surgical treatment prior to other therapy, and differences in response to therapy can impact assessment of cancer stage (*AJCC Cancer Staging Manual*, 2017).

In cases with a No Cancer Signal Detected (negative) test result, participants were instructed not to interpret a negative test result as the absence of cancer, and to continue to adhere to guideline-recommended cancer screening.

Safety was evaluated during the study in terms of invasive diagnostic procedures performed in participants with positive MCED-V2 test results, and AEs were reported for all study participants. In addition, participant-reported outcomes were collected at several time points during the study to assess participants' perceptions about the test, including state anxiety, health-related quality of life, and adherence to guideline-recommended screening.

The Galleri PMA included data from the first 25,125 eligible study participants with 12 months of complete follow-up and evaluable MCED-V2 test results. All participants are being actively followed for 3 years from the time of enrollment to assess for cancer status and utilization of guideline-recommended cancer screening on an annual basis.

5.1.1 Enrollment Criteria

Key inclusion criteria included:

- Participants must be at least 50 years of age, inclusive.

Key exclusion criteria included:

- Undergoing or referred for diagnostic evaluation due to clinical suspicion for cancer (e.g., referred to a medical or surgical oncologist, or scheduled for biopsy on the basis of a suspicious imaging abnormality).
- Personal history of invasive solid tumor or hematologic malignancy, diagnosed within the 3 years prior to expected enrollment date, or diagnosed greater than 3 years prior to expected enrollment date and never treated. Individuals with a diagnosis of non-metastatic basal cell carcinoma and squamous cell carcinoma of the skin were not excluded.
- Prior/Concurrent Concomitant Therapy (Medications/Treatments): Definitive treatment for invasive solid tumor or hematologic malignancy within the 3 years prior to expected enrollment date. Adjuvant hormone therapy for cancer (e.g., for Breast or prostate cancer) was not an exclusion criterion.
- Current pregnancy (by self-report of pregnancy status).

5.1.2 Statistical Analyses

5.1.2.1 Study Objectives and Endpoints

The primary safety objective was to evaluate the number and type of invasive procedures performed, and number and type of AEs due to diagnostic testing in all participants with Cancer Signal Detected test results.

The primary effectiveness objective was to evaluate Galleri test performance based on cancer status at 12 months including the following metrics:

- PPV
- Negative predictive value (NPV)
- Episode sensitivity
- Specificity
- Positive likelihood ratio
- Negative likelihood ratio
- CSO prediction accuracy
- MCED cancer detection rate
- Number needed to screen to detect one cancer.

Key secondary objectives and endpoints included the following:

- Evaluate test performance in selected demographic and clinical subgroups
- Evaluate utilization of guideline-recommended cancer screening procedures after use of the test
- Assess participant-reported state anxiety resulting from use of the test

- State anxiety as assessed by STAI-6 questionnaire.

5.1.2.2 Sample Size Determination

Based on microsimulations similar to those described in Dai et al. (2024) and conservative assumptions about cancer incidence, at least 264 participants with cancer diagnosis, including 102 participants with cancer diagnosis and MCED-V2 positive test results, were expected among 25,000 enrolled participants during 12 months of follow-up time. These expected counts, together with approximately 7,500 samples from participants with MCED-V2-negative results and no cancer diagnosis during 12 months. selected for Galleri testing, were considered adequate to characterize episode sensitivity, specificity, and CSO prediction accuracy, with uncertainty quantified using two-sided 95% CIs.

5.1.2.3 Cancer Status Assessment and Loss to Follow-Up

The 12-month cancer status assessment was considered complete (i.e., no loss to follow-up) when:

- The cancer diagnosis date was within the first 12 months of follow-up period, or
- No cancer diagnosis was documented within the first 12 months of follow-up period based on electronic medical record/direct contact.

Participants with an incomplete cancer status assessment at 12 months were defined as those with no cancer diagnosis reported at the time of the last electronic medical record/direct contact and the last electronic medical record/direct contact occurred less than 11 months after the blood draw.

5.1.2.4 Analysis of Test Performance

Galleri test performance was evaluated using endpoints defined based on a 2x2 contingency table that was constructed based on cancer status at 12 months as the reference standard (Table 10).

Table 10: 2x2 Contingency Table for Galleri Test Performance

		Cancer Status	
		Present	**Absent**
MCED Test Result for Cancer Signal Detection	**Positive**	True Positive	False Positive
	Negative	False Negative	True Negative

12-month episode sensitivity was analyzed for all cancers, by specific cancer type, and for prespecified cancer subgroups:

- 12 cancers responsible for two-thirds of US cancer deaths (anus; bladder or urothelial tract; colon or rectum; esophagus; head and neck; liver or intrahepatic bile duct; lung; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; and stomach)

- 6 aggressive cancers with low 5-year survival in the US (esophagus; liver or intrahepatic bile duct; lung; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; and stomach)
- Cancers without common screening options (anus; bladder or urothelial tract; bone or soft tissue sarcoma; esophagus; head and neck; kidney; liver or intrahepatic bile duct; lung; myeloid lineage; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; skin; stomach; thyroid; uterus; and “other”)
- Solid cancers with common screening options (breast, cervix, colon or rectum, and prostate)
- Solid cancers without common screening options (anus; bladder or urothelial tract; bone or soft tissue sarcoma; esophagus; head and neck; kidney; liver or intrahepatic bile duct; lung; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; skin; stomach; thyroid; uterus; and “other”)
- Hematologic malignancies (myeloid lineage, lymphoid lineage, plasma cell lineage).

Other test performance metrics such as PPV and specificity are for all cancer types combined. Because Galleri is designed to detect a shared cancer signal across multiple cancer types, specificity is not clinically meaningful when calculated by individual cancer type. Participants without cancer would contribute to the false-positive count for each cancer type, resulting in repeated counting of the same false-positive results across multiple cancer-specific analyses.

Galleri performance was evaluated using weighted analysis with adjustment for sampling probabilities. The weight was 1 for participants with a cancer diagnosis or MCED-V2-positive test result, since all of these participants were selected for Galleri analysis. The weights for participants with MCED-V2-negative test results and no cancer diagnosis were calculated as the reciprocal of the sampling probabilities. Sampling probabilities were calculated as the proportion of participants selected out of all participants eligible for selection within each stratum.

5.2 Study Participants

5.2.1 Demographics and Baseline Characteristics

Of the consented participants with cleaned clinical data at the time of data lock, 25,490 had 12 months of follow-up by the data cutoff date (December 31, 2024). Of these participants, 96 were not clinically eligible, 261 were not clinically evaluable (e.g., did not have an evaluable blood draw), and 8 did not have evaluable MCED-V2 test results. Thus, the MCED-V2 analyzable set included 25,125 participants. Of these, 229 had an MCED-V2-positive result, including 133 with a cancer diagnosis within 12 months. Among 24,896 participants with an MCED-V2-negative result, 196 had a cancer diagnosis within 12 months.

PATHFINDER 2 enrolled a large and diverse participant population representative of the intended-use population (Table 11).

Mean age of participants was approximately 65 years of age, and slightly more than half (57%) were female. Approximately 8% of participants were Black or African American, 6% were Asian, and 81% were White. The majority of participants were never smokers (69%), with light or no alcohol use (44% and 24%, respectively), and no prior history of cancer (90%).

Demographic and baseline characteristics of participants in the Galleri analyzable set, assessed using weighted analysis, were generally consistent with the MCED-V2 analyzable set.

Table 11: PATHFINDER 2: Participant Demographics and Baseline Characteristics in the MCED-V2 Analyzable Set

Characteristic	Participants with 12M follow-up time as of December 31, 2024 (N = 25,125)
Age (years)	
Mean (standard deviation)	64.7 (8.2)
Median (interquartile range)	65.0 (59.0, 71.0)
Min, Max[1]	50.0, 90.0
Age group	
50-59 years	6796 (27.0%)
60-69 years	11143 (44.4%)
70-79 years	6315 (25.1%)
≥80 years	871 (3.5%)
Biological sex	
Female	14269 (56.8%)
Male	10856 (43.2%)
Race	
American Indian or Alaska Native only	182 (0.7%)
Asian only	1420 (5.7%)
Black or African American only	2066 (8.2%)
Native Hawaiian or other Pacific Islander only	60 (0.2%)
White only	20402 (81.2%)
More than one race reported	324 (1.3%)
Missing	671 (2.7%)
Ethnicity	
Hispanic or Latino	1735 (6.9%)
Not Hispanic or Latino	23102 (91.9%)

Characteristic	Participants with 12M follow-up time as of December 31, 2024 (N = 25,125)
Missing	288 (1.1%)
Body mass index category	
<25 kg/m^2	8208 (32.7%)
25 to <30 kg/m^2	9053 (36.0%)
≥30 kg/m^2	7798 (31.0%)
Missing	66 (0.3%)
Smoking status	
Current smoker	918 (3.7%)
Former smoker	6927 (27.6%)
Never smoker	17280 (68.8%)
Current alcohol use (past 12 months)	
Heavy	1693 (6.7%)
Moderate	5995 (23.9%)
Light	11010 (43.8%)
None	6049 (24.1%)
Missing	378 (1.5%)
Prior cancer history[2]	
Yes	2507 (10.0%)
No	22618 (90.0%)

1 Age reporting was truncated at 90 years
2 Non-metastatic basal cell carcinoma and squamous cell carcinoma of the skin are not included

5.3 Galleri Testing

Results returned during the entirety of the PATHFINDER 2 clinical study were from MCED-V2. However, iterative refinement is standard practice for *in vitro* diagnostics to support the continuous improvement of test performance. Consistent with this approach, the strategy to assess the performance of Galleri, which is described below, was prespecified and discussed with the FDA prior to the lock of the statistical analysis plan.

Frozen plasma samples from a subset of PATHFINDER 2 participants were used to assess Galleri performance. A sampling scheme was implemented so that a subset of samples could be tested with Galleri to evaluate its performance with statistical efficiency and ensure that the analysis results are representative of the overall study population. Samples from the following groups of clinically eligible and clinically evaluable participants were selected:

- All participants with positive MCED-V2 test results;
- All participants with cancer diagnosis during 12 months of follow-up time; and

- Samples from a stratified random subset of participants with negative MCED-V2 test results and no cancer diagnosis during 12 months of follow-up time and completed cancer status assessment at 12 months.

Stratification factors included age, race/ethnicity, prior cancer history, smoking status, and selected conditions that may affect cfDNA shedding or methylation such as inflammatory conditions (e.g., pancreatitis), use of demethylating agents, and prior organ transplant. These factors were chosen to provide sufficient representation of subsets of interest, especially relatively small subsets of population that are important to characterize diversity and representativeness in terms of race and ethnicity, and Galleri test performance in terms of false-positive rate.

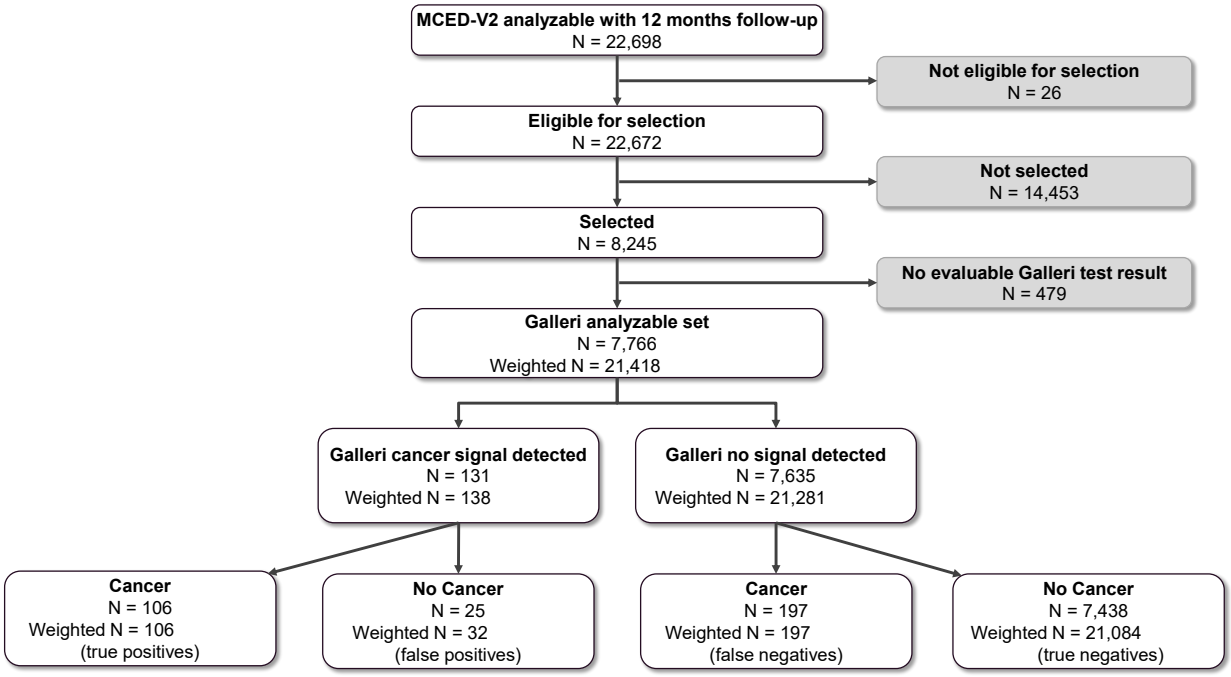
The number of samples in the subset of participants with negative MCED-V2 test results and no cancer diagnosis during 12 months was chosen to ensure sufficient power for demonstrating that the specificity of Galleri is significantly higher than 99%. Estimates of test performance were calculated with adjustment for sampling weights.

The sampling scheme implemented for Galleri processing is a statistically justified and highly efficient approach that allows representative evaluation of Galleri performance in the PATHFINDER 2 study.

5.3.1 Galleri Disposition

Of the 25,125 participants with analyzable MCED-V2 results, 22,698 participants with completed 12-month assessments were considered for selection for testing with the Galleri test (Figure 6). A total of 8,245 frozen plasma samples were selected for testing with Galleri, which included all eligible participants with MCED-V2 Cancer Signal Detected results, all eligible participants who were diagnosed with cancer, and a subset of participants with MCED-V2 No Cancer Signal Detected results and no cancer diagnosis. Of the 8,245 participants selected, 479 did not have valid Galleri test results, leaving 7,766 participants (21,418 weighted) in the Galleri analyzable set.

Figure 6: PATHFINDER 2: Participant Flow Diagram for Galleri Analyzable Set (Participants with 12 Months of Follow-up Time as of December 31, 2024)



5.4 Galleri Test Performance

Table 12 shows the 2x2 contingency table of the primary effectiveness evaluation results for Galleri in PATHFINDER 2. Galleri met all prespecified study success criteria.

Episode sensitivity was 35.0%. Galleri had high specificity (99.85%), which substantially exceeds the specificities based on usual care for cancer detection (Table 1). This high specificity is a critical safety feature of the test that limits the occurrence of false-positive results (0.15% in PATHFINDER 2) and resultant unnecessary diagnostic work-up.

Galleri also had a very high PPV (77.0%), which increases the clinical confidence in a positive test result and reduces the risk of anxiety due to a false-positive test result. Galleri's PPV substantially exceeds the PPVs for usual care for cancer detection (Table 1).

Table 12: PATHFINDER 2: Galleri Test Performance at 12-Month Follow-up Time Point

	Cancer diagnosis within 12 Months (N=303)	No cancer diagnosis within 12 Months (Weighted N*=21,115)	Total (Weighted N*=21,418)	
Galleri Cancer Signal Detected	106	32	138	**PPV=77.0%** (65.8%, 85.4%)
Galleri No Cancer Signal Detected	197	21,084	21,281	**NPV=99.07%** (98.93%, 99.2%)
	Episode Sensitivity=35.0% (29.8%, 40.5%)	**Specificity=99.85 %** (99.75%, 99.91%)		

NPV, negative predictive value; PPV, positive predictive value.
*Weights were calculated for participants with no cancer diagnosis and MCED-V2 no cancer signal detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected.
CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity); logistic regression with robust sandwich variance for weighted measures (specificity, PPV, and NPV).

Table 13: PATHFINDER 2: Additional Galleri Test Performance Metrics at 12-Month Follow-up Time Point

	Total (Weighted N* = 21,418)
False positive rate (n/N) (95% CI)	0.15% (32/21115) (0.09%, 0.25%)
Positive Likelihood Ratio (95% CI)	233.7 (135.6, 402.7)
Negative Likelihood Ratio (95% CI)	0.65 (0.60, 0.71)
MCED cancer detection rate (n/N) (95% CI)	0.49% (106/21418) (0.41%, 0.60%)
Number needed to screen (n/N) (95% CI)	202 (21418/106) (167, 245)
MCED cancer signal detection rate (n/N) (95% CI)	0.64% (138/21418) (0.53%, 0.78%)

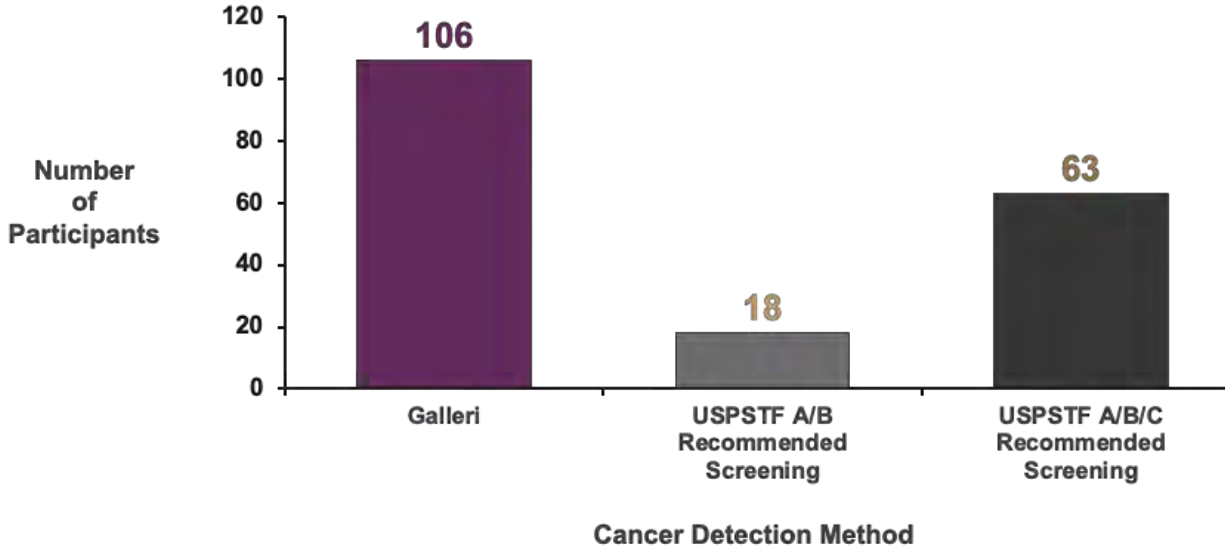
*Weights were calculated for participants with no cancer diagnosis and MCED-V2 no cancer signal detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected.
CIs were calculated as follows: logistic regression with robust sandwich variance for weighted measures (false-positive rate, Galleri cancer detection rate, Galleri cancer signal detection rate, number needed to screen); and delta method for positive likelihood ratio and negative likelihood ratio.
MCED cancer detection rate = true positives/total; MCED cancer signal detection rate = (true positives + false positives)/total

5.4.1 Distribution of Cancers Observed

The number of cancers detected by screening when Galleri was added to USPSTF Grade A/B-recommended screening (n=124) was nearly seven times the number based on USPSTF Grade A/B screening only (n=18), and the number detected by screening when Galleri was added to USPSTF Grade A/B/C-recommended screening (n=169)

was almost three times the number based on USPSTF Grade A/B/C screening only (n=63) (Figure 7).

Figure 7: PATHFINDER 2: Distribution of Cancers That Were Detected by Screening When Galleri was Added to Guideline-Recommended Screening



Note: For participants with multiple primary cancers, only the first diagnosed is included.
4 participants are not shown who had cancers detected by MCED-V2 but not Galleri, and whose cancer types have USPSTF Grade A/B/C screening options. If the negative Galleri test result had been returned, these participants might otherwise have had their cancer detected by USPSTF guideline-recommended screening (if they were eligible), clinically detected, or not detected during the 12-month follow-up.

A total of 90 participants were diagnosed with new cancers, 15 with recurrent cancers, and one with a cancer of unknown new or recurrent status. The distribution of new cancers by stage is presented in Table 14. Of these, 68.9% were detected at stages I-III and 48.9% at stages I-II. Of the participants with a Galleri Cancer Signal Detected and stages I-III at diagnosis, most (81%, 50/62) had cancers with no common screening options in the US (as defined in Section 5.1.2.4).

Table 14: PATHFINDER 2: Distribution of Stage for Participants with Galleri-Detected New Cancers

Cancer stage	Galleri-Detected (N = 90[1])
Stage I	27 (30.0%)
Stage II	17 (18.9%)
Stage III	18 (20.0%)
Stage IV	24 (26.7%)
Stages I-II	44 (48.9%)
Stages I-III	62 (68.9%)
No tumor-node-metastasis stage expected[2]	4 (4.4%)
Missing	0

[1] Excludes 15 participants with recurrent cancer 1 participant with unknown recurrent or new cancer status.
[2] No tumor-node-metastasis stage is expected for cancers such as brain and spinal cord, leukemia, myeloma and plasma cell disorders, polycythemia vera, and cancer of unknown primary.

Treatment intent was curative (defined as treatment undertaken with the goal of cure) for 82% of new primary cancers diagnosed at stages I–III and 38% of those diagnosed at stage IV among participants with Galleri-positive tests.

Of the cancers not detected by Galleri (false negatives), approximately 80% were cancer types that have guideline-recommended screening (59%) or were diagnosed at stage I based on incidental findings or signs and symptoms (20%). Of the false-negative cancers with guideline-recommended screening options, 69% (27/39) of the breast cancers were stages I-II, 67% (2/3) of the colorectal cancers were stage I, and 69% (46/67) of the prostate cancers were stages I-II.

5.4.2 Galleri 12-Month Episode Sensitivity by Cancer Type, Prespecified Cancer Type Subgroups, and Selected Demographic and Clinical Subgroups in PATHFINDER 2

Galleri 12-month episode sensitivity by cancer type is shown in Table 15, and ranged from 0.0% for myeloid lineage and skin cancers (excluding basal cell carcinoma (BCC)/squamous cell carcinoma of the skin (SCC)) to 81.2% for head and neck and liver/intrahepatic bile duct cancers. Point estimates and 95% CIs are not shown for cancer types with fewer than 5 cases.

Table 15: PATHFINDER 2: Galleri 12-Month Episode Sensitivity by Cancer Type

Cancer Type (Based on First-Diagnosed Cancer)	12-Month Episode Sensitivity (n/N) (95% CI)
Anus	2/4
Bladder, Urothelial Tract	28.6% (2/7) (8.2%, 64.1%)
Bone or Soft Tissue Sarcoma	(1/4)
Breast	26.4% (14/53) (16.4%, 39.6%)
Colon/Rectum	62.5% (5/8) (30.6%, 86.3%)
Esophagus	(1/2)
Head and Neck	81.2% (13/16) (57.0%, 93.4%)
Kidney	18.8% (3/16) (6.6%, 43.0%)
Liver, Intrahepatic Bile Duct	81.2% (13/16) (57.0%, 93.4%)
Lung	47.1% (8/17) (26.2%, 69.0%)
Lymphoid Lineage	63.0% (17/27) (44.2%, 78.5%)
Myeloid Lineage	0.0% (0/6) (0.0%, 39.0%)
Ovary or Fallopian Tubes	60.0% (3/5) (23.1%, 88.2%)
Pancreas, Extrahepatic Bile-Duct, Gallbladder	66.7% (6/9) (35.4%, 87.9%)
Plasma Cell Lineage	60.0% (3/5) (23.1%, 88.2%)
Prostate	10.7% (8/75) (5.5%, 19.7%)
Skin (excluding BCC/SCC)	0.0% (0/14) (0.0%, 21.5%)
Stomach	(1/4)
Thyroid	(0/4)
Uterus	(1/4)
Other	71.4% (5/7) (35.9%, 91.8%)

Episode sensitivity is not estimated for cancer types with <5 cases.
Other cancer types include thymus (n = 2), ampulla of Vater (n = 1), brain and spinal cord (n = 1), cancer of unknown primary (n = 1), small intestine (n = 1), and testis (n = 1).

As shown in Table 16, 12-month episode sensitivity was highest for the subgroups of 12 cancers responsible for two-thirds of US cancer deaths and the 6 aggressive cancers with low 5-year survival in the US. Galleri 12-month episode sensitivity was lowest for the subgroup of solid cancers with common screening options. Of the 12 cancers responsible for two-thirds of US cancer deaths, which also includes the subset of 6 aggressive cancers with low 5-year survival in the US, 7 cancer types had a Galleri 12-month episode sensitivity point estimate of 60% or higher (colon/rectum, head and

neck, liver/intrahepatic bile-duct, lymphoid lineage, ovary/fallopian tubes, pancreas/extrahepatic bile-duct/gallbladder, and plasma cell lineage) (Table 15).

Table 16: PATHFINDER 2: Galleri 12-Month Episode Sensitivity in Prespecified Cancer Subgroups

	Episode Sensitivity		
	%	95% CI	n/N
12 cancers responsible for two-thirds of US cancer deaths[1]	61.3%	52.4%-69.6%	73/119
6 aggressive cancers with low 5-year survival in US[2]	60.4%	46.9%-72.4%	32/53
Cancers without common screening options[3]	47.3%	39.9%-54.9%	79/167
Solid cancers with common screening options[4]	20.0%	14.1%-27.5%	27/135
Solid cancers without common screening options[5]	45.7%	37.4%-54.3%	59/129
Hematologic malignancies[6]	50.0%	34.5%-65.5%	18/36

1 Anus, bladder/urothelial tract, colon/rectum, esophagus, head and neck, liver/intrahepatic bile duct, lung, lymphoid lineage, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, plasma cell lineage, and stomach
2 Esophagus, liver/intrahepatic bile duct, lung, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, and stomach
3 Anus, bladder/urothelial tract, bone/soft tissue sarcoma, esophagus, head and neck, kidney, liver/intrahepatic bile duct, lung, myeloid lineage, lymphoid lineage, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, plasma cell lineage, skin, stomach, thyroid, uterus, and “other”
4 Breast, cervix, colon/rectum, prostate
5 Anus, bladder/urothelial tract, bone/soft tissue sarcoma, esophagus, head and neck, kidney, liver/intrahepatic bile duct, lung, ovary/fallopian tube, pancreas/extrahepatic bile duct/gallbladder, skin, stomach, thyroid, uterus, and “other”
6 Myeloid lineage, lymphoid lineage, and plasma cell lineage

Galleri per-cancer-type 12-month episode sensitivity for breast, cervix, colon/rectum, lung, and prostate cancers was assessed among study participants who were and were not eligible for USPSTF guideline-recommended screening (Table 17). The 12-month per-cancer episode sensitivity estimates for participants eligible for USPSTF-recommended screening were consistent with the corresponding overall episode sensitivity for these cancers, except for subgroups with smaller sample sizes such participants eligible for lung cancer screening. These data show that Galleri detects a meaningful number of cancers both in individuals who are eligible and those who are ineligible for guideline-recommended cancer screening tests. Therefore, these results demonstrate that when added to guideline-recommended cancer screening tests, Galleri offers broader coverage for detecting multiple types of cancers, including those with guideline-recommended screening options.

Table 17: PATHFINDER 2: 12-Month Episode Sensitivity for Galleri by Cancer Type for Cancers With USPSTF Guideline-Recommended Screening

Cancer Type[1]	Eligible[2]	Not eligible	Overall[3]
Breast	23.4% (11/47) (13.6%, 37.2%)	50.0% (3/6) (18.8%, 81.2%)	26.4% (14/53) (16.4%, 39.6%)
Cervix[4]	NA	NA	NA
Colorectal	50.0% (3/6) (18.8%, 81.2%)	(2/2)	62.5% (5/8) (30.6%, 86.3%)
Lung	(0/4)	61.5% (8/13) (35.5%, 82.3%)	47.1% (8/17) (26.2%, 69.0%)
Prostate	7.7% (3/39) (2.7%, 20.3%)	13.9% (5/36) (6.1%, 28.7%)	10.7% (8/75) (5.5%, 19.7%)

1 First cancer diagnosis is used in analysis.
2 Per USPSTF Grade A/B recommendations, breast cancer screening is recommended for women aged 40–74 years; cervical cancer screening is recommended for women aged 21–65 years; colorectal cancer screening is recommended for women and men aged 45–75 years; and lung cancer screening is recommended for women and men aged 50–80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Per USPSTF grade C recommendations, prostate cancer screening should be undertaken as an individual decision for men aged 55–69 years. Individuals not meeting the age, sex (for breast cancer), and/or smoking (for lung cancer) eligibility criteria are classified as "not eligible."
3 Episode sensitivity estimates for subgroups with <5 observations were not calculated in the Clinical Study Report and are provided here only for completeness.
4 There were no cervical cancers diagnosed during the 12-month follow-up period.
Episode sensitivity is not estimated for cancer types with <5 cases.

Galleri test performance results stratified by 10-year age intervals showed that PPV was highest in participants aged 60-69 years old and lowest in participants aged 80 years and older (Table 18). Galleri specificity decreased with age but was > 99% in all age groups. Galleri 12-month episode sensitivity was similar in most age groups and highest in participants aged 80 years and older, although this was a relatively small subgroup.

PPV, episode sensitivity, and specificity were generally consistent between sexes, in participants with and without a prior cancer history, and across race and ethnicity categories when considering the small numbers of participants for some of the groups and the overlapping 95% CIs.

Table 18: PATHFINDER 2: Galleri Test Performance in Selected Demographic and Clinical Subgroups

Characteristic	12-month Episode Sensitivity % (n/N) (95% CI)	Specificity % (n/N) (95% CI)	PPV % (n/N) (95% CI)
Age Group			
50–59 years	29.3% (12/41) (17.6%, 44.5%)	99.95% (5603/5606) (99.83%, 99.98%)	80.0% (12/15) (53.0%, 93.4%)
60–69 years	33.3% (48/144) (26.2%, 41.4%)	99.95% (9430/9435) (99.87%, 99.98%)	90.6% (48/53) (79.3%, 96.0%)
70–79 years	36.4% (36/99) (27.6%, 46.2%)	99.69% (5339/5355) (99.25%, 99.87%)	68.4% (36/53) (45.8%, 84.7%)
≥ 80 years	52.6% (10/19) (31.7%, 72.7%)	99.03% (712/719) (97.96%, 99.54%)	58.8% (10/17) (35.2%, 79.0%)
Biologic Sex			
Female	36.4% (47/129) (28.6%, 45.0%)	99.92% (11992/12002) (99.85%, 99.96%)	82.5% (47/57) (70.4%, 90.3%)
Male	33.9% (59/174) (27.3%, 41.2%)	99.76% (9092/9113) (99.52%, 99.88%)	73.2% (59/81) (56.3%, 85.3%)
Race and Ethnicity			
American Indian or Alaska Native	(1/4)	99.65% (287/288) (97.58%, 99.95%)	(1/2)
Asian, Native, Hawaiian or other Pacific Islander	31.2% (5/16) (14.2%, 55.6%)	99.85% (1342/1344) (99.41%, 99.96%)	71.4% (5/7) (32.7%, 92.8%)
Black or African American	42.3% (11/26) (25.5%, 61.1%)	99.77% (1740/1744) (99.39%, 99.91%)	73.3% (11/15) (46.7%, 89.6%)
White	34.4% (86/250) (28.8%, 40.5%)	99.85% (17481/17507) (99.73%, 99.92%)	77.1% (86/112) (63.6%, 86.6%)
Hispanic or Latino	50.0% (9/18) (29.0%, 71.0%)	100.00% (1373/1373) (99.72%, 100.00%)	100.0% (9/9) (70.1%, 100.0%)
Prior Cancer History			
Yes	39.7% (25/63) (28.5%, 52.0%)	99.71% (2068/2074) (99.36%, 99.87%)	80.6% (25/31) (63.1%, 91.0%)
No	33.8% (81/240) (28.1%, 39.9%)	99.87% (19016/19041) (99.75%, 99.93%)	76.0% (81/107) (62.2%, 85.9%)

Estimates are not provided for subgroups with <5 cases.

5.4.3 CSO Prediction Accuracy

Galleri reported one CSO prediction for all individuals with a Cancer Signal Detected test result. In addition, a CSO-S prediction could be reported for certain CSOs to provide additional information intended to help localize the cancer. CSO prediction accuracy was assessed in participants with true positive Galleri test results. Prediction accuracy did not change when CSO-S prediction accuracy was also considered.

CSO prediction accuracy was 94.3%, as shown in Table 19. There were six participants whose CSO prediction was inaccurate. Of these, four participants were diagnosed with a cancer that did not have a defined clinical CSO (small intestine, testis, and two thymus cancers) and one participant was diagnosed with a cancer of unknown primary site.

The accuracy of CSO-S prediction in participants with true-positive results who had an assigned clinical CSO-S was 97.6% (41/42).

Table 19: PATHFINDER 2: Galleri CSO Prediction Accuracy in Participants with True-Positive[1] Test Results

Metric	n/N	% (95%CI)
CSO Prediction Accuracy	100/106	94.3% (88.2%, 97.4%)
CSO or CSO-S Prediction Accuracy[2]	100/106	94.3% (88.2%, 97.4%)

[1] True positive is defined as Galleri Cancer Signal Detected, cancer diagnosis within 12 months.
[2] All participants with a correct CSO-S prediction also had a correct CSO prediction.

Because the PATHFINDER 2 study was designed to enrich for older age groups, an adjusted analysis was performed with standardization by 10-year age group (based on the 2020 US Census age distribution (Blakeslee et al., 2023)) and the prevalence of cancer in each age group to estimate Galleri test performance in the general US population aged 50+ years. The age- and cancer-prevalence-adjusted test performance of Galleri was similar to that observed in PATHFINDER 2: 12-month episode sensitivity = 37.1%; specificity = 99.80%; PPV = 72.3%; NPV = 99.11%; CSO prediction accuracy = 93.4%.

5.5 Primary Safety Endpoint Results

In discussion with FDA, PATHFINDER 2 safety results are presented for the MCED-V2 test results. The primary safety objective for PATHFINDER 2 was to evaluate the safety of the Galleri test in terms of diagnostic testing triggered by a Cancer Signal Detected test result. Of 229 participants in the MCED-V2 Cancer Signal Detected Analysis Set with 12 months of follow-up time, 218 were eligible to be included in the primary safety analysis (i.e., they had at least one diagnostic evaluation performed and all of their diagnostic evaluations were initiated after communication of their MCED-V2 test result). Nine participants were excluded from the primary safety analysis due to initiation of diagnostic evaluation prior to communication of test results, and two participants were excluded who had no diagnostic evaluations performed. Among participants included in

the primary safety analysis, 128 had a cancer diagnosis and 90 had no cancer diagnosis during the 12-month follow-up period.

5.5.1 Number and Type of Invasive Procedures Performed

Approximately twice as many participants who were diagnosed with cancer after a MCED-V2 Cancer Signal Detected test result had at least one invasive procedure (e.g., surgical procedure, biopsy, or endoscopy) performed during diagnostic evaluation, compared with participants who were not diagnosed with cancer (91% vs. 48%) (Table 20). In the 128 participants who were diagnosed with cancer, 53% had a biopsy and 16% had surgery. By contrast, only 11% of the 90 participants who were not diagnosed with cancer after a positive test had a biopsy, and 4% had surgery. All 4 participants who had a surgical procedure during diagnostic evaluation and were not diagnosed with cancer had benign neoplasms that warranted surgical intervention.

Diagnostic evaluations performed following positive MCED-V2 test results were consistent with the CSO-specific recommendations provided in the study protocol for 189/218 (86.7%) of participants. Among participants who were not diagnosed with cancer, most (52.2%) did not undergo an invasive procedure (Table 20); among those who did, most had endoscopies, as appropriate for their CSO. These data show that CSO-guided diagnostic evaluations led to clinically appropriate use of invasive procedures after a positive MCED-V2 test result was returned.

Table 20: PATHFINDER 2: Number of MCED-V2 Cancer Signal Detected Participants with At Least One Invasive Procedure During Diagnostic Evaluation by Cancer Status

Number of participants with at least one	MCED-V2 Cancer Signal Detected, Cancer Diagnosis within 12 Months (N=128)	MCED-V2 Cancer Signal Detected, No Cancer Diagnosis within 12 Months (N=90)	Total (N=218)
Invasive procedure	116 (90.6%)	43 (47.8%)	159 (72.9%)
Surgical procedure	20 (15.6%)	4 (4.4%)	24 (11.0%)
Non-surgical procedure	103 (80.5%)	42 (46.7%)	145 (66.5%)
Endoscopy[1]	47 (36.7%)	33 (36.7%)	80 (36.7%)
Biopsy[2]	68 (53.1%)	10 (11.1%)	78 (35.8%)
Other[3]	2 (1.6%)	2 (2.2%)	4 (1.8%)
No invasive procedures	12 (9.4%)	47 (52.2%)	59 (27.1%)

1 e.g., bronchoscopy, colonoscopy, cystoscopy
2 e.g., incisional or excisional biopsy, core needle biopsy, fine needle aspiration biopsy
3 All 4 “other” non-surgical invasive procedures were Pap smears.

5.5.2 Number and Type of Adverse Events Due to Diagnostic Testing

Nine participants (9/218, 4.1%) in the MCED-V2 Cancer Signal Detected Analysis Set with 12 months of follow-up time experienced a total of 10 AEs (regardless of study-relatedness) during the time of diagnostic evaluation (Table 21). None of the AEs were related to the device, and all occurred during the targeted diagnostic evaluation.

There were four participants with a total of five study-related AEs during the time of diagnostic evaluation; all of these participants were diagnosed with cancer during the 12-month follow-up time. These AEs included one emergency department visit to initiate anticoagulant injections prior to a lung biopsy, one planned perioperative hospitalization to optimize pain control, one report of anxiety after receipt of a Cancer Signal Detected MCED test result, one report of mild post-operative pain, and one report of low glomerular filtration rate due to nephrectomy.

There was one participant who experienced an unrelated serious AE of hyponatremia during the time of diagnostic evaluation.

Table 21: PATHFINDER 2: Summary of Adverse Events During the Time of Diagnostic Evaluation in MCED-V2 Cancer Signal Detected Participants

Number of Adverse Events (AEs)	AEs in participants with a cancer diagnosis (N = 9)	AEs in participants with no cancer diagnosis (N = 1)	Total number of AEs (N = 10)
Non-serious AE	8 (88.9%)	1 (100.0%)	9 (90.0%)
Study-related AE	5 (55.6%)	0	5 (50.0%)
Serious AE (SAE)	1 (11.1%)	0	1 (10.0%)
Study-related SAE	0	0	0
AE setting			
Diagnostic procedure prompted by a “Cancer Signal Detected” test result	6 (66.7%)	1 (100.0%)	7 (70.0%)
Other	3 (33.3%)	0	3 (30.0%)
AE related to device among study-related AEs			
Device-related	0	0	0

5.6 Secondary Endpoint Results

5.6.1 Utilization of Guideline-recommended Cancer Screening After Use of the MCED-V2 Test

Table 22 shows the utilization of USPSTF Grade A- or B-recommended cancer screening in PATHFINDER 2 participants who were eligible for each screening test. The proportion of eligible participants who reported being up-to-date changed minimally between the baseline and 12-month follow-up time periods for any of the recommended cancer screening tests.

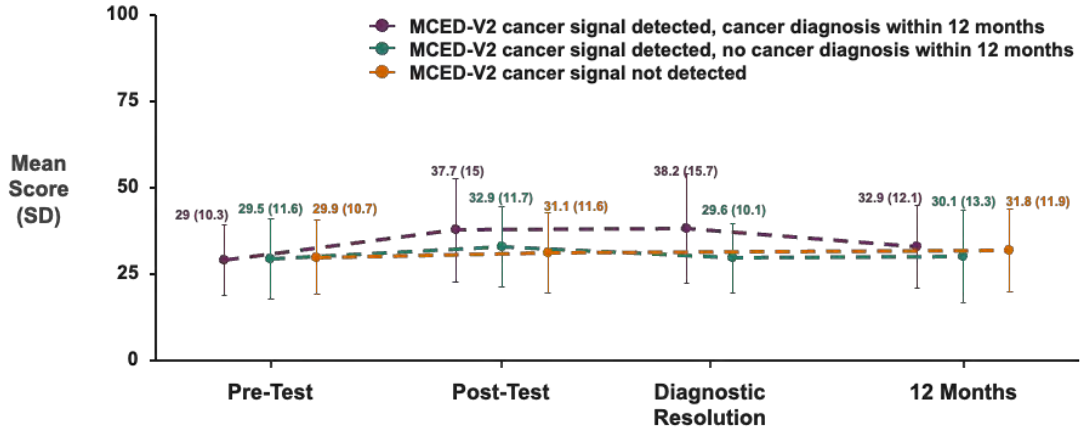
Table 22: PATHFINDER 2: Utilization of Guideline-Recommended Cancer Screening at Baseline and 12 Months in Eligible Participants

USPSTF Grade A- or B-Recommended Screening	Number of Participants Eligible for Screening at the time of the Blood Draw	Up-to-Date Participants	
		Baseline	12 Months
Breast cancer	12,659	10,147 (80.2%)	10,211 (80.7%)
Cervical cancer	8,129	3,995 (49.1%)	3,990 (49.1%)
Colorectal cancer	22,668	18,271 (80.6%)	18,446 (81.4%)
Lung cancer	1,094	165 (15.1%)	216 (19.7%)

5.6.2 State-Trait Anxiety Inventory-6

Participant-reported state anxiety measured by the STAI-6 questionnaire showed that baseline levels of state anxiety in all study participants were within the expected range reported in the STAI user manual for men and women aged 50–69 years (Spielberger, 2015). Participants with an MCED-V2 Cancer Signal Detected test result reported a temporary increase in state anxiety after test results were returned, but state anxiety decreased towards pre-test levels at 12 months. This temporary increase in state anxiety levels was comparable to that experienced by patients undergoing general, medical, and surgical procedures, and other cancer screening tests (Spielberger, 2015). The magnitude of the temporary increase in state anxiety levels was also small relative to the observed population spread (standard deviations) in state anxiety scores (Figure 8).

Figure 8: PATHFINDER 2: Distribution of STAI-6 Standardized Total Scores at Different Time Points by MCED-V2 Test Result and Cancer Status in Participants with 12 Months of Follow-up Time



Group	Number of participants			
	Pre-test	Post-test	Diagnostic resolution	12 months
	127	82	57	77
	96	57	40	52
	23874	17751	N/A	14,967

5.6.3 Time to Diagnostic Resolution

Among participants with a MCED-V2 Cancer Signal Detected test result, the median time from test result return to diagnostic resolution (defined as the number of days from communication of a positive test result to the participant until the date of the last diagnostic evaluation used to determine the presence or absence of cancer) was 46 days. Participants who were diagnosed with cancer based on diagnostic work-up (true positives) had a shorter time to diagnostic resolution (36 days) than those who did not have a cancer found (false positives, 75 days). These time intervals compare favorably with the time to diagnostic resolution estimated in a claims-based study of 458,818 insured US patients with cancer, among whom the median time to diagnosis was 118 days (interquartile range 33–215 days).

6 NHS-GALLERI

Summary

- In the prevalent screening round of NHS-Galleri, which was the subject of the PMA, Galleri demonstrated high PPV, a very low false-positive rate, clinically meaningful episode sensitivity, and highly accurate CSO prediction.
    - Galleri episode sensitivity for cancers responsible for two-thirds of US cancer deaths was 52.1%, and overall episode sensitivity was 31.6%.
    - Specificity was 99.74%, PPV was 66.2%, and CSO prediction accuracy was 91.9%.
    - Galleri testing increased the number of cancers detected by screening by approximately 6-fold, and more than two-thirds of cancers were stages I-III at diagnosis.
- Test performance estimates in NHS-Galleri were consistent with those in PATHFINDER 2; this consistency supports the applicability of these findings to the intended use population in the US.
- Study-related AEs were uncommon and were primarily related to phlebotomy at the time of the Galleri test blood draw.
- All prespecified study success criteria were exceeded, including episode sensitivity across all cancer types (31.6%), specificity (99.74%), and CSO prediction accuracy (91.9%).

6.1 Study Design

The NHS-Galleri study is an IDE-approved, prospective, randomized controlled trial using MCED-V2 (investigational device) in which 142,826 participants were enrolled and consented to assess Galleri test performance for population screening in England when added to guideline-recommended screening (Neal et al., 2026; Neal et al., 2022; Sasieni et al., 2026). In brief, blood collection, 142,250 participants were randomized 1:1 to either the intervention arm, where their blood samples were analyzed using MCED-V2, or the control arm, where blood samples were stored for potential future use in research. Plasma samples remaining after MCED-V2 testing were frozen and stored for future use. A subset of the frozen plasma samples were selected for testing with Galleri to evaluate Galleri test performance (see Section 6.3 for additional details).

All trial participants and staff were blinded to randomization throughout the trial, except for participants with a positive test result, the study nurses returning the results, and a small number of required staff to enable them to perform duties related to positive test results.

MCED-V2 test results with a finding of Cancer Signal Detected were reported to the participants and their General Practitioner. Participants with a positive test were referred

to an NHS Urgent Suspected Cancer Referral pathway for diagnostic assessment. At the point of the referral, the diagnostic work-up was guided by NHS-recommended pathways rather than protocol-recommended. Any subsequent treatment was administered as part of NHS routine care. No Cancer Signal Detected test results were not returned to the participant or their General Practitioner to maintain blinding. Cancer outcome data for the trial were provided by the National Cancer Registration and Analysis Service (NCRAS). NCRAS works according to European and International Best practice standards in the data curation and quality assurance of cancer registrations. Registry stage at diagnosis was provided in line with NCRAS' remit to capture a comprehensive picture of population cancer burden. This is a single registry-derived stage from all relevant clinical, imaging, and pathological information available to NCRAS for cancer registration, using the applicable tumor-node-metastasis or site-specific staging system. Although cancers are not staged under the American Joint Committee on Cancer system, registry stage is typically equivalent to either clinical or pathological stage according to that system.

Participants who were not diagnosed with cancer returned for additional study visits at approximately 12 and 24 months for the second and third screening tests, respectively. Cancer status was assessed at each screening round, with approximately 12 months of follow-up, to inform test performance. Positive test results returned to participants during the NHS-Galleri trial were based on MCED-V2; therefore, safety results in this document are reported for all participants based on MCED-V2 results. Galleri performance presented in this document is based on the first screening round, also called the prevalent screening round (i.e., single Galleri with approximately 12 months of follow-up).

6.1.1 Enrollment Criteria

The study population consisted of adults, aged 50–77 years at invitation, with the following exclusion criteria:

- Previous or current participation in another GRAIL-sponsored study
- Personal history of invasive cancer or hematological malignancy, diagnosed within the 3 years prior to expected enrollment date
    - Note: Individuals with a diagnosis of non-melanoma skin cancer and prostate cancer patients whose only treatment was active surveillance were NOT excluded
- Definitive treatment for invasive cancer or hematological malignancy within the 3 years prior to expected enrollment date, including adjuvant hormone therapy for cancer (e.g., for breast or prostate cancer)
- Currently taking demethylating or cytotoxic agents for any condition

- Undergoing current investigation for suspected cancer, defined as having been referred to a Two-Week-Wait clinic or undergoing investigations at a Rapid Diagnostic Center or other clinic with a stated suspicion of cancer
- Currently on a palliative care pathway

6.1.2 Statistical Analyses

6.1.2.1 Objectives and Endpoints for PMA Analysis

There were two separate analyses of the NHS-Galleri trial data, each defined in a separate statistical analysis plan: (1) a protocol analysis to meet the NHS-Galleri trial protocol-defined objectives and to inform a potential roll-out by the NHS; and (2) a PMA analysis to align with GRAIL's FDA submission and to allow combining data from the NHS-Galleri and PATHFINDER 2 studies where appropriate to do so. The PMA objectives are relevant to the FDA for assessing the safety and effectiveness of the Galleri test.

The primary objective of the PMA analysis for the NHS-Galleri trial was to evaluate the performance of the Galleri test in the intervention arm in the first screening round (12 months follow-up time analysis period) in alignment with the primary objective for PATHFINDER 2.

Test performance was evaluated using the following endpoints:

- PPV
- NPV
- Episode sensitivity
- Specificity
- Positive likelihood ratio
- Negative likelihood ratio
- CSO prediction accuracy
- MCED cancer detection rate
- Number needed to screen to detect one cancer.

6.1.2.2 Sample Size Determination for the Study and for PMA

The overall study enrollment was determined based on the protocol-specified primary endpoint (reduction of stages III-IV cancer incidence with 3 annual screening rounds and at least 12 months follow-up after the third screening round) (Neal et al., 2022).

Separately, for evaluation of Galleri performance supporting the PMA, based on microsimulations similar to those described in Dai et al. (2024) and conservative assumptions about cancer incidence, at least 882 participants with cancer diagnosis, including 294 participants with cancer diagnosis and MCED-V2-positive results, were expected among approximately 70,000 enrolled participants during 12 months of follow-up. These expected counts, together with approximately 7,500 samples from

participants with no cancer diagnosis and MCED-V2-negative results during 12 months of follow-up, selected for Galleri testing, were considered adequate to characterize episode sensitivity, specificity, and CSO prediction accuracy, with uncertainty quantified using two-sided 95% CIs.

6.1.2.3 Analysis of Test Performance

Analysis methods for Galleri test performance were identical to those in PATHFINDER 2 (see Section 5.1.2.4). Similar to PATHFINDER 2, Galleri performance was evaluated using weighted analysis with adjustment for sampling probabilities.

6.1.3 Applicability of United Kingdom (UK) Data to US Population

Galleri test performance (and the performance of any MCED test) depends in part on the mix of cancer types in a population (Chang et al., 2023), which in turn depends on population demographic characteristics, other cancer risk factors, and screening behaviors. The age and sex distributions and prevalence of major risk factors for cancer such as smoking and obesity, as well as cancer incidence, mortality, and stage-specific survival rates, are largely similar between England and the US (Appendix 10.2) (Arnold et al., 2019; CDC, 2021, 2025; NCRAS, 2022; NHS England Digital, 2025a, 2025b; SEER, 2026; Sung et al., 2026). For nearly all major cancer types, rates are broadly comparable at the population level, with most relative and absolute differences being modest, and rate differences among cancer types exceeding differences between the countries. The comparability of these characteristics between the two countries broadly supports the applicability of findings from NHS-Galleri to the US population.

Self-identified racial and ethnic categories are composed of different groups in England and the US due to historical differences in immigration patterns between the countries. Overall, there is a higher proportion of non-White individuals in the US compared with England. Although differences in cancer case mix are expected to produce variation in some (but not all) test performance metrics across racial/ethnic groups (e.g., more liver and stomach cancers in Asian populations), the lack of substantial heterogeneity in observed Galleri test performance by race/ethnicity in PATHFINDER 2 indicates that racial and ethnic differences between England and the US are unlikely to affect the applicability of NHS-Galleri data to the US population.

Current cancer screening recommendations in England and the US are broadly aligned in terms of the cancers screened (breast, colorectal, cervical, and smoking-associated lung), the age groups recommended for screening, and the tests used for screening (Appendix 10.3). The differences in screening recommendations, specifically with recommendations in England being more conservative than in the US (e.g., narrower age range, use of fecal immunochemical testing as first-line screening, partial roll-out of lung cancer screening, and intervals between screens, and no organized screening program for prostate cancer in the UK), are likely to contribute to small observed differences in the incidence and stage distribution of the relevant cancer types.

As shown in Appendix 10.1, which summarizes the expected targeted diagnostic evaluation according to CSO in PATHFINDER 2 and NHS-Galleri, national guidelines for recommended diagnostic procedures by anticipated cancer type are broadly comparable between England and the US.

6.2 Demographics and Baseline Characteristics

Of the 71,122 participants randomized to the intervention arm, 71,032 were clinically eligible and clinically evaluable. Of these participants, 709 had no evaluable MCED-V2 test result, leaving 70,323 participants in the MCED-V2 analyzable set. Of these, 722 had an MCED-V2-positive result, including 419 with a cancer diagnosis within 12 months. Among 69,601 participants with an MCED-V2-negative result, 713 had a cancer diagnosis within 12 months.

Demographics and baseline characteristics of the NHS-Galleri MCED-V2 analyzable set are presented in

Table 23. The study was enriched for older participants and participants from areas of greater socioeconomic deprivation (Swanton et al., 2022). The mean age of participants was 65 years, and half (50.2%) were female. Most participants (93.6%) were White, with 3.3% Asian/Asian British and 1.4% Black/African/Caribbean/Black British. The lowest (most deprived) quintile of socioeconomic deprivation had the highest proportion of participants (22.6%) and the highest (least deprived) quintile had the lowest proportion of participants (16.1%). Slightly more than half of participants were never smokers (54.9%) and most had no prior history of cancer (92.6%).

Demographic and baseline characteristics of participants in the Galleri analyzable set, assessed using weighted analysis, were generally consistent with the MCED-V2 analyzable set.

Table 23: NHS-Galleri: Participant Demographics and Baseline Characteristics in the MCED-V2 Analyzable Set

	Total (N=70,323)
Age (years)	
Mean (standard deviation)	65.0 (7.6)
Median (interquartile range)	66.0 (59.0, 71.0)
Min, Max	50.0, 78.0
Age group	
50–59 years	18,592 (26.4%)
60–69 years	28,245 (40.2%)
70–79 years	23,486 (33.4%)
Biological sex	
Female	35,332 (50.2%)

	Total (N=70,323)
Male	34,991 (49.8%)
Race/ethnicity (UK)	
White	65,825 (93.6%)
Black, African, Caribbean or Black British	1,003 (1.4%)
Asian or Asian British	2,334 (3.3%)
Mixed or Multiple ethnic groups	765 (1.1%)
Other ethnic group	311 (0.4%)
Body mass index category	
< 25 kg/m^2	22,824 (32.5%)
25 to < 30 kg/m^2	27,707 (39.4%)
≥ 30 kg/m^2	19,492 (27.7%)
Smoking status	
Current smoker	4,679 (6.7%)
Former smoker	26,984 (38.4%)
Never smoker	38,573 (54.9%)
Alcohol use	
Heavy drinker	8,726 (12.4%)
Moderate drinker	22,838 (32.5%)
Light drinker	23,694 (33.7%)
Former drinker	10,771 (15.3%)
Never drinker	4,004 (5.7%)
Prior cancer history	
Yes	5,227 (7.4%)
No	65,096 (92.6%)
Index of multiple deprivation (quintile)	
Quintile 1 (most deprived)	15,862 (22.6%)
Quintile 2	13,780 (19.6%)
Quintile 3	14,887 (21.2%)
Quintile 4	14,215 (20.2%)
Quintile 5 (least deprived)	11,347 (16.1%)

6.3 Galleri Testing

As also noted in Section 5.3 for PATHFINDER 2, results returned during the entirety of the NHS-Galleri clinical study were from MCED-V2. However, iterative refinement is standard practice for *in vitro* diagnostics to support the continuous improvement of test performance. Consistent with this approach, the strategy to assess the performance of Galleri, which is described below, was prespecified and discussed with the FDA prior to the lock of the statistical analysis plan.

Frozen plasma samples from a subset of NHS-Galleri participants were used to assess Galleri performance. A sampling scheme was implemented so that a subset of samples could be tested with Galleri to evaluate its performance with statistical efficiency and ensure that the analysis results are representative of the overall study population. Samples from the following groups of clinically eligible and clinically evaluable intervention arm participants were selected:

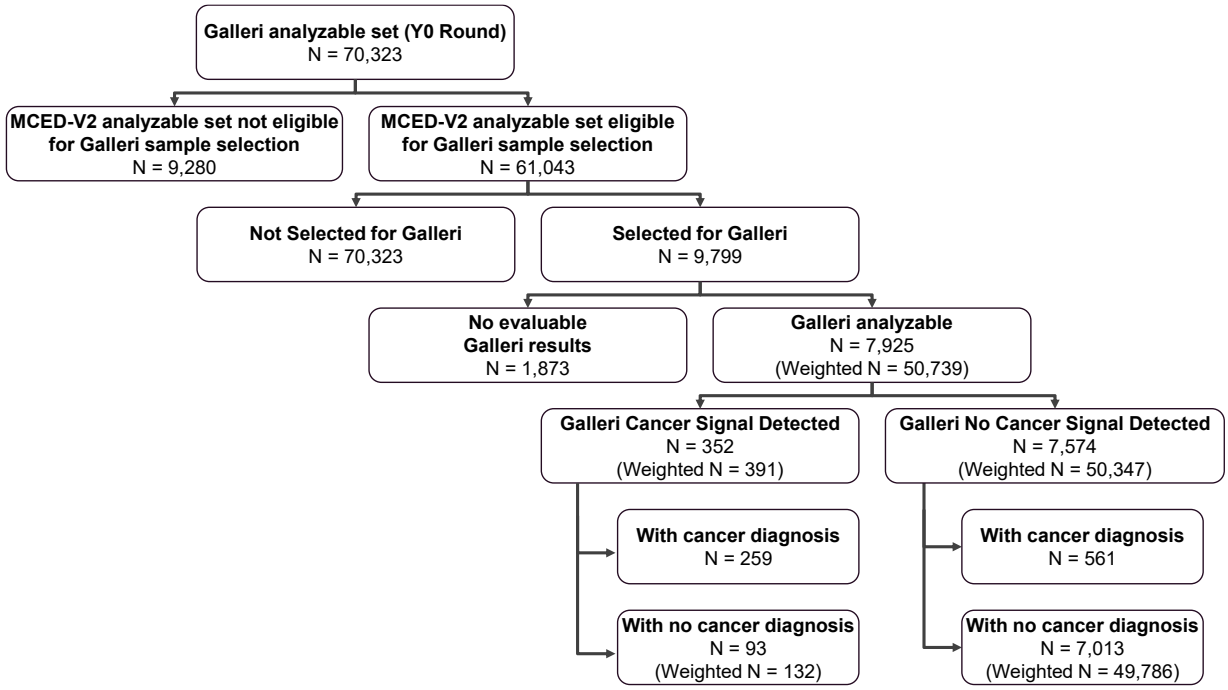
- All participants with a positive MCED-V2 test result in the first screening round;
- All participants diagnosed with cancer during the first screening round (with approximately 12-months follow-up time); and
- Samples from a stratified random sample of participants with negative MCED-V2 test results and no cancer diagnosis in the first screening round (with approximately 12 months of follow-up).

Stratification factors included age, race/ethnicity, prior cancer history and smoking status.

6.3.1 Galleri Disposition

Of the 70,323 intervention arm participants with analyzable MCED-V2 results, 61,043 participants were eligible for selection for testing with the Galleri test (Figure 9). A total of 9,799 frozen plasma samples were selected for testing with Galleri. Of the 9,799 participants selected, 1,873 did not have evaluable Galleri test results, leaving 7,926 participants in the Galleri Analyzable Set. The weighted number of participants in the Galleri Analyzable Set was 50,739.

Figure 9: NHS-Galleri: Participant Flow Diagram for Galleri Analyzable Set



6.4 Galleri Test Performance

Table 24 shows the 2x2 contingency table of the Galleri test in NHS-Galleri. Galleri met all prespecified study success criteria.

Galleri test specificity of 99.74% corresponds to a false-positive rate of 0.26%. This high specificity substantially exceeds benchmarks based on usual care for cancer detection and is a critical safety feature of the test that limits the occurrence of false-positive results and resultant unnecessary diagnostic work-up.

Overall PPV and NPV for Galleri were 66.2% and 98.89%, respectively. Galleri's high PPV compares favorably with usual care for cancer detection and satisfies an essential criterion for a population-wide screening test.

Table 24: NHS-Galleri: Galleri Test Performance at 12-Month Follow-up Time Point (Prevalent Screening Round)

	Cancer diagnosis by 12 Months (N=820)	No cancer diagnosis by 12 Months (Weighted N[1]=49,919)	Total (Weighted N[1]=50,739)	
Galleri Cancer Signal Detected	259	132	391	**PPV=66.2%** (56.7%, 74.6%)
Galleri No Cancer Signal Detected	561	49,786	50,347	**NPV=98.89%** (98.78%, 98.98%)
	Episode Sensitivity =31.6% (28.50%, 34.85%)	**Specificity=99.74%** (99.61%, 99.82%)		

1 Weights were calculated for participants with no cancer diagnosis and MCED-V2 No Cancer Signal Detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected.
CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity) logistic regression with robust sandwich variance for weighted measures (specificity, PPV, and NPV
NPV, negative predictive value; PPV, positive predictive value.

Table 25: NHS-Galleri: Additional Galleri Test Performance Metrics at 12-Month Follow-up Time Point (Prevalent Screening Round)

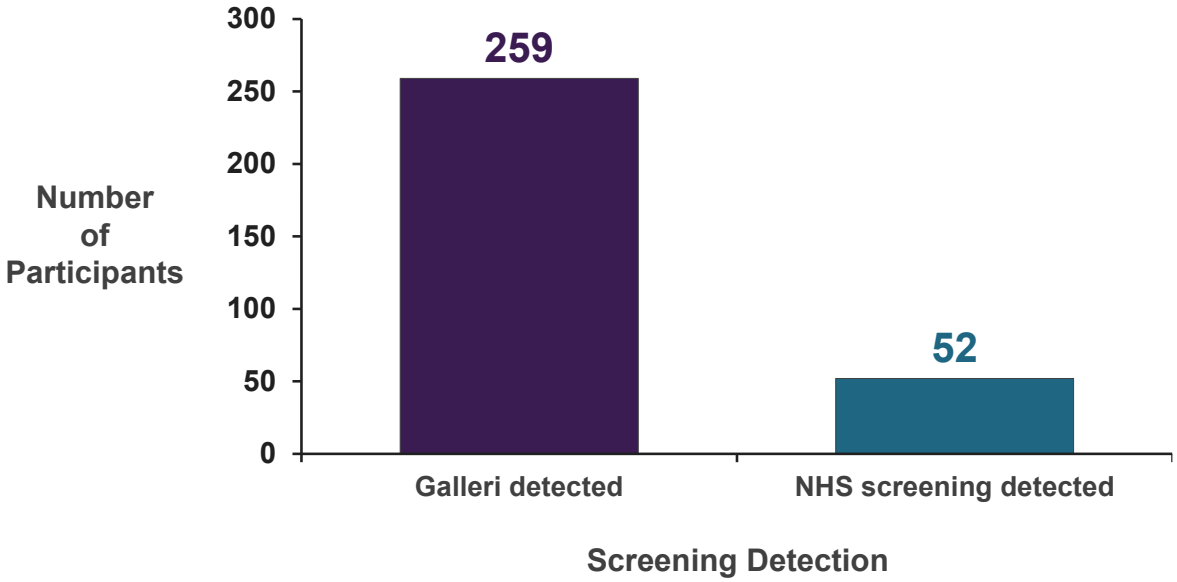
	Total (Weighted N[1] = 50739)
False positive rate (n/N) (95% CI)	0.26% (132/49919) (0.18%, 0.39%)
Positive Likelihood Ratio (95% CI)	119.2 (80.1, 177.4)
Negative Likelihood Ratio (95% CI)	0.69 (0.65, 0.72)
MCED cancer detection rate (n/N) (95% CI)	0.51% (259/50739) (0.45%, 0.58%)
Number needed to screen (n/N) (95% CI)	196 (50739/259) (173, 222)
MCED cancer signal detection rate (n/N) (95% CI)	0.77% (391/50739) (0.66%, 0.90%)

1 CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity; accuracy and precision of CSO prediction in true positives; accuracy and precision of CBS prediction in true positives); logistic regression with robust sandwich variance for weighted measures false-positive rate, MCED cancer detection rate, MCED cancer signal detection rate, number needed to screen); and delta method for positive likelihood ratio and negative likelihood ratio.
MCED cancer detection rate = true positives/total; MCED cancer signal detection rate = (true positives + false positives)/total

6.4.1 Distribution of Cancers Observed

In the Galleri analyzable set, the number of cancers detected by Galleri and NHS screening (n=311) was 6 times the number detected by NHS screening alone (n=52) (Figure 10).

Figure 10: NHS-Galleri: Distribution of Cancers that Were Galleri-Detected vs. NHS Screening-Detected in the Intervention Arm (Prevalent Screening Round)



Note: 13 participants are not shown who had cancers detected by MCED-V2 but not Galleri, and whose cancer types have NHS screening programs available. If the negative Galleri test result had been returned, these participants might otherwise have had their cancer detected by NHS guideline-recommended screening (if they were eligible), clinically detected, or not detected during the 12-month follow-up.

Table 26 shows the distribution of stage for 259 participants with Galleri-detected new cancers in NHS-Galleri. Of these, 178 (68.7%) were detected at stages I-III.

Table 26: NHS-Galleri: Distribution of Stage at Diagnosis for Participants with Galleri-Detected New Cancers (Prevalent Screening Round)

Cancer Stage[1]	Galleri-Detected (N = 259)
Stage I	43 (16.6%)
Stage II	54 (20.8%)
Stage III	81 (31.3%)
Stage IV	66 (25.5%)
Stages I–II	97 (37.5%)
Stages I–III	178 (68.7%)
No stage expected[2]	4 (1.5%)
Missing	11 (4.2%)

1 For participants with multiple primary cancers, only information from the first diagnosed cancer is included in the participant-level summary.
2 No stage expected=no valid staging system exists for the combination of topography/morphology codes. Binet stages are mapped as follows: A=I, B=II, C=III.

Between the two randomization arms, the number of cancers diagnosed via emergency presentation decreased by 26% in the intervention arm (n=60; 5.2%) relative to the control arm (n=81; 8.5%). Notably, emergency presentation for cancer diagnosis is associated with substantially poorer one-year survival in both England (Elliss-Brookes et al., 2012) and the US (Thompson et al., 2026), with nearly four-fold higher 30-day mortality for inpatient emergency presentation compared with non-emergency presentation among US Medicare beneficiaries (Thompson et al., 2026).

6.4.2 Galleri 12-Month Episode Sensitivity by Cancer Type, Cancer Type Subgroups, and Selected Demographic and Clinical Subgroups in NHS-Galleri

Galleri 12-month episode sensitivity by cancer type is shown in Table 27, and ranged from 3.4% for skin (excluding BCC/SCC) to 80.0% for liver/intrahepatic bile duct. Point estimates and 95% CIs are not shown for cancers with fewer than 5 cases.

Table 27: NHS-Galleri: Galleri 12-Month Episode Sensitivity by Cancer Type (Prevalent Screening Round)

Cancer Type (Based on First-Diagnosed Cancer)	12-Month Episode Sensitivity % (N) (95% CI)
Anus	1/3
Bladder, Urothelial Tract	38.5% (5/13) (17.7%, 64.5%)
Bone or Soft Tissue Sarcoma	20.0% (1/5) (3.6%, 62.4%)
Breast	19.1% (21/110) (12.8%, 27.4%)
Cervix	1/2
Colon/Rectum	53.3% (49/92) (43.1%, 63.1%)
Esophagus	65.4% (17/26) (46.2%, 80.6%)
Head and Neck	42.9% (9/21) (24.5%, 63.5%)
Kidney	41.7% (10/24) (24.5%, 61.2%)
Liver, Intrahepatic Bile Duct	80.0% (12/15) (54.8%, 93.0%)
Lung	63.8% (37/58) (50.9%, 74.9%)
Lymphoid Lineage	46.6% (27/58) (34.3%, 59.2%)
Myeloid Lineage	8.3% (1/12) (1.5%, 35.4%)
Ovary or Fallopian Tubes	75.0% (12/16) (50.5%, 89.8%)
Pancreas, Extrahepatic Bile Duct, Gallbladder	38.7% (12/31) (23.7%, 56.2%)
Plasma Cell Lineage	24.0% (6/25) (11.5%, 43.4%)
Prostate	10.7% (23/215) (7.2%, 15.5%)

Cancer Type (Based on First-Diagnosed Cancer)	12-Month Episode Sensitivity % (N) (95% CI)
Skin (excluding BCC/SCC)	3.4% (1/29) (0.6%, 17.2%)
Stomach	57.1% (4/7) (25.0%, 84.2%)
Thyroid	(0/3)
Uterus	18.5% (5/27) (8.2%, 36.7%)
Other	17.9% (5/28) (7.9%, 35.6%)

Episode sensitivity is not estimated for cancer types with <5 cases.
Other cancer types include brain and spinal cord (n = 8), cancer of unknown primary (n = 4), jejunum and ileum - neuroendocrine tumors (n = 4), malignant pleural mesothelioma (n = 4), vulva (n = 2), ampulla of Vater (n = 1), eyelid carcinoma (n = 1), other unspecified (n = 1), testis (n = 1), thymus (n = 1), and uveal melanoma (n = 1).

Galleri exhibited strong performance for episode sensitivity for prespecified cancer subgroups, particularly for subgroups where there is significant unmet need in terms of cancer screening (Table 28). Episode sensitivity was highest for the 12 cancers responsible for two-thirds of US cancer deaths, and lowest for cancers with common screening options.

Table 28: NHS-Galleri: Galleri 12-Month Episode Sensitivity for Cancer Signal Detection for Cancer Type Subgroups (Prevalent Screening Round)

Prespecified Subgroup	12-month Episode Sensitivity (95% CI)
12 cancers responsible for two-thirds of US cancer deaths[1]	52.1% (46.9%, 57.2%)
6 aggressive cancers with low 5-year survival in US[2]	60.9% (53.0%, 68.3%)
Cancers without common screening options[3]	40.6% (35.8%, 45.5%)
Solid cancers with common screening options[4]	22.6% (18.8%, 26.9%)
Solid cancers without common screening options[5]	41.8% (36.4%, 47.5%)
Hematologic malignancies[6]	35.1% (26.2%, 45.2%)

1 Anus; Bladder or Urothelial Tract; Colon or Rectum; Esophagus; Head and Neck; Liver or Intrahepatic Bile Duct; Lung; Lymphoid Lineage; Ovary or Fallopian Tubes; Pancreas, Extrahepatic Bile Duct or Gallbladder; Plasma Cell Lineage; Stomach
2 Esophagus; Liver or Intrahepatic Bile Duct; Lung; Ovary or Fallopian Tubes; Pancreas, Extrahepatic Bile Duct or Gallbladder; Stomach
3 Anus; Bladder or Urothelial Tract; Bone or Soft Tissue Sarcoma; Esophagus; Head and Neck; Kidney; Liver or Intrahepatic Bile Duct; Lung; Myeloid Lineage; Lymphoid Lineage; Ovary or Fallopian Tubes; Pancreas, Extrahepatic Bile Duct or Gallbladder; Plasma Cell Lineage; Skin (excluding BCC/SCC); Stomach; Thyroid; Uterus; Other
4 Breast, Cervix, Colon or Rectum, Prostate
5 Anus; Bladder or Urothelial Tract; Bone or Soft Tissue Sarcoma; Esophagus; Head and Neck; Kidney; Liver or Intrahepatic Bile Duct; lung; Ovary or Fallopian Tubes; pancreas, Extrahepatic Bile Duct or Gallbladder; Skin (excluding BCC/SCC); Stomach; Thyroid; Uterus; Other
6 Myeloid Lineage, Lymphoid Lineage, Plasma Cell Lineage

Galleri per-cancer-type 12-month episode sensitivity for breast, cervix, colon/rectum, lung, and prostate cancers was assessed among study participants who were and were not eligible for USPSTF guideline-recommended screening (

Table 29). The 12-month per-cancer-type episode sensitivity estimates for participants who would have been eligible for USPSTF-recommended screening were consistent with the corresponding overall episode sensitivity for these cancers, except for subgroups with smaller sample sizes, such as participants eligible for cervical cancer screening. These data show that Galleri detects a meaningful number of cancers both in individuals who are eligible and those who are ineligible for guideline-recommended cancer screening tests. Therefore, these results demonstrate that when added to guideline-recommended cancer screening tests, Galleri offers broader coverage for detecting multiple types of cancers, including those with guideline-recommended screening options.

Table 29: NHS-Galleri: 12-Month Episode Sensitivity for Galleri by Cancer Type for Cancers With USPSTF Guideline-Recommended Screening (Prevalent Screening Round)

Cancer Type[1]	Eligible[2]	Not eligible	Overall
Breast	16.1% (15/93) (10.0%, 24.9%)	35.3% (6/17) (17.3%, 58.7%)	19.1% (21/110) (12.8%, 27.4%)
Cervix	(1/1)	(0/1)	(1/2)
Colorectal	51.9% (40/77) (41.0%, 62.7%)	60.0% (9/15) (35.7%, 80.2%)	53.3% (49/92) (43.1%, 63.1%)
Lung	63.9% (23/36) (47.6%, 77.5%)	63.6% (14/22) (43.0%, 80.3%)	63.8% (37/58) (50.9%, 74.9%)
Prostate	11.0% (12/109) (6.4%, 18.3%)	10.4% (11/106) (5.9%, 17.6%)	10.7% (23/215) (7.2%, 15.5%)

1 First cancer diagnosis is used in analysis,
2 Per USPSTF Grade A/B recommendations, breast cancer screening is recommended for women aged 40–74 years; cervical cancer screening is recommended for women aged 21–65 years; colorectal cancer screening is recommended for women and men aged 45–75 years; and lung cancer screening is recommended for women and men aged 50–80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. (For 6 participants in NHS-Galleri, grams of tobacco were converted to cigarette packs based on the NHS Stoke-on-Trent Primary Care Toolkit (p. 41)). Per USPSTF grade C recommendations, prostate cancer screening should be undertaken as an individual decision for men aged 55–69 years. Individuals not meeting the age, sex (for breast cancer), and/or smoking (for lung cancer) eligibility criteria are classified as “not eligible.”
3 Episode sensitivity estimates for subgroups with <5 observations are not calculated.

Galleri test performance results stratified by 10-year age intervals showed that PPV and episode sensitivity were consistent across all age groups (Table 30).

The interpretation of the results from demographic subgroups based on race and ethnicity data was limited, as some subgroups were very small. PPV was higher in participants without prior cancer history than those with prior cancer history, and episode sensitivity was similar between these groups. It is a known limitation of the NCRAS dataset that recurrence data are not available. Participants with a prior cancer history with a recurrence may have tested positive and been classified as a false positive, as there is no new primary cancer registration.

Table 30: NHS-Galleri: Galleri Test Performance in Selected Demographic and Clinical Subgroups (Prevalent Screening Round)*

Characteristic	12-month Episode Sensitivity % (n/N) (95% CI)	Specificity % (n/N) (95% CI)	PPV % (n/N) (95% CI)
Age Group			
50–59 years	28.4% (29/102) (20.6%, 37.8%)	99.91% (13051/13064) (99.83%, 99.95%)	70.2% (29/41) (53.7%, 82.7%)
60–69 years	30.2% (93/308) (25.3%, 35.5%)	99.78% (20030/20074) (99.52%, 99.90%)	67.8% (93/137) (48.5%, 82.5%)
70–79 years	33.4% (137/410) (29.0%, 38.1%)	99.55% (16705/16781) (99.27%, 99.72%)	64.4% (137/213) (52.0%, 75.1%)
Biologic Sex			
Female	32.9% (107/325) (28.0%, 38.2%)	99.81% (24713/24759) (99.74%, 99.86%)	69.8% (107/153) (61.5%, 77.0%)
Male	30.7% (152/495) (26.8%, 34.9%)	99.66% (25074/25160) (99.40%, 99.81%)	63.9% (152/238) (49.6%, 76.1%)
Race and Ethnicity			
White	32.3% (252/780) (29.1%, 35.7%	99.73% (46944/47069) (99.60%, 99.82%)	66.9% (252/377) (56.9%, 75.5%)
Black, African, Caribbean or Black British	10.0% (1/10) (1.8%, 40.4%)	99.48% (637/640) (97.95%, 99.87%)	(1/4)
Asian or Asian British	21.1% (4/19) (8.5%, 43.3%)	99.79% (1408/1411) (99.34%, 99.93%)	57.1% (4/7) (23.0%, 85.6%)
Mixed or Multiple ethnic groups	20.0% (2/10) (5.7%, 51.0%)	99.81% (519/520) (98.65%, 99.97%)	(2/3)
Other ethnic group	(0/1)	100.00% (228/228) (98.34%, 100.00%)	N/A
Prior Cancer History			
Yes	30.4% (21/69) (20.8%, 42.1%)	98.89% (3473/3512) (98.40%, 99.23%)	35.0% (21/60) (23.4%, 48.7%)
No	31.7% (238/751) (28.5%, 35.1%)	99.80% (46313/46407) (99.66%, 99.88%)	71.8% (238/331) (59.8%, 81.4%)

*Weights were calculated for participants with no cancer diagnosis and MCED-V2 no cancer signal detected group based on sampling strata defined in the statistical analysis plan. In each stratum, analysis weights were calculated

as the ratio of the number of participants eligible for Galleri sample selection to the number of participants selected.
When specificity is at boundary values (0% or 100%), weighting is not applied and the 95% CI is conservatively estimated using modified Wilson method.
Estimates are not provided for subgroups with <5 cases.

6.4.3 CSO Prediction Accuracy

CSO prediction accuracy was assessed in participants with true-positive Galleri test results. Results for NHS-Galleri CSO prediction accuracy are provided in Table 31, showing that prediction accuracy increased when CSO-S prediction accuracy was also considered. The accuracy of CSO-S prediction in participants with true-positive results who had an assigned clinical CSO-S was 97.2% (69/71).

Given the high accuracy of CSO prediction, incorporating the CSO-S added only three cases where the CSO prediction was incorrect but the CSO-S prediction was accurate (Table 31).

Table 31: NHS-Galleri: CSO Prediction Accuracy in Participants with True-Positive Galleri Test Results (Prevalent Screening Round)

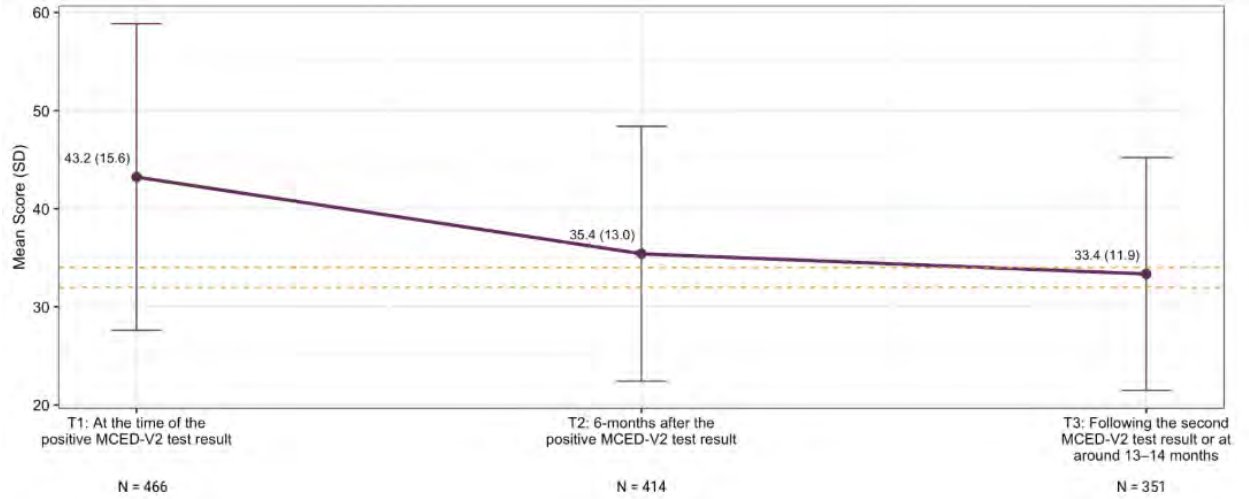
Metric	n/N	CSO Prediction Accuracy (95% CI)
CSO Prediction Accuracy	238/259	91.9% (87.9%, 94.6%)
CSO or CSO-S Prediction Accuracy	241/259	93.1% (89.3%, 95.6%)

Because the NHS-Galleri study was designed to enrich for older age groups, an adjusted analysis was performed with standardization by 10-year age group (based on the 2020 US Census age distribution (Blakeslee et al., 2023)) and the prevalence of cancer in each age group to estimate Galleri test performance in the general US population aged 50+ years. The age- and cancer-prevalence-adjusted test performance of Galleri was similar to that observed in NHS-Galleri: 12-month episode sensitivity = 31.1%; specificity = 99.78%; PPV = 66.8%; NPV = 99.02%; CSO prediction accuracy = 92.7%.

6.4.4 State-Trait Anxiety Inventory-6

At T1 (at the time of the positive MCED-V2 test result), the mean STAI-6 score was consistent with that of patients undergoing general, medical, and surgical procedures reported in the STAI user manual (Spielberger, 2015) (Figure 11). Mean STAI-6 scores subsequently decreased at T2 (6 months after the positive MCED-V2 test result) and T3 (following the second MCED-V2 test result or at around 13–14 months), with values that were comparable to scores for the normative reference population of men and women aged 50–69 years (Spielberger, 2015). The magnitude of the elevation in state anxiety levels at T1 was small relative to the observed population spread (standard deviations) in state anxiety scores.

Figure 11: NHS-Galleri: Distribution of STAI-6 Standardized Total Scores at Each Time Point for Participants Who Had a Cancer Signal Detected Result (Prevalent Screening Round)



Note: As indicated by the two dashed reference lines, the STAI user manual reports mean scores of 32–34 (standard deviation=8-10) for adults aged 50–69 years, which represent the expected range within the normative reference population for this age group.

6.4.5 Self-reported Adherence to Current Cancer Screening Guidelines

The majority of participants had high self-reported adherence to guideline-recommended cancer screening at their baseline visit.

6.5 Adverse Events

Both study-procedure-related and device-related AEs were captured during the NHS-Galleri trial. AEs occurring up to the point of referral into the NHS were assessed for relatedness to the study procedures and were classified as *study-procedure-related* AEs. AEs occurring after the point of referral (i.e., AEs outside of protocol-defined study procedures that may have occurred in the setting of subsequent evaluations after MCED testing) were assessed for their relationship to the device and were classified as *device related* AEs. There were 569 study-procedure/device-related AEs (Table 32). Of these, 547 were study-procedure-related, 20 were device-related, and two were both study-procedure- and device-related. The majority (n=495) of study-procedure-related AEs were considered related to the phlebotomy procedure and included events such as bruising/hematoma, syncope/presyncope, dizziness, pain/swelling at puncture site, nausea and vomiting, and anxiety.

There were 52 AEs that were related to “other” study procedures, including filling out the questionnaire and the communication of results, which were associated with anxiety, emotional distress, and dizziness. More study-procedure-related AEs associated with “other” study procedures were observed in the intervention arm than the control arm (40 vs 12, respectively), as typically these occurred during the return of results call.

Among 71 related AEs of anxiety, emotional distress, and stress, 50 were study-procedure-related and 19 were device-related (these were due to waiting to be scheduled for diagnostic procedures or awaiting the results from the diagnostic procedures after referral to the NHS). Two AEs of anxiety were both study-procedure-related and device-related, as they were reported to start at the time of the test result communication and continued throughout the diagnostic procedures.

Importantly, there were no serious AEs that were related to study procedures or the device during the 12-month follow-up time analysis period. This supports the safety profile of the test given evidence from these large participant cohorts.

Table 32: NHS-Galleri: Number of Adverse Events Related to Study Procedures or Device by Clinical Visit and by Arm (Prevalent Screening Round)

	Intervention arm (N = 71122)			Control arm (N = 71128)			Not randomized (N = 576)	
Number of Adverse Events	**On Blood Draw Visit[1]**	**Off Blood Draw Visit[2]**	**Overall**	**On Blood Draw Visit[1]**	**Off Blood Draw Visit[2]**	**Overall**	**Overall**	**Y0 Total**
AE Relatedness								
Study-procedure-related[3]	211	40	251	257	6	263	33	547
Phlebotomy	205	6	211	246	5	251	33	495
Other	6	34	40	11	1	12	0	52
Device-related	0	20	20	0	0	0	0	20
Study-procedure-related and device-related	0	2	2	0	0	0	0	2
Unrelated[4]	0	0	0	0	0	0	0	0
AE Severity								
Mild	175	49	224	223	5	228	23	475
Moderate	35	11	46	32	1	33	10	89
Severe	1	2	3	2	0	2	0	5
Serious AE[5]	0	0	0	0	0	0	0	0
Unexpected AE	6	22	28	7	2	9	3	40
Serious and Unexpected AE	0	0	0	0	0	0	0	0

[1] AEs collected on Blood Draw form.
[2] AEs collected on AE form.
[3] 1 AE was reported with multiple study-procedure-related events, of which 1 was reported with Phlebotomy and Other.
[4] Neither study-procedure-related nor device-related.
[5] 0 SAEs were reported with multiple serious criteria.
Note: this table summarizes the total number of adverse events per category. No percentage will be calculated, given that this is AE-level summary, not participant-level summary.

7 COMBINED ANALYSES FROM PATHFINDER 2 AND NHS-GALLERI

Based on a prespecified statistical analysis plan shared in advance with FDA, the combined analysis of PATHFINDER 2 and NHS-Galleri data was conducted to improve the stability and precision of cancer-type-specific performance estimates for less common cancers for which study-specific sample sizes were limited. The combined analysis evaluated three test performance measures: (1) episode sensitivity, (2) episode sensitivity accounting for CSO prediction accuracy, and (3) accuracy and precision of CSO prediction among true positives by clinical CSO. The primary combined estimates were generated using a weighted approach. This approach was selected to incorporate information from both pivotal studies while reducing the influence of study-level differences in sample size. As a sensitivity analysis, these metrics were calculated combining data with simple pooling to understand the influence of the study size and the heterogeneity of results on metrics.

The combined analysis is intended to contribute to the totality of evidence by providing more stable estimates where study-specific sample sizes are limited, while study-specific results, heterogeneity assessments, and sensitivity analyses remain important for interpretation.

Because of the differences in screening recommendations between the US and UK, data were not combined for cancers with guideline-recommended screening options. Therefore, the 12-month episode sensitivity by cancer type for screened cancers is presented separately for PATHFINDER 2 and NHS-Galleri in Table 33 below.

7.1 Episode Sensitivity by Cancer Type

There were 144 cancers from PATHFINDER 2 and 325 cancers from NHS-Galleri available for inclusion in the primary combined analysis for Galleri test performance. Episode sensitivity was estimated only for cancer types with at least 5 cases in the combined dataset, as prespecified in the statistical analysis plan for the combined analysis.

The combined results were generally consistent with the study-specific findings. For several clinically meaningful cancer types, including many cancer types within the prespecified subgroup of 12 cancers responsible for two-thirds of US cancer deaths, episode sensitivity was higher than overall episode sensitivity. These findings support Galleri's ability to detect a broad range of cancer types, including cancers associated with high mortality and limited or no guideline-recommended screening options (Table 33).

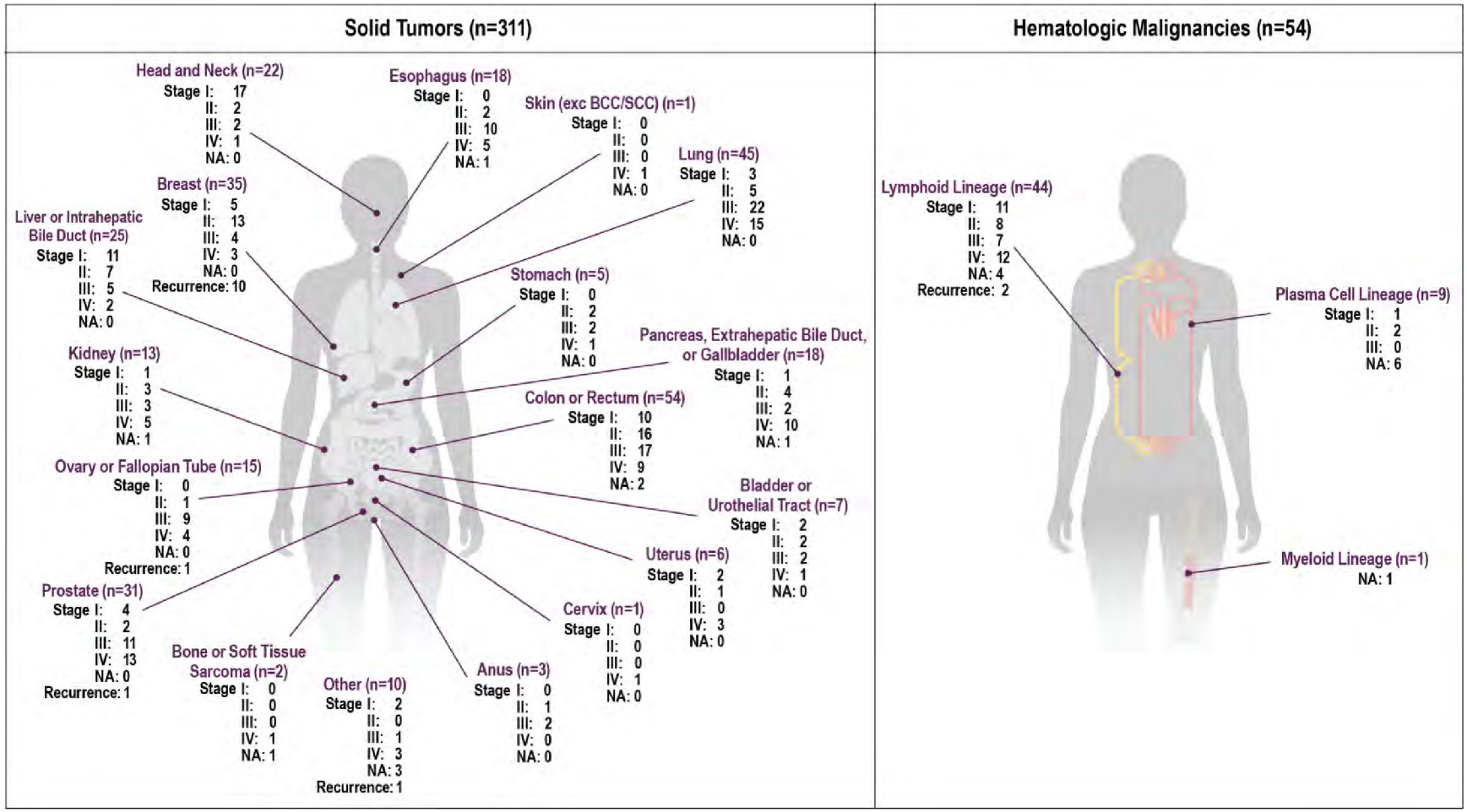
Table 33: PATHFINDER 2 and NHS-Galleri Combined Analysis: Galleri 12-Month Episode Sensitivity for Cancer Signal Detection by Cancer Type

	Episode sensitivity, % (n/N) (95% CI)		
Cancer type	**PATHFINDER 2 (N=144)**	**NHS-Galleri (N=325)**	**Weighted average[1]**
Anus*	(2/4)	(1/3)	43.1% (14.2%, 77.6%)
Bladder, Urothelial Tract	28.6% (2/7) (8.2%, 64.1%)	38.5% (5/13) (17.7%, 64.5%)	35.2% (17.7%, 57.7%)
Bone or Soft Tissue Sarcoma	(1/4)	20.0% (1/5) (3.6%, 62.4%)	22.3% (5.6%, 58.1%)
Cervix[2]	(0)	(1/2)	NA
Esophagus*	(1/2)	65.4% (17/26) (46.2%, 80.6%)	64.2% (45.3%, 79.6%)
Head and Neck*	81.2% (13/16) (57.0%, 93.4%)	42.9% (9/21) (24.5%, 63.5%)	62.9% (23.4%, 90.4%)
Kidney	18.8% (3/16) (6.6%, 43.0%)	41.7% (10/24) (24.5%, 61.2%)	31.1% (13.2%, 57.2%)
Liver, Intrahepatic Bile Duct*	81.2% (13/16) (57.0%, 93.4%)	80.0% (12/15) (54.8%, 93.0%)	80.6% (63.1%, 91.0%)
Lymphoid Lineage*	63.0% (17/27) (44.2%, 78.5%)	46.6% (27/58) (34.3%, 59.2%)	53.2% (37.5%, 68.4%)
Myeloid Lineage	0.0% (0/6) (0.0%, 39.0%)	8.3% (1/12) (1.5%, 35.4%)	4.0% (0.0%, 21.4%)
Ovary or Fallopian Tubes*	60.0% (3/5) (23.1%, 88.2%)	75.0% (12/16) (50.5%, 89.8%)	71.1% (48.6%, 86.5%)
Pancreas, Extrahepatic Bile Duct, Gallbladder*	66.7% (6/9) (35.4%, 87.9%)	38.7% (12/31) (23.7%, 56.2%)	49.0% (24.5%, 74.0%)
Plasma Cell Lineage*	60.0% (3/5) (23.1%, 88.2%)	24.0% (6/25) (11.5%, 43.4%)	36.1% (11.4%, 71.2%)
Skin (excluding BCC/SCC)	0.0% (0/14) (0.0%, 21.5%)	3.4% (1/29) (0.6%, 17.2%)	1.6% (0.0%, 9.2%)
Stomach*	(1/4)	57.1% (4/7) (25.0%, 84.2%)	46.6% (20.0%, 75.3%)
Thyroid	(0/4)	(0/3)	0.0% (0.0%, 26.3%)
Uterus	(1/4)	18.5% (5/27) (8.2%, 36.7%)	19.4% (9.0%, 37.1%)
Brain and Spinal Cord[c]	(0/1)	12.5% (1/8) (2.2%, 47.1%)	3.8% (0.0%, 40.8%)

* These cancers are part of the prespecified subgroup “12 cancers responsible for two-thirds of all cancer deaths in the US.”
1 Estimates were derived using a random-effects inverse-variance meta-analysis of proportions. For cancer types with non-zero true positives and cases in both studies, the logit transformation was applied; for those with zero true positives in any study, the Freeman–Tukey double-arcsine transformation was used; for cancer types with zero cases in any study, meta-analysis was not performed; instead, the weighted average from the study with evaluable results was carried forward.
2 As a rare cancer with < 5 cases across studies, it was prespecified in the statistical analysis plan as out-of-scope for the primary combined analysis and is presented here only as a post hoc descriptive estimate for completeness.
BCC, basal cell carcinoma; SCC, squamous cell carcinoma of the skin.

Figure 12 illustrates the clinical CSO and stage distribution of the diagnosed cancer types with a Cancer Signal Detected by Galleri in PATHFINDER 2 and NHS-Galleri combined.

Figure 12: PATHFINDER 2 and NHS-Galleri Combined Analysis: Distribution of Cancer Types (by Clinical CSO) and Stage at Diagnosis With Cancer Signal Detected by Galleri Among Participants With 12-Month Follow-Up Time



If a participant had multiple cancers, this participant was counted in the Galleri-detected group if any cancer was detected by Galleri. Cancer type and stage are based on the earliest diagnosed cancer if multiple cancers were detected by Galleri. One participant in PATHFINDER 2 with unknown status for new or recurrent cancer at an "other" site is classified as stage = not applicable (NA). NA also includes cancers with missing stage or with no tumor-node-metastasis stage expected.

7.2 CSO Prediction Accuracy

Galleri CSO prediction accuracy was evaluated among participants with true-positive Galleri results in the combined PATHFINDER 2 and NHS-Galleri analysis. Overall, CSO prediction accuracy was high across the combined dataset, with accuracy above 90% for most clinical CSO predictions, providing supportive evidence that CSO prediction performance was consistently high across the two large prospective studies.

8 BENEFIT-RISK CONCLUSIONS

Cancer is a leading cause of morbidity and mortality in the US, with approximately two million new cases and over 600,000 deaths reported annually (ACS, 2026). Despite the proven benefit of guideline-recommended screening programs, these are estimated to detect only 14% of incident cancers in the US (NORC, 2022), while more than 70% of cancer-related deaths are due to cancer types for which no population-based screening recommendation currently exists (Ofman et al., 2025). Galleri is a blood-based, non-invasive test that detects a shared methylation-based cancer signal across multiple tumor types; no FDA-approved or cleared alternative medical device exists. This multi-cancer approach represents an opportunity for early detection across the spectrum of cancer types, including those with and without guideline-recommended screening options.

8.1 Benefits

The Galleri test provides the important clinical benefit of detecting multiple types of cancers, including those with and without current guideline-recommended screening in individuals with no clinical suspicion of cancer, through a non-invasive blood test.

The magnitude and robustness of the benefit of Galleri were validated in two prospective, IDE-approved interventional studies totaling more than 165,000 participants that reflected the intended-use population: PATHFINDER 2 and NHS-Galleri. PATHFINDER 2 and NHS-Galleri demonstrated consistent test performance of Galleri across all metrics and met all prespecified study success criteria. Additionally, performance was similar across categories of age, sex, and racial/ethnic background. The PPV was 77.0% in PATHFINDER 2 and 66.2% in NHS-Galleri. 12-month episode sensitivity was 35.0% and 31.6%, respectively, with specificity of 99.85% and 99.74%, respectively. These performance metrics demonstrate confidence in the benefit of a positive test result.

The 12-month episode sensitivity in a prespecified subgroup of 12 cancers responsible for two-thirds of US cancer deaths, most without guideline-recommended screening options, was 61.3% and 52.1% in PATHFINDER 2 and NHS-Galleri, respectively.

More than two-thirds of cancers were detected at stages I–III (68.9% and 68.7%, respectively, including 82% treated with curative intent in PATHFINDER 2). In addition, nearly half of cancers were detected at stages I-II (48.9% and 37.5%, respectively). The high accuracy of CSO prediction (94.3% and 91.9%, respectively) supports the test's

ability to guide an efficient and appropriate diagnostic work-up (median time to diagnostic resolution of 46 days in PATHFINDER 2). The majority of cancers detected by Galleri in the two studies (75% in PATHFINDER 2 and 62% in NHS-Galleri) were cancer types that lack common screening options.

In PATHFINDER 2, the Galleri cancer detection rate was 0.49%. When added to USPSTF-recommended screenings, Galleri increased the total number of screen-detected cancers by approximately 3-fold in combination with USPSTF Grade A/B/C recommendations and by approximately 7-fold in combination with USPSTF Grade A/B recommendations, demonstrating the population-scale opportunity of MCED testing. In NHS-Galleri, the Galleri cancer detection rate was 0.51%. When added to NHS screening programs, this represented a 6-fold increase in screen-detected cancers over NHS screening programs alone.

Galleri substantially increased cancer detection and identified most cancers at a stage with opportunity for curative-intent treatment, while meeting all prespecified study success criteria for specificity, episode sensitivity, and CSO prediction accuracy. By detecting cancers not addressed by existing guideline-recommended screening programs and accurately predicting CSO to direct an efficient diagnostic work-up, Galleri complements guideline-recommended screening.

8.2 Risks

The risks associated with Galleri, which were evaluated in large, IDE-approved interventional studies, can be categorized in terms of testing and device performance; psychosocial and mental health impacts during testing or while waiting for test results (Kim et al., 2022); non-adherence to guideline-recommended cancer screening or disregarding cancer-related signs and symptoms after a false-negative test result, potentially contributing to a delay in cancer diagnosis and worse clinical outcomes (Cooper et al., 2017); and overdiagnosis and overtreatment of cancers that would never have caused harm to an individual during their lifetime (e.g., indolent breast, prostate, and thyroid cancers (Dunn et al., 2022; Srivastava et al., 2019)). When patients consent to follow-up diagnostic procedures, they face additional risks of physical harm from invasive procedures (e.g., bowel perforation during colonoscopy) and/or ionizing radiation from imaging tests (Huffstetler et al., 2023).

There is minimal probable risk from testing, given the non-invasive and accessible nature of phlebotomy.

In PATHFINDER 2, 0.6% of participants had an invasive procedure performed during diagnostic investigation, and most of these procedures were non-surgical. For context, the 0.6% frequency of invasive procedures after MCED testing in PATHFINDER 2 participants is lower than the 1.8%–2.3% frequency of biopsy after digital mammography or digital breast tomosynthesis (Henderson et al., 2024); the 6.1% frequency of biopsy, bronchoscopy, thoracoscopy, thoracotomy, mediastinoscopy, or mediastinotomy after low-dose computed tomography (CT) of the lung (The National

Lung Screening Trial Research Team, 2011); the 2.6%–4.8% frequency of colonoscopy after fecal immunochemical testing and 9.7% after multitarget stool DNA testing (Imperiale et al., 2014; Mohan et al., 2022; Mohl et al., 2023); and the 12.6% frequency of biopsy after prostate-specific antigen (PSA) testing (Fenton et al., 2018).

In terms of device performance, the very high specificity of the test minimizes the risk of false-positive results. All patients with a positive test result should be referred for diagnostic evaluation for confirmation of cancer. A false-positive result could expose patients to unnecessary risks from follow-up diagnostic evaluations, such as imaging or invasive procedures; however, the exceptionally low false-positive rate minimizes this risk (0.15% in PATHFINDER 2 and 0.26% in NHS-Galleri).

Participants reported high satisfaction with the test and modest, transient, and reversible effects of the test on state anxiety. Mean state anxiety scores and patterns over time were consistent with those for patients undergoing guideline-recommended cancer screening or other health-related procedures, as well as mean scores in the general US population, and reported state anxiety among PATHFINDER 2 study participants returned toward baseline by 12 months.

While a false-negative test result has the potential to result in a delay of guideline-recommended screening or evaluation of signs or symptoms of cancer, Galleri testing had no adverse impact on observed adherence to guideline-recommended cancer screening in PATHFINDER 2, and self-reported adherence in NHS-Galleri and PATHFINDER. (Negative test results were not returned to NHS-Galleri participants to maintain blinding.) Among PATHFINDER 2 participants, observed use of USPSTF Grade A/B cancer screening was unchanged between baseline and 12 months. Adherence to mammography screening up to 24 months after a negative MCED-V2 test (investigational device) has also been demonstrated using real-world evidence (McDonnell et al., 2026). Thus, there were no findings from the large interventional studies that a false-negative test result would result in a delay of guideline-recommended screening or evaluation of signs or symptoms of cancer.

To mitigate the risk of non-adherence to guideline-recommended cancer screening, patient and provider educational and labeling materials have been developed to clearly indicate that a negative Galleri test result does not rule out the presence of cancer, and patients should continue with guideline-recommended screening regardless of Galleri result. For example:

The test result report states the following for a No Cancer Signal Detected (Negative) result:

> “Galleri test does not detect all cancers. Next steps: Recommended cancer screenings: Continue with cancer screening tests as recommended by a healthcare provider. Other cancer screening may be recommended based on age and risk factors, such as screening tests for breast, cervical, colorectal, lung or prostate cancer. Any new or concerning symptoms should be evaluated by a

healthcare provider. This result does not predict whether cancer will develop in the future."

The provider's brochure states the following:

- "A result of No Cancer Signal Detected does not rule out the presence of cancer. Individuals should continue with guideline-recommended single cancer screenings.
- The Galleri test is intended to be used in addition to routine guideline-recommended single cancer screening tests, and is not a replacement for diagnostic tests, other screening tests, or surveillance tests in symptomatic or other high-risk individuals."

Notably, for the majority of cancers, there are no available alternative screening options besides usual care based on signs, symptoms, incidental findings, and/or physician "gut feeling."

The risk of false-negative test results is also mitigated by the observation that approximately 80% of the cancers not detected by Galleri in PATHFINDER 2 have guideline-recommended cancer screening options and/or were detected at stage I based on incidental findings or signs/symptoms.

The potential for overdiagnosis is limited by the biology of the cfDNA test analyte, as demonstrated in prior long-term follow-up studies of users of MCED-V2 (investigational device; not the Galleri PMA device). Specifically, individuals with a Cancer Signal Detected result had cancers that exhibited more aggressive clinical behavior as measured by survival than those with No Cancer Signal Detected (i.e., test-positive cancers did not resemble overdiagnosed cancers) (Mahal et al., 2024; Patel et al., 2023; Swanton et al., 2026). Additionally, in CCGA3, MCED-V2 preferentially detected prostate cancer with Gleason grade group 3+, while not detecting Gleason grade group 1 disease (Mahal et al., 2024), and had limited detection of thyroid cancer, which is predominantly indolent. At the same time, MCED-V2-positive cancers had long-term outcomes that were consistent with stage-specific outcomes in the general US population (i.e., cancers detected by the test before distant metastasis were generally amenable to curative-intent treatment).

Galleri demonstrated a favorable safety profile characterized by modest and transient effects on state anxiety, no adverse impact on adherence to guideline-recommended screening, no device-related AEs, a very low false-positive rate, and limitation of overdiagnosis.

8.3 Benefit-Risk Analysis

Across two large studies totaling more than 165,000 participants, Galleri substantially increased the total number of cancers detected by screening, predominantly at stages with the opportunity for curative-intent treatment. Galleri also exhibited a high PPV, a

very low false-positive rate, clinically meaningful episode sensitivity, highly accurate CSO prediction, and efficient time to diagnostic resolution.

The Galleri test demonstrates a highly favorable safety profile. Study-related AEs were uncommon, participant-reported changes in state anxiety were modest and transient, and the test did not reduce intended or actual adherence to guideline-recommended cancer screening. The low false-positive rate and accurate CSO prediction facilitated targeted diagnostic evaluation and minimized unnecessary diagnostic procedures.

Galleri meets all recommendations for multi-cancer detection tests that were discussed during the 2023 Molecular and Clinical Genetics Panel (Table 7). The key recommendations made by the Panel include the following:

Table 7 (Reprise): Galleri Meets 2023 Molecular and Clinical Genetics Panel's Recommendations for Multi-Cancer Detection Tests

	2023 Panel Recommendations	Galleri's Performance
✅	Detect multiple, clinically significant cancers, particularly those that lack recommended screening options	Galleri detects a shared cancer signal across a diverse range of cancer types, most of which have no available screening options, yet collectively account for most cancer deaths in the US. Galleri's performance across all cancers and unscreened cancers is strong. Episode sensitivity was >60% in PATHFINDER 2 and >50% in NHS-Galleri for key prespecified subgroups such as the 12 cancers accounting for two-thirds of US cancer deaths.[1] For cancers without common screening options,[2] episode sensitivity was 47.3% in PATHFINDER 2 and 40.6% in NHS-Galleri. As an adjunct to guideline-recommended screening, Galleri has the potential to significantly increase the number of screen-detected cancers at stages amenable to curative-intent treatment (82% of PATHFINDER 2 participants with Galleri-detected stages I-III cancers were treated with curative-intent treatment[3]).
✅	Provide tissue-of-origin (in this document called CSO) information to guide effective diagnostic evaluation	Galleri's CSO prediction is highly accurate (91.9%-94.3%) to guide targeted diagnostic work-up. Specifically, the median time to diagnostic resolution in PATHFINDER 2 was 46 days (interquartile range: 29-93 days).
✅	Demonstrate high PPV and very low false-positive rate to minimize unnecessary work-ups	Galleri has a high PPV of 66%-77% and an extremely low false positive rate of 0.15%-0.26%, minimizing unnecessary diagnostic procedures. Safety-relevant endpoints tied to high PPV and low false positive rate provide reassurance for healthcare providers and patients that a positive test result translates into a high likelihood of cancer, and low risk of unnecessary diagnostic investigations due to false positive results.
✅	Additive to, and not a replacement for, guideline-recommended single-cancer screenings	Galleri substantially increased the number of cancers detected by screening when added to guideline-recommended screening programs. Trial data demonstrated no decline in participant adherence to breast, cervical, colorectal, or lung

		cancer screenings at 12 months. Additionally, adherence to mammography screening up to 24 months after a negative MCED-V2 test has also been demonstrated using real-world evidence.

[1] 12 cancers responsible for two-thirds of US cancer deaths: anus; bladder or urothelial tract; colon or rectum; esophagus; head and neck; liver or intrahepatic bile duct; lung; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; and stomach

[2] Cancers without common screening options: anus; bladder or urothelial tract; bone or soft tissue sarcoma; esophagus; head and neck; kidney; liver or intrahepatic bile duct; lung; myeloid lineage; lymphoid lineage; ovary or fallopian tube; pancreas, extrahepatic bile duct, or gallbladder; plasma cell lineage; skin; stomach; thyroid; uterus; and "other"

[3] Curative-intent treatment was defined in PATHFINDER 2 as "treatment undertaken with goal of cure."

The totality of clinical test performance and safety evidence provides strong assurance that the probable benefits of Galleri outweigh its probable risks when used in addition to guideline-recommended screening tests. Galleri meets all previously discussed recommendations for a multi-cancer screening test discussed during the 2023 Panel meeting.

By increasing the total number of screen-detected cancers – predominantly earlier-stage disease with the opportunity for curative-intent treatment – and providing accurate CSO prediction to guide efficient diagnostic evaluation, Galleri has the potential to enhance the overall efficiency of cancer screening and reduce the burden of cancer at the population level.

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10 APPENDICES

10.1 NHS-Galleri and PATHFINDER 2: Protocol-Recommended Diagnostic Evaluations by MCED-V2 CSO Prediction Based on National Guidelines in England and the US

Cancer Signal Origin Type	Expected Diagnostic Evaluation	
	NHS-Galleri (GRAIL NHS-interface supplementary information document pack)	**PATHFINDER 2** (GRAIL-012, version 4.0)
Anus	Direct visualization via anoscopy, flexible sigmoidoscopy or colonoscopy CT chest/abdomen/pelvis if needed	Direct visualization via anoscopy or sigmoidoscopy
Bladder, Urothelial Tract	Flexible cystoscopy CT abdomen/pelvis (triple-phase or pre- and post-contrast) Further imaging with CT chest if needed	Flexible cystoscopy CT urogram or retrograde pyelogram with contrast
Bone and Soft Tissue	MRI with contrast or CT chest/abdomen/pelvis Radionuclide bone scan if needed	MRI with contrast or CT of chest/abdomen/pelvis or PET-CT
Breast	Physical examination, diagnostic mammography or ultrasound, and biopsy of any identified lesions Further imaging with MRI if needed	Diagnostic mammography MRI if participant has recently had screening mammogram
Cervix	Speculum exam and/or biopsy and/or cervical screening (HPV and/or cytology if overdue) MRI pelvis CT chest/abdomen/pelvis if needed	Cytology, HPV testing, colposcopy
Colon, Rectum	Direct visualization via colonoscopy, CT colonography, or colon capsule endoscopy Further imaging with liver ultrasound and/or chest X-ray CT chest/abdomen/pelvis if needed	Direct visualization via colonoscopy

Cancer Signal Origin Type	Expected Diagnostic Evaluation	
	NHS-Galleri (GRAIL NHS-interface supplementary information document pack)	**PATHFINDER 2** (GRAIL-012, version 4.0)
Head and Neck	Direct visualization via endoscopy, imaging (fiber-optic panendoscopy, ultrasound of neck) CT chest/abdomen/pelvis if needed	Direct visualization via flexible nasal endoscopy Head and neck CT or MRI
Kidney	Test urine for blood CT renal, pre- and post-contrast CT chest/abdomen/pelvis if needed	Triple-phase renal CT
Liver, Bile duct	Tumor markers (e.g., alpha-fetoprotein) Triple-phase CT of liver to include pancreas CT chest/abdomen/pelvis if needed	Alpha-fetoprotein Triple-phase abdominal CT
Lung	Contrast-enhanced CT of thorax 6-month follow-up CT if needed	Chest CT
Lymphoid Lineage	CBC, peripheral blood film, biochemistry screen, LDH, viral serology (hepatitis B, hepatitis C, HIV), immunoglobulins and protein electrophoresis Bone marrow biopsy if needed CT chest/abdomen/pelvis if needed	CBC with differential, peripheral blood film, LDH, hepatitis B and C serology, CMP Bone marrow biopsy after blood tests if needed CT of chest/abdomen/pelvis with contrast or PET-CT if needed
Melanocytic Lineage	Skin inspection Panendoscopy of oropharynx CT chest/abdomen/pelvis	Full-body skin exam

Cancer Signal Origin Type	Expected Diagnostic Evaluation	
	NHS-Galleri (GRAIL NHS-interface supplementary information document pack)	**PATHFINDER 2** (GRAIL-012, version 4.0)
Myeloid Lineage	CBC, peripheral blood film, biochemistry screen, LDH Bone marrow biopsy if needed CT chest/abdomen/pelvis if needed	CBC with differential, peripheral blood film, LDH, uric acid, CMP Bone marrow biopsy after blood tests if needed
Neuroendocrine Cells of Lung or other Organs	CT neck/chest/abdomen/pelvis Ga68 Dotatate PET if needed	CT of chest with or without contrast, CT of abdomen/pelvis/head & neck
Ovary	CA-125 blood test Transvaginal ultrasound or MRI pelvis	CA-125 blood test Transvaginal ultrasound
Pancreas, Gallbladder	Pre-imaging comprehensive blood panels including CA-19-9, hemoglobin A1c Dual-phase contrast-enhanced CT of abdomen/pelvis covering pancreas, liver, bile ducts, and gallbladder in detail Endoscopic ultrasound of pancreas with view of duodenum and ampulla of Vater if needed MRI with MRCP component if needed	Multiphasic contrast-enhanced CT of chest/abdomen/pelvis MRI with MRCP component
Plasma Cell Lineage	CBC, peripheral blood film, biochemistry screen, beta-2-microglobulin, immunoglobulins including protein electrophoresis, serum free light chains, urine protein electrophoresis Bone marrow biopsy if needed Skeletal survey or MRI if needed	CBC with differential, peripheral blood film, LDH, uric acid, beta-2-microglobulin, creatinine clearance, serum immunoglobulins, serum free light chain assay, serum and urine protein electrophoresis, CMP Bone marrow biopsy after blood and urine tests if needed Whole-body low-dose CT or PET-CT if needed

Cancer Signal Origin Type	Expected Diagnostic Evaluation	
	NHS-Galleri (GRAIL NHS-interface supplementary information document pack)	**PATHFINDER 2** (GRAIL-012, version 4.0)
Prostate	PSA level Digital rectal examination Multi-parametric MRI of the prostate	PSA level Multi-parametric MRI of the prostate
Stomach, Esophagus (upper GI)	Upper GI endoscopy CT chest/abdomen/pelvis if needed	Upper GI endoscopy
Thyroid Gland	Ultrasound imaging of thyroid by thyroid-trained sonographer or radiologist	Ultrasound imaging of thyroid
Uterus	Transvaginal ultrasound Pipelle biopsy Hysteroscopy if indicated by ultrasound findings	Transvaginal ultrasound
Diagnostic resolution not achieved through targeted diagnostic testing	CT of chest/abdomen/pelvis	PET-CT

CBC, complete blood count; CMP, comprehensive metabolic panel; CT, computed tomography; GI, gastrointestinal; HIV; human immunodeficiency virus; LDH, lactate dehydrogenase; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen.

10.2 Demographic Characteristics, Other Cancer Risk Factors, and Cancer Incidence, Mortality, and Stage-Specific Survival Rates in England/UK and the US

Demographic Characteristics and Other Cancer Risk Factors

Characteristic	England (%)	US (%)
Age group (years)[1,2]		
0-49	63.0	64.3
50-59	13.4	12.8
60-69	10.5	11.7
70-79	8.2	7.3
80 and older	4.9	3.9
Sex by age group (years)[3]		
Females		
0-49	50.7	49.4
50-59	50.7	51.1
60-69	51.2	52.5
70-79	52.8	54.4
80 and older	59.2	61.1
Males		
0-49	49.3	50.6
50-59	49.3	48.9
60-69	48.8	47.5
70-79	47.2	45.6
80 and older	40.8	38.9
Smoking status[4,5]		
Current smoking	14.4	14.5
Body mass index[6,7]		
Women: 25-<30 kg/m^2 (overweight)	31	30.2
Women: 30+ kg/m^2 (obesity)	29	37.4
Men: 25-<30 kg/m^2 (overweight)	41	37.7
Men: 30+ kg/m^2 (obesity)	27	35.1
Cardiovascular disease[8,9]		
Proportion of all deaths from cardiovascular disease	26	22

Characteristic	England (%)	US (%)
Diabetes[10,11]		
Physician-diagnosed diabetes	7	11.3
Chronic obstructive pulmonary disease (COPD)[12,13]		
Physician-diagnosed COPD	4.9	6.5

1. Age Group, England: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea24principalprojectionenglandpopulationinagegroups; Accessed : 02 February 2022.
2. Age Group, US Census Table Results: https://data.census.gov/cedsci/table?q=United%20States&t=Age%20and%20Sex&g=0USfalse&tid=ACSST1Y2019.S0101; Accessed: 02 February 2022.
3. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland; Accessed: 16 February 2022.
4. Cigarette smoking habits in England, ages 16+, 2020: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/datasets/adultsmokinghabitsinengland; Accessed: 8 December 2025.
5. Combustible tobacco product use in US, ages 18+, 2021: Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention (CDC), National Health Interview Survey, 2021;. Accessed: 8 December 2025: 8 December 2025.
6. Body mass index in England, ages 16+, 2019: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2019/health-survey-for-england-2019-data-tables; Accessed: 8 December 2025.
7. Body mass index in US, ages 18+, 2017: CDC BRFSS Graph of Current Adult Obesity Prevalence - Nationwide (States and DC); Accessed: 8 December 2025.
8. Proportion of all UK deaths caused by cardiovascular disease, Heart & Circulatory Disease Statistics 2025; Accessed: 18 December 2025.
9. Proportion of all US deaths caused by heart disease, CDC, About Heart Disease; Accessed: 8 December 2025.
10. Self-reported physician-diagnosed diabetes in England, ages 16+, 2022: Health Survey for England, 2022, Part 2; Accessed: 8 December 2025.
11. Self-reported physician-diagnosed diabetes in US, ages 18+, 2017-2020: National Diabetes Statistics Report, CDC; Accessed: 8 December 2025.
12. Physician-diagnosed COPD in England based on validated events in primary or secondary care, ages 40+, 2019, Stone et al., Prevalence of chronic obstructive pulmonary disease in England from 2000 to 2019, Int J Chron Obstruct Pulmon Dis 2023;18:1565-1574.
13. Self-reported physician-diagnosed COPD in US, ages 18+, 2021: Morbidity and Mortality Weekly Report, CDC, Behavioral Risk Factor Surveillance System, 2021; Accessed: 8 December 2025.

Age-Standardized Cancer Incidence Rates (per 100,000 Person-Years) in Adults Aged 50-79 Years, 2013-2018

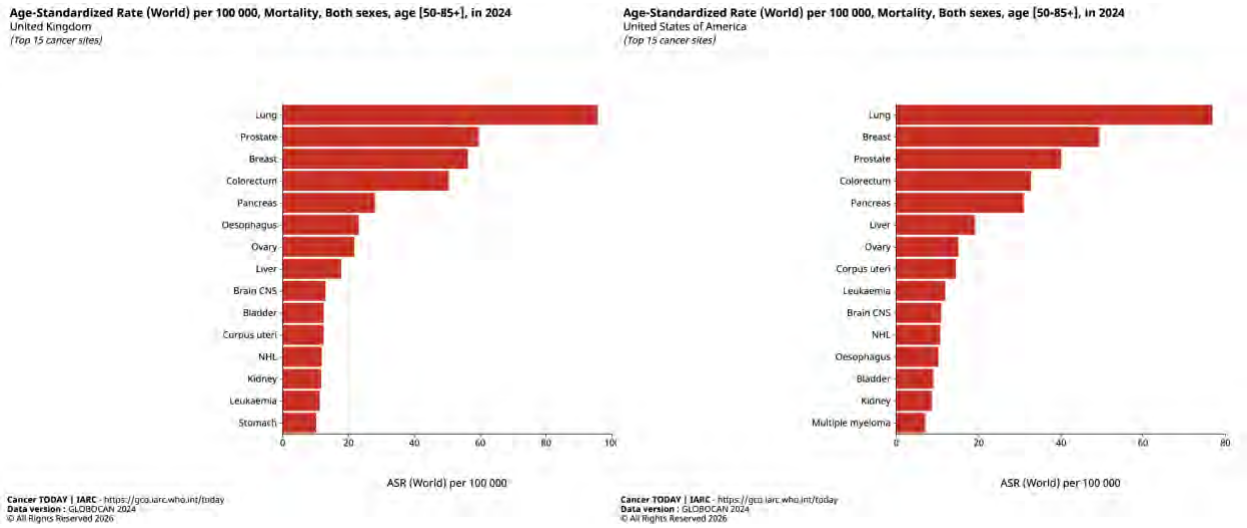
Cancer Type	England (NCRAS)[1]	US (SEER)[2]	Absolute Difference	Relative Difference
	a	b	(a-b)	(a-b)/b
Thyroid	8.51	25.72	-17.21	-66.90%
Bladder	30.35	48.31	-17.96	-37.20%
Sarcoma	9.73	12.86	-3.13	-24.30%
Liver, Bile duct	22.34	29.48	-7.14	-24.20%
Uterus	34.64	43.25	-8.61	-19.90%
Cervix	4.78	5.92	-1.14	-19.20%
Myeloid Neoplasm	13.71	16.10	-2.39	-14.90%
Melanoma	51.8	60.21	-8.41	-14.00%
Gallbladder	6.80	7.90	-1.10	-14.00%
Anus	5.11	5.90	-0.79	-13.40%
Kidney	37.34	42.99	-5.65	-13.10%
Lymphoid Leukemia	16.31	18.66	-2.35	-12.60%
Pancreas	32.58	34.89	-2.31	-6.60%
Head and Neck	42.57	43.91	-1.34	-3.10%
Breast	176.53	178.9	-2.37	-1.30%
Plasma Cell Neoplasm	19.50	19.08	0.42	2.20%
Lymphoma	51.23	48.64	2.59	5.30%
Stomach	18.95	17.98	0.97	5.40%
Lung	158.3	150.02	8.28	5.50%
Prostate	200.38	178.12	22.26	12.50%
Colon, Rectum	131.72	97.05	34.67	35.70%
Urothelial Tract	6.06	4.05	2.01	49.60%
Ovary	26.58	17.75	8.83	49.80%
Esophagus	30.92	12.25	18.67	152.40%

Note: Cancer types are ordered from the largest negative difference to the largest positive difference between England and the US.

1. National Cancer Registration and Analysis Service. Cancer Data: Incidence: https://www.cancerdata.nhs.uk/incidence/base_numbers; Analysis performed on custom data provided to GRAIL by NCRAS - data on file.
2. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 18 Registries, Nov 2020 Submission (2000-2018) - Linked To County Attributes - Time Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer

Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission; Accessed: 10 December 2021.

Aged-Standardized Cancer Mortality Rates (per 100,000 Person-Years) in Adults Aged 50+ Years, 2024[1]



1 Ervik M, Laversanne M, Lam F, Colombet M, Ferlay J, Filho AM, Bray F (2026). Global Cancer Observatory: Cancer Today (2024 estimates, version 1.0). Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed 23 July 2026.

Stage-Specific Cancer Survival Rates, 2010-2014 or 2012-2014

		United Kingdom[1-5]		United States[6]	
Cancer Type	**Stage at Diagnosis**	**1-Year Net Survival**	**3-Year Net Survival***	**1-Year Cause-Specific Survival**	**3-Year Cause-Specific Survival***
Pancreas, non-neuroendocrine					
	All	22.5	6.6	29.5	9.2
	Localized	52.7	27.1	44.4	24.0
	Regional	49.1	16.2	50.9	16.8
	Distant	9.0	1.0	16.5	2.7
Esophagus, adenocarcinoma					
	All	50.7	23.0	54.6	29.3
	Localized	87.0	66.0	79.6	63.2
	Regional	65.6	28.4	69.5	37.0
	Distant	24.5	3.8	33.3	8.9
Esophagus, squamous cell carcinoma					
	All	43.9	20.6	46.0	25.9

		United Kingdom[1-5]		United States[6]	
Cancer Type	**Stage at Diagnosis**	**1-Year Net Survival**	**3-Year Net Survival***	**1-Year Cause-Specific Survival**	**3-Year Cause-Specific Survival***
	Localized	74.4	53.3	62.5	42.5
	Regional	56.0	27.1	58.9	34.4
	Distant	24.1	6.2	27.3	10.5
Stomach, non-neuroendocrine					
	All	44.8	22.3	53.4	31.4
	Localized	85.7	70.1	79.0	65.7
	Regional	65.0	32.3	71.4	41.1
	Distant	20.7	3.8	28.7	7.2
Lung, non-small-cell					
	All	44.2	22.2	54.8	33.4
	Localized	89.3	69.6	89.0	74.7
	Regional	61.4	28.8	72.6	47.5
	Distant	22.7	4.7	34.6	12.5
Lung, small-cell					
	All	28.1	7.7	34.1	10.6
	Localized	72.9	42.3	69.6	41.1
	Regional	52.6	17.7	57.4	25.1
	Distant	20.1	3.6	26.2	5.2
Colon					
	All	77.1	59.1	83.5	64.6
	Localized	96.0	91.2	96.5	91.0
	Regional	86.0	62.5	90.9	71.7
	Distant	40.7	8.0	54.5	14.6
Rectum					
	All	84.8	62.1	88.6	68.4
	Localized	96.0	85.2	97.0	89.6
	Regional	90.0	62.1	93.6	72.5
	Distant	52.3	8.8	63.5	17.0
Ovary, non-borderline					

		United Kingdom[1-5]		United States[6]	
Cancer Type	**Stage at Diagnosis**	**1-Year Net Survival**	**3-Year Net Survival***	**1-Year Cause-Specific Survival**	**3-Year Cause-Specific Survival***
	All	70.4	47.3	80.4	61.9
	Localized	95.9	91.8	98.5	95.9
	Regional	86.0	74.5	91.6	82.1
	Distant	63.2	33.4	73.1	47.3

Missing stage is imputed for UK data, excluded for US data.
*5-year survival for colon and rectum.

1. Cabasag, C.J. et al. (2020) Exploring variations in ovarian cancer survival by age and stage (ICBP SurvMark-2): A population-based study, Gynecologic Oncology, 157(1), pp. 234–244. Available at: https://doi.org/10.1016/j.ygyno.2019.12.047.
2. Cabasag, C.J. et al. (2022) Pancreatic cancer survival by stage and age in seven high-income countries (ICBP SURVMARK-2): a population-based study, British Journal of Cancer, 126(12), pp. 1774–1782. Available at: https://doi.org/10.1038/s41416-022-01752-3.
3. Araghi, M. et al. (2021) Colon and rectal cancer survival in seven high-income countries 2010–2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project), Gut, 70(1), pp. 114–126. Available at: https://doi.org/10.1136/gutjnl-2020-320625.
4. Araghi, M. et al. (2022) International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SURVMARK-2 Study, Thorax, 77(4), pp. 378–390. Available at: https://doi.org/10.1136/thoraxjnl-2020-216555.
5. Arnold, M. et al. (2022) International variation in oesophageal and gastric cancer survival 2012–2014: differences by histological subtype and stage at diagnosis (an ICBP SURVMARK-2 population-based study), Gut, 71(8), pp. 1532–1543. Available at: https://doi.org/10.1136/gutjnl-2021-325266.
6. SEER (2025) Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 17 Registries, Nov 2024 Sub (2000-2022) - Linked To County Attributes - Time Dependent (1990-2023) Income/Rurality, 1969-2023 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2025, based on the November 2024 submission.

10.3 Cancer Screening Recommendations in England and the US

Cancer Type	Screening Recommendations	
	National Screening Committee (England)	**United States Preventive Services Task Force (USPSTF)**
Breast[1,2]	**Target group**: women aged 50–70 years **Method**: screening mammogram **Interval:** every 3 years **Additional Information**: AgeX[3] trial investigating age extension (47–49 years, 71–73 years)	**Target group**: women aged 40–74 years **Method**: screening mammogram **Interval:** every 2 years **Additional Information**: During PATHFINDER 2 follow-up (April 2024), USPSTF lowered the recommended starting age from 50 years to 40 years; previously "an individual decision" to screen before 50 years
Bowel/ Colorectal[4,5]	**Target group**: adults aged 50–74 years **Method**: fecal immunochemical test (FIT); if positive, followed by repeat FIT test, or colonoscopy **Interval:** every 2 years **Additional Information**: During the active phase of NHS-Galleri, extension of the NHS Bowel Cancer Screening Program from age 60 years to 50 years began with invitations to adults aged 56 years in 2021–22, 58 years in 2022–23, 54 years in 2023–24, and 50 and 52 years in 2024–25; adults aged 75 years and older can request a FIT test.	**Target group**: adults aged 45–75 years **Method**: stool-based tests (e.g., FIT), or direct visualization tests (e.g., colonoscopy) **Interval:** FIT: annually; colonoscopy: every 10 years **Additional Information**: selectively offer to adults aged 76–85 years
Cervical[6,7]	**Target groups:** women aged 25–64 years. **Method:** human papillomavirus **(**HPV) test on cervical swab, with potential follow-up of cervical cytology. Colposcopy follow-up for positive tests. **Interval:** every 3 years for ages 25–49 years, every 5 years for ages 50–64 years	**Target groups:** women aged 21–65 years. **Method:** cervical cytology, high-risk HPV (hrHPV) testing alone, or hrHPV + cytology (co-testing) **Interval:** every 3 years for ages 21–29 years (cervical cytology), every 5 years for ages 30–65 years (hrHPV or co-testing)
Lung[8,9]	**Target group:** adults aged 55–74 years who are current smokers, or who have a history of smoking **Method:** lung health check visit followed by low-dose computed tomography scan for individuals assessed as high-risk **Interval:** every 2 years **Additional Information:** During the active phase of NHS-Galleri, lung cancer screening was not a national program; the Targeted Lung Health Check (a one-time intervention) was available in selected regions in England	**Target group:** adults aged 50–80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. **Method:** low-dose computed tomography scan **Interval:** annually

Cancer Type	Screening Recommendations	
	National Screening Committee (England)	**United States Preventive Services Task Force (USPSTF)**
Prostate[10]	There is currently no guideline-recommended screening for prostate cancer in England.	For men aged 55–69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening should be an individual one. The USPSTF recommends against PSA-based screening in men aged 70 years and older.

[1] UK NHS Overview-Breast cancer in women: https://www.nhs.uk/conditions/breast-cancer/; Accessed: 11 February, 2022.
[2] USPSTF Final Recommendation Statement Breast Cancer: Screening: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening; Accessed: 29 January, 2022.
[3] NHS Breast Screening Programme AgeX Trial: http://www.agex.uk/; Accessed: 06 February 2022.
[4] UK NHS Overview-Bowel cancer screening: https://www.nhs.uk/conditions/bowel-cancer-screening/; Accessed: 14 February 2022.
[5] USPSTF Final Recommendation Statement Colorectal Cancer: Screening: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening; Accessed: 29 January 2022.
[6] UK NHS Cervical screening: https://www.nhs.uk/conditions/cervical-screening/; Accessed: 11 February 2022.
[7] USPSTF Final Recommendation Statement Cervical Cancer: Screening: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening; Accessed: 29 January 2022.
[8] UK NHS Evaluation of the Targeted Lung Health Check programme: https://www.england.nhs.uk/contact-us/privacy-notice/how-we-use-your-information/our-services/evaluation-of-the-targeted-lung-health-check-programme/; Accessed: 11 February 2022.
[9] USPSTF Final Recommendation Statement Lung Cancer: Screening: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening; Accessed: 29 January 2022.
[10] USPSTF Final Recommendation Statement Prostate Cancer: Screening: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening; Accessed: 29 January 2022.

10.4 Concordance Results for Galleri and MCED-V2

Among cancer cases, the positive percent agreement (PPA) between MCED-V2 and Galleri was 86.4% in PATHFINDER 2 (Table 34) and 80.7% in NHS-Galleri (Table 35). The observed PPA for cancer cases is affected by the lower episode sensitivity (smaller number of true positives) of Galleri than MCED-V2, as expected based on the more stringent classifier training specification.

Among participants without cancer, the PPA of 28.6% in PATHFINDER 2 and 38.8% in NHS-Galleri is attributable to the higher specificity (smaller number of false positives) of Galleri than MCED-V2, as expected based on the more stringent classifier training specifications. The low PPA for non-cancers reflects the intended design of the Galleri algorithm to reduce the false-positive rate (which was cut in half), leading to fewer false-positive test results (a desirable outcome) based on Galleri among individuals without cancer. Thus, the PPA indicates a material improvement in the specificity/false-positive rate for Galleri. The important outcome among non-cancer participants is not agreement in the particular individuals who have false-positive test results (as reflected by PPA), but rather that the false-positive rate is sufficiently low to ensure safety in a population that would receive Galleri, and that the number of individuals is sufficient to characterize this rate accurately. Notably, the low PPA for non-cancer participants does not appreciably affect outcomes resulting from the test, since individuals with a negative test result do not receive a diagnostic work-up, treatment, or any other intervention.

The strong negative percent agreement (NPA: 99.9% in PATHFINDER 2 and 99.9% in NHS-Galleri) supports the concordance of the performance characteristics of MCED-V2 with Galleri for accurate return of negative results for individuals without cancer.

Table 34: PATHFINDER 2: Concordance between MCED-V2 and Galleri

Participants	MCED-V2+/ Galleri+	MCED-V2-/ Galleri+	MCED-V2+/ Galleri-	MCED-V2-/ Galleri-	PPA (n/N) (95% CI)	NPA (n/N) (95% CI)
All	124	14	71	21,210	63.6% (124/195) (56.6%, 70.0%)	99.94% (21210/21223) (99.82%, 99.98%)
With Cancer	102	4	16	181	86.4% (102/118) (79.1%, 91.5%)	97.84% (181/185) (94.57%, 99.16%)
Without Cancer	22	10	55	21,029	28.6% (22/77) (19.7%, 39.5%)	99.95% (21029/21038) (99.81%, 99.99%)

Table 35: NHS-Galleri: Concordance between MCED-V2 and Galleri

Participants	MCED-V2+/ Galleri +	MCED-V2-/ Galleri +	MCED-V2+/ Galleri-	MCED-V2-/ Galleri-	PPA (n/N) (95% CI)	NPA (n/N) (95% CI)
All	320	71	185	50,162	63.4% (320/505) (59.1%, 67.5%)	99.86% (50162/50234) (99.72%, 99.93%)
With Cancer	239	20	57	504	80.7% (239/296) (75.9%, 84.8%)	96.18% (504/524) (94.16%, 97.52%)
Without Cancer	81	51	128	49,658	38.8% (81/209) (32.4%, 45.5%)	99.90% (49658/49710) (99.74%, 99.96%)

Note: MCED-V2 test results are used as a denominator for calculation of PPA and NPA.

10.5 Galleri Cancer Signal Detected Test Results: Follow-up Guide for Clinicians

This document is provided to clinicians following a Cancer Signal Detected test result to provide guidance for the diagnostic work-up based on the predicted CSO. This document is intended as guidance, is not prescriptive, and is not intended to replace clinical judgment or expertise.

Note: This document will be revised for the Galleri PMA device.

Note on nomenclature:

Additional Prediction Information (API) = CSO-Supplemental (CSO-S)

Galleri® Cancer Signal Detected Test Results

Follow-Up Guide for Clinicians

Diagnostic Considerations Based on Cancer Signal Origin (CSO) Prediction and Additional Prediction Information (API)

The Galleri test is intended to detect cancer signals from a blood sample and predict where in the body the cancer signal originated. Galleri is a screening test and does not diagnose cancer. Diagnostic workup is needed to confirm cancer. The diagnostic considerations outlined in this document are intended as guidance, are not prescriptive, and should not replace clinical judgment or expertise. Results should be interpreted by clinicians in the context of the patient's medical history, clinical signs, and symptoms.

If comprehensive diagnostic workup based on the CSO prediction does not identify cancer, additional investigation based on the API should be considered (see page 3).

Adapted from Atwood C, et al. 2026.[1]

CSO Prediction	Diagnostic Considerations
All CSO Predictions	**Patient history, physical, CBC, and comprehensive metabolic panel, as well as expert and/or specialist consultation**
Anus	• Anoscopy or sigmoidoscopy with colorectal surgery consultation • If anoscopy is negative, CT chest/abdomen/pelvis (to examine lymph node involvement)
Bladder, Urothelial Tract	• Urinalysis • CT/MR urography or retrograde ureteropyelography • Refer to urology specialist for cystoscopy
Bone	• CT chest/abdomen/pelvis with contrast or MRI with contrast or PET/CT
Breast[a]	• Diagnostic mammogram with or without tomosynthesis • Breast ultrasound • Breast MRI with and without contrast • Refer to breast radiology specialist or surgeon for biopsy • CT chest
Cervix	• Pap smear and HPV testing • Refer to gynecology specialist/oncologist for colposcopy with biopsy • If colposcopy negative, CT abdomen/pelvis with contrast
Colon, Rectum	• Refer to gastroenterology or colorectal surgeon specialist for colonoscopy
Head and Neck	• CT with contrast or PET/CT • Refer to an ENT specialist for flexible nasal endoscopy[b]
Kidney	• Urinalysis • Triple-phase renal CT or MRI without contrast
Liver, Bile Duct	• AFP, liver function tests, CEA, and CA 19-9 • Multiphase contrast-enhanced abdominal CT or MRI • If CT/MRI negative, MRCP or ERCP (for bile duct)
Lung	• Noncontrast CT chest • If abnormal finding on CT, then bronchoscopy

Melanocytic Lineage		• Full-body skin exam (preferably by dermatologist) and dermoscopy with consideration of noncutaneous origin and unusual locations of melanoma • CT chest/head/pelvis or whole-body PET/CT or whole-body MRI • Refer to ophthalmologist for eye exam
Ovary		• CA 125 • Transvaginal/pelvic ultrasound • If negative, CT pelvis with contrast and refer to gynecology specialist
Pancreas, Gallbladder		• CT with pancreas protocol • Refer to gastroenterology specialist for endoscopic ultrasound
Prostate		• PSA • Multiparametric MRI of the prostate
Stomach, Esophagus		• Refer to gastroenterology specialists for esophagogastroduodenoscopy
Thyroid		• Thyroid ultrasound
Uterus		• Transvaginal ultrasound • Refer to gynecology specialist for endometrial biopsy, ideally with hysteroscopy visualization
Hematopoietic and Lymphoid Organs	**Lymphoid Lineage**	• CBC with differential • Peripheral blood flow cytometry, bone marrow examination/ morphology • Serum LDH • PET/CT (preferred) or CT • For abnormal findings, refer to hematologist for excision biopsy (preferred) or core biopsy[c]
	Myeloid Lineage	• CBC with differential • Peripheral blood flow cytometry (myeloid panel) • For abnormal findings, refer to hematologist for bone marrow biopsy
	Plasma Cell Lineage	• CBC with differential • Comprehensive chemistry panel (renal) • Serum protein electrophoresis • Serum free light chain detection (note that analysis for urine free light chain is not appropriate here) • For abnormal findings, refer to hematologist for complete skeletal imaging and bone marrow biopsy

[a] Order and mode as indicated. Chest CT should be considered as part of the diagnostic workup for patients with a cancer signal detected Galleri test result and Breast CSO, given that breast cancers detected in clinical studies of the Galleri test were mostly advanced, aggressive subtypes (eg, triple-negative breast cancer) and/or recurrences.[2-4]
[b] Biopsy should be considered for any abnormal appearances during endoscopy, given the high positive predictive value of the Galleri test.[3]
[c] Fine needle aspiration is not appropriate in this scenario.

AFP, alpha fetoprotein; CA, cancer antigen; CBC, complete blood count; CEA, carcinoembryonic antigen; CSO, cancer signal origin; CT, computed tomography; ENT, ear, nose, throat; ERCP, endoscopic ultrasound and/or retrograde cholangiopancreatography; HPV, human papillomavirus; LDH, lactate dehydrogenase; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen.

API Category *This category identifies the shared biologic origin of certain cancers and therefore suggests additional cancer types to consider if a comprehensive diagnostic workup based on the CSO does not identify cancer*	Associated Cancers	Diagnostic Workup Considerations
Female Reproductive Tract Signal	Cervix	• See page 1
	Ovary	• See page 2
	Uterus	• See page 2
HPV-Associated Methylation Signal	Anus	• See page 1
	Cervix, vagina, vulva	• See page 1 (Cervix) • Pelvic exam
	Head and Neck	• See page 1
	Penis	• Genital and groin lymph node exam
Neuroendocrine Signal	Neuroendocrine tumors (NETs) can develop in any part of the body but are most commonly found in the gastrointestinal tract and lungs[5]	• Immunohistochemistry with neuroendocrine markers (chromogranin A and synaptophysin)[5] • Hormone-specific testing (eg, serotonin/5-HIAA, gastrin, insulin, glucagon, VIP)[5] • ^{68}Ga-DOTATATE PET/CT and/or octreoscan[5]
Squamous Cell Signal	Esophagus	• See page 2 (Stomach, Esophagus)
	Head and Neck	• See page 1
	Lung	• See page 1
For diagnostic considerations for lymphoid, myeloid, and plasma cell lineages, see page 2.		

5-HIAA, 5-hydroxyindoleacetic acid; HPV, human papillomavirus; PET/CT, positron emission tomography/computed tomography; VIP, vasoactive intestinal peptide.

Test Performance

The Galleri test was validated in the Circulating Cell-free Genome Atlas (CCGA) Study. In this validation study, the false-positive rate was 0.5%.[2] Test performance was also evaluated in the intended-use population in the interventional PATHFINDER 2 study, which demonstrated a false-positive rate of 0.4%.[3] Among participants with a cancer signal detected who achieved diagnostic resolution, the positive predictive value was 60%.[3] CSO accuracy is 93.4%.[6]

Unresolved Cancer Signal Detected Results

If comprehensive workup based on the CSO and API does not identify cancer, it is possible that cancer is not present, that the evaluation was insufficient to detect cancer, or that the cancer is located in a different part of the body from that suggested by the CSO and API. ***A Galleri retest at no charge should be considered within 6 months or immediately following a comprehensive workup that does not yield a cancer diagnosis.*** Preliminary data indicate that a negative retest is associated with a low likelihood of subsequent cancer diagnosis: among 100 patients with negative retests, no cancers were identified over 16.7 months of follow-up.[7] In contrast, a positive retest is associated with higher likelihood of subsequent cancer diagnosis, with 29% (13/45) of patients diagnosed with cancer over 10.3 months of follow-up.[7]

Contact GRAIL Medical Information to initiate a no-charge retest (medicalinformation@grailbio.com or 833-694-2553). Review and approval are required prior to submitting another blood sample.

Retest Result	Follow-Up Considerations
Negative	• Diagnostic workup resolved • Continue with all clinician- and guideline-recommended standard-of-care screening and MCED testing
Positive	If CSO is consistent with the previous prediction: • Continue diagnostic testing and refer to relevant specialists • PET/CT If a new CSO is predicted: • Restart the diagnostic process guided by the new CSO, with possible PET/CT depending on clinical judgment • Close surveillance/monitoring with primary care team and relevant specialists (based on CSO) • Continue with all recommended standard-of-care screening

CSO, cancer signal origin; MCED, multi-cancer early detection; PET/CT, positron emission tomography/computed tomography.

For additional information, healthcare professionals may contact GRAIL Medical Information at 833-MY-Galleri (833-694-2553) or visit www.galleri.com

For clinical guidelines related to diagnosis, treatment, and follow-up for specific cancer types, visit www.nccn.org/guidelines/category_1

Important Safety Information

The Galleri test is recommended for use in adults aged 50 years and older. The test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider. The Galleri test is intended to detect cancer signals and predict where in the body the cancer signal is located. Use of the test is not recommended in individuals who are pregnant, under 22 years of age, or undergoing active cancer management.

Results should be interpreted by a healthcare provider in the context of medical history, clinical signs, and symptoms. A test result of No Cancer Signal Detected does not rule out cancer. A test result of Cancer Signal Detected requires confirmatory diagnostic evaluation by medically established procedures (eg, imaging) to confirm cancer.

If cancer is not confirmed with further testing, it could mean that cancer is not present or testing was insufficient to detect cancer, including due to the cancer being located in a different part of the body. False-positive (a cancer signal detected when cancer is not present) and false-negative (a cancer signal not detected when cancer is present) test results do occur. Rx only.

Laboratory/Test Information

The GRAIL clinical laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and accredited by the College of American Pathologists. The Galleri test was developed— and its performance characteristics were determined—by GRAIL. The Galleri test has not been cleared or approved by the US Food and Drug Administration. The GRAIL clinical laboratory is regulated under CLIA to perform high-complexity testing. The Galleri test is intended for clinical purposes.

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