FDA Executive Summary

Prepared for the
September 23, 2026 meeting of the
Molecular and Clinical Genetics Panel of the
Medical Devices Advisory Committee

Pxxxxxx
Galleri
GRAIL, Inc.

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1. Introduction

This document is the FDA Executive Summary for the meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee on the Galleri test from GRAIL, Inc. The device is a qualitative *in vitro* diagnostic test intended to detect cancer-specific methylation patterns in cell-free DNA (cfDNA) isolated from peripheral whole blood. The test is intended for screening for the early detection of multiple types of cancer in adults aged 50 years or older. The test returns a positive (Cancer Signal Detected) or negative (No Cancer Signal Detected) result for a cancer signal. If a Cancer Signal Detected result is returned, a Cancer Signal Origin (CSO) result is also returned, which predicts the likely anatomic location of the detected cancer signal. 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.

On January 29, 2026, GRAIL, Inc. submitted a Premarket Approval (PMA) application to obtain approval of Galleri under Pxxxxxx. This submission has been reviewed by the Division of Molecular Genetics and Pathology (DMGP), Office of Health Technology 7: Office of *In Vitro* Diagnostic Devices (OHT7), Office of Product Evaluation and Quality (OPEQ), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). This document may not include all evidence relevant to the final regulatory recommendation and instead summarizes the areas for which FDA seeks expert input from the Panel. In particular, FDA seeks input on whether the data from the two pivotal clinical studies demonstrate that the probable benefits of the device outweigh its probable risks in screening for the early detection of multiple types of cancer in adults aged 50 years or older.

2. Background Information

2.1 Cancer Burden in the United States

Cancer is the second-leading cause of death in the United States (U.S.) and the leading cause of death among women aged 40-79 and men aged 60-79 (Siegel et al., 2026). In 2026, more than 2.1 million new cancer cases and nearly 630,000 cancer deaths are expected to occur. Cancer predominantly occurs in adults aged 50 years and older, who account for 88% of all diagnoses, with incidence rates approximately doubling each decade after age 50 (Siegel et al., 2026). Interventions, such as an improved treatment landscape, have led to increased 5-year relative survival for cancer diagnoses, which reached 92% for localized-stage disease, 69% for regional-stage disease, and 35% for distant-stage (spread beyond regional lymph nodes or adjacent structures to distant organs or sites) disease during 2015-2021, compared to 88%, 54%, and 17%, respectively, during 1995-1997 (Siegel et al., 2026). As such, detecting cancer earlier, when the disease is amenable to curative treatment, may lead to significant benefits to public health.

2.2 Current Cancer Screening Guidelines and Challenges

The United States Preventive Services Task Force (USPSTF) makes evidence-based recommendations about preventative services, including cancer screening. The USPSTF has issued grade A, B, or C recommendations for breast, cervical, colorectal, lung, and prostate cancer (Table 1) (USPSTF Recommendations). Grade A recommendations indicate that USPSTF recommends the service and there is a high certainty that the net benefit is substantial. Grade B recommendations indicate that USPSTF recommends the service and there is a high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Grade C recommendations indicate USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences, and there is at least moderate certainty that the net benefit is small.

Table 1. USPSTF Cancer Screening Recommendations as of June 2026

Cancer Type	Grade	Eligible Population	Cancer Screening Recommendation
Breast	B	Women aged 40 to 74 years	Biennial screening mammography
Cervical	A	Women aged 21 to 65 years	• Cervical cytology every 3 years in ages 21 to 29 years • Cervical cytology every 3 years, hrHPV testing alone every 5 years, or hrHPV testing in combination with cytology every 5 years in ages 30-65 years
Colorectal	A	Adults aged 50 to 75 years	• High-sensitivity gFOBT or FIT every year • sDNA-FIT every 1 to 3 years • CT colonography every 5 years • Flexible sigmoidoscopy every 5 years • Flexible sigmoidoscopy every 10 years + FIT every year • Colonoscopy screening every 10 years
	B	Adults aged 45 to 49 years	
	C	Adults aged 76 to 85 years	Selective screening to be determined appropriate in individual cases patients and clinicians should consider the patient's overall health, prior screening history, and preferences
Lung	B	Adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years	Annual low-dose computed tomography
Prostate	C	Men aged 55 to 69 years	Individual decision to undergo periodic prostate-specific antigen-based screening after discussion of the potential benefits and harms of screening with their clinician

CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; HPV, human papillomavirus; hrHPV, high-risk HPV; sDNA-FIT, stool DNA-FIT.

In general, other professional societies, including the American Cancer Society (ACS), American Academy of Family Physicians (AAFP), and National Comprehensive Cancer Network (NCCN), endorse the USPSTF recommendations, with some differences with respect to age criteria, screening cadence, and definitions of groups at elevated risk for specific cancers.

According to the ACS' Cancer Prevention & Early Detection Facts & Figures 2025-2026 report, across cancer types, there is variability in the prevalence of up-to-date screening in eligible screening populations (Table 2).

Table 2. Prevalence of Up-to-Date Screening in Eligible Screening Populations

Cancer Type	Eligible Population[1]	Prevalence Up-to-Date with Screening (Year)
Breast	Women aged 50 to 74 years	~80% (2023)
Cervical	Women aged 25 to 65 years	~76% (2021)
Colorectal	Adults aged 45 years and older	~65% (2023)
Lung	Adults aged 50 to 80 years who currently smoke or formerly smoked, with a 20+ pack-year smoking history, regardless of years since quitting	~14% (2022)
Prostate	Men aged 50 years and older	~37% (2023)

[1]Eligible populations described in the ACS' Cancer Prevention & Early Detection Facts & Figures 2025-2026 report are similar, but not identical, to the USPSTF guidelines

Approximately half of the new cancers expected to be diagnosed in 2026 will be cancer types for which guideline-recommended screening exists. Notably, most cancer deaths will result from cancer types that do not have guideline-recommended screening programs. Of the nearly 630,000 cancer deaths expected to occur in the U.S. in 2026, approximately 58% are expected to be attributed to cancer types for which there is no USPSTF Grade A, B, or C screening recommendation (Siegel et al., 2026).

2.3 Potential Benefits and Risks of a Liquid Biopsy Multi-Cancer Detection Test

GRAIL's Galleri test is a blood-based multi-cancer detection test and the subject of this panel discussion. Blood-based multi-cancer detection tests offer the potential to detect multiple types of cancer through a single blood draw. Screening tests, such as Galleri, that detect cancers for which there are no guideline-recommended screening options may provide detection of cancers that would otherwise go undetected, thereby helping to address an unmet medical need. They may also have the benefit of higher adherence, in part, because they are less invasive than other screening methods, which could have a significant public health benefit. However, risks associated with false positive and false negative results of a blood-based screening test should be carefully considered. Individuals erroneously identified as having cancer may be exposed to unnecessary risks from follow-up diagnostic evaluations (e.g., imaging, invasive procedures) and emotional

distress, while individuals erroneously identified as not having cancer may be at risk for delayed cancer detection or diagnosis of cancer at a more advanced stage due to false reassurance from a negative test result or because they have chosen to forgo guideline-recommended screening in favor of the perceived convenience of a blood-based method. Determining whether the probable benefits of a multi-cancer screening test outweigh its probable risks is important, including when such a test screens for cancer types for which guideline-recommended screening already exists.

3. Proposed Indications For Use

This section describes the indications for use, precautions, and limitations proposed by the sponsor. FDA seeks input from the Panel on whether the probable benefits of the Galleri test outweigh the probable risks for the proposed indications for use. In addition, taking into account currently available guideline-recommended cancer screening in the U.S. and the demonstrated performance of Galleri to detect multiple cancer types, including cancers with and without guideline-recommended screening, FDA seeks input from the Panel on how test performance and use, including benefits, risks, and limitations, should be communicated to providers and patients to support shared decision-making in determining whether to use Galleri.

The sponsor has proposed the following Indications for Use statement:

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 workup 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 only.

3.1 Precautions and Limitations

The sponsor has proposed the following Precautions and Limitations to be communicated in labeling.

- The Galleri test is not a replacement for existing recommended single-cancer screening tests or diagnostic modalities for cancer.

- A result of No Cancer Signal Detected does not rule out the presence of cancer. Individuals should continue with guideline-recommended single-cancer screenings.
- A result of Cancer Signal Detected requires diagnostic testing with a medically established procedure to confirm the presence of cancer. Galleri is a screening test and does not diagnose cancer. Galleri does not detect a signal for all cancers.
- The Galleri test may produce false positive or false negative results. A false positive result occurs when Galleri indicates Cancer Signal Detected and there is no cancer diagnosed within a pre-specified follow-up period. A false negative result occurs when Galleri indicates No Cancer Signal Detected and an individual is diagnosed with cancer within a pre-specified follow-up period.
- The benefits and risks of programmatic cancer screening (i.e., repeat testing over an established period of time) with Galleri is currently being studied.

4. Device Description

The Galleri test is a qualitative, next-generation sequencing-based cancer screening test that detects DNA methylation patterns on cfDNA in plasma from individuals aged 50 years or older. The test begins with the collection of whole blood, followed by plasma isolation, cfDNA extraction, and bisulfite conversion of the extracted cfDNA. A library is prepared and enriched for cfDNA fragments potentially associated with cancer signals. The enriched library is then sequenced. The resulting cfDNA data are analyzed using proprietary bioinformatics algorithms, including three locked, machine learning-based classifiers, designed to detect distinct methylation patterns that the Galleri test can recognize as a cancer signal. Following analysis, a test result report is generated for the sample.

Test Result Reporting

The Galleri test has three possible classes of reportable results based on the cancer signal detected within the cfDNA sample, which are assessed by three distinct GRAIL-developed classifiers:

- A **Cancer Signal Classifier**, which determines whether the sample is positive (Cancer Signal Detected) or negative (No Cancer Signal Detected) for a cancer signal.

- A conditional (i.e., only in the event of a Cancer Signal Detected result) **Cancer Signal Origin (CSO) classifier**, which predicts the likely anatomic location of the detected signal. The Galleri test will report 1 of the following 18 CSO classifiers for each Cancer Signal Detected result: anus, bladder/urothelial tract, breast, cervix, colon/rectum, head and neck, kidney [excluding renal pelvis], liver/bile duct, lung, melanocyte-containing tissues/skin, ovary, pancreas/gallbladder, prostate, stomach/esophagus, thyroid, uterus, bone and soft tissue, and hematopoietic and lymphoid organs.

- For a subset of Cancer Signal Detected results, a **Cancer Signal Origin - Supplemental (CSO-S) classifier**, predicts cancer biology, including histologic type

and cellular lineage of the CSO. This information is returned on the TRR as additional clinical information to guide the diagnostic workup. The Galleri test may report 1 of 7 possible categories of CSO-S: HPV-associated methylation signal, Female Reproductive Tract Signal, Squamous Cell Signal (Head & Neck, Lung, Esophagus), Neuro-Endocrine Signal, Lymphoid Lineage, Myeloid Lineage, and Plasma Cell Lineage.

If no sufficient cancer signal is detected, the result is reported as No Cancer Signal Detected. For positive results, the test always returns a single CSO prediction and may also return a single CSO-S prediction, if compatible with the predicted CSO (See Appendix 1 for a list of all CSO predictions and possible CSO-S predictions associated with each predicted CSO).

5. Regulatory History

There are currently no FDA-authorized devices indicated for the screening for multiple types of cancer.

- The Galleri test was granted Breakthrough Device Designation in August 2018.
- GRAIL has two approved Investigational Device Exemptions (IDEs) relevant to this panel discussion:
    - PATHFINDER 2 – IDE approved in September 2021, ClinicalTrials.gov Identifier NCT05155605
    - NHS-Galleri – IDE approved in November 2022, ClinicalTrials.gov Identifier NCT05611632

Galleri has not previously received FDA marketing authorization in the U.S. or any foreign country. An earlier version of the test was launched in June 2021, available by prescription in the U.S.

6. Non-Clinical Studies

GRAIL has conducted non-clinical studies to evaluate the analytical performance of the Galleri test. FDA has reviewed the data from these studies and has no questions for the panel regarding the analytical performance of the Galleri test. Accordingly, these data will not be discussed during the panel meeting.

7. Pivotal Clinical Studies

Two pivotal studies, PATHFINDER 2 and NHS-Galleri, were conducted to generate data to support the safety and effectiveness of the Galleri test. Each pivotal study is presented separately. In both studies, an earlier version of the candidate device in Pxxxxxx (Galleri), called MCED-V2, was used to prospectively test subjects enrolled in the trials. Participants with MCED-V2 Cancer Signal Detected test results underwent targeted diagnostic evaluation guided by CSO predictions. Up to two (2) CSO predictions could be returned by MCED-V2. Participants with MCED-V2 No Cancer Signal Detected test results were encouraged to continue to follow their healthcare providers' cancer screening recommendations.

The Galleri test is a different device from MCED-V2. Differences between Galleri and MCED-V2 include, but are not limited to, the assay workflow, classifier, and bioinformatics pipeline. No data from PATHFINDER 2 or NHS-Galleri were used in the development of Galleri.

The Galleri test performance bridged from PATHFINDER 2 and NHS-Galleri was determined by testing frozen plasma samples from a subset of study participants using the Galleri test, which included all available plasma samples from the following groups: 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 during 12 months of follow-up time. A stratified random sampling approach was used to select a representative subset of samples from participants with MCED-V2 No Cancer Signal Detected results and no cancer diagnosis during 12 months of follow-up time for testing by the Galleri test. Sampling strata were defined by age, race, ethnicity, prior cancer history, smoking status, and selected conditions that may affect cfDNA shedding or methylation, to ensure the selected subset was representative of the broader study population. To account for the fact that not all eligible participants were selected, analysis weights were applied. Within each stratum, the weight assigned to each selected participant was calculated as the ratio of the total number of participants eligible for selection to the number actually selected. These weights were used in all analyses involving participants with no cancer diagnosis or a No Cancer Signal Detected result, so that the weighted results reflect the full eligible population rather than only the tested subset.

Appendix 2 summarizes the concordance between MCED-V2 and Galleri for each pivotal trial. FDA has reviewed the concordance assessments, including sampling approach and results. FDA does not have outstanding questions for the Panel on the concordance assessments.

Safety results are presented for **MCED-V2**, which was assessed by characterizing diagnostic procedures performed in participants with positive MCED-V2 results in PATHFINDER 2 or as reported adverse events (AEs) for study participants in PATHFINDER 2 and NHS-Galleri. Effectiveness results are presented for **Galleri** from the retrospectively tested frozen plasma samples from PATHFINDER 2 and NHS-Galleri.

7.1 PATHFINDER 2

Sections 7.1.1 through 7.1.6 describe the PATHFINDER 2 study design (i.e., study objectives, enrollment criteria, follow-up schedule), accountability, and population demographics. FDA has reviewed this information and does not have outstanding questions for the Panel on these aspects of the study.

PATHFINDER 2 is a prospective, interventional multi-center study of the GRAIL MCED test in healthcare systems in North America in which participants aged 50 years or older who were not clinically suspected of having cancer were enrolled. The purpose of the study is to evaluate the safety and performance of the GRAIL MCED test in an eligible screening population.

Following informed consent, participants received the GRAIL MCED-V2 test, and results were returned to clinical site study investigators. In cases with a Cancer Signal Detected (positive) test result, a diagnostic work-up was coordinated by the study medical team at the enrolling sites. Up to two CSO predictions could be returned by 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. If no cancer was identified based on the first CSO, site study medical teams were asked to evaluate the participant for the second CSO prediction, if one was reported. For participants where diagnostic resolution of cancer diagnosis was not achieved through targeted diagnostic testing and Positron Emission Tomography-Computed Tomography (PET-CT) was not used as part of diagnostic evaluation, a confirmatory PET-CT was performed to assess cancer status. For participants where diagnostic resolution of cancer diagnosis was achieved, clinical information including but not limited to cancer type, pathology, imaging, and clinical staging information was collected. 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 reported for all study participants. AEs were collected and summarized in terms of seriousness, and relatedness to study procedures and/or the MCED-V2 test. In addition, participant-reported outcomes (PRO) were collected at several time points during the study, including participant state (situational) anxiety following an MCED-V2 result.

7.1.1 PATHFINDER 2 Study Objectives

There are two primary objectives of PATHFINDER 2: 1) evaluate the safety of the MCED test in terms of diagnostic testing triggered by the MCED test result and 2) evaluate performance of the MCED test in individuals eligible for cancer screening. There are several secondary objectives of PATHFINDER 2, including time to diagnostic resolution, participant-reported outcomes, and evaluation of MCED test performance in selected subgroups.

7.1.2 PATHFINDER 2 Enrollment Criteria

7.1.2.1 Inclusion Criteria

- Participants must be at least 50 years of age, inclusive, at the time of signing the Informed Consent Form (ICF).

- Informed Consent: Capable of giving signed and legally effective informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Consent provided by a legally authorized representative is not permitted in this protocol.

7.1.2.2 Exclusion Criteria

- 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 are 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) is not an exclusion criterion.
- Individuals who will not be able to comply with the protocol procedures.
- Individuals who are not currently registered patients at a participating center.
- Previous or current participation in another GRAIL-sponsored study. “Participation” is defined as having signed consent and provided a blood sample.
- Previous or current employees or contractors of GRAIL.
- Current pregnancy (by self-report pregnancy status)

7.1.3 PATHFINDER 2 Target Clinical Outcome Definitions

Section 7.1.3 describes how the target clinical outcome of cancer and non-cancer status were defined in PATHFINDER 2. For the PMA submission, non-cancer status was determined after approximately 12-months follow-up time. Thus, the sensitivity of the Galleri test is reported as 12-month episode sensitivity, which is defined as the ability of Galleri to identify cancer diagnosed during a 12-month follow-up period after testing (i.e., a 12-month episode duration). True cancer status, including disease stage, at the time of the Galleri test is unknown for cancer patients not detected by the Galleri test, and there is uncertainty in the extent to which 12-month episode sensitivity is representative of true test sensitivity. Differential bias can also exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw. The Panel should take these uncertainties into consideration during discussions of test performance.

Cancer diagnosis was supported by pathologic confirmation of an invasive solid tumor or hematologic malignancy, by imaging confirmation in the absence of pathology, by

assigned clinical stage of I-IV by the treating physician, or by other clinical confirmation of disease per treating clinician (e.g. biochemical evidence of recurrence of prior cancer). Clinical stage was determined by the healthcare providers through clinical information, pathology reports and/or imaging findings for new primary cancers. Cancers that do not have a tumor, node, metastasis (TNM)-type staging system were analyzed based on the clinical stage provided by the study site using the relevant staging system for each condition, if applicable. If a clinical stage was not available, a pathologic stage based on an abstracted pathology report was used. For recurrent cancers, the extent of recurrence is documented as local, lymph nodes (regional) or distant (metastatic).

The clinical outcome of non-cancer was defined as absence of the diagnosis of cancer. For the PMA submission, absence of cancer diagnosis for participants with MCED-V2 positive test results was assessed at both the time of the diagnostic resolution and at 12-months follow-up time. For participants with MCED-V2 negative test results, absence of cancer diagnosis was determined at the 12-month follow-up time only. Non-cancer status in participants with MCED-V2 negative test results was determined by review of the medical records at approximately 12 months after the blood draw for evidence of cancer diagnosis in the participant's electronic medical record (EMR) or participant self-report through a phone call.

7.1.4 PATHFINDER 2 Cancer Status Assessments and Loss to Follow-up

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

- The cancer diagnosis date is within the first 12 months of follow-up period, or
- No cancer diagnosis has been documented within the first 12 months of follow-up period based on EMR/direct contact

Participants were considered to have an incomplete 12-month cancer status assessment if their most recent EMR review or direct contact occurred less than 11 months after the blood draw and no cancer diagnosis had been reported at that time.

7.1.5 Accountability of PATHFINDER 2

The full consented analysis set for the study included 35,878 participants from 35 enrollment sites.

- There were 88 participants who were excluded from the analysis because these participants' clinical data were not clean at the time of data lock.
- Among the 35,790 consented participants who underwent data cleaning activities and were included in the data lock, 25,490 had 12 months of follow-up time as of December 31, 2024.
- Of those, 25,133 participants were clinically eligible and evaluable, and 25,125 had evaluable MCED-V2 test results.
- 25,125 participants were included in the MCED-V2 Analyzable Set.
- Of these, there were 22,698 analyzable participants that had a completed 12-month cancer status assessment.

- All 22,698 participants with MCED-V2 test results and 12 months of follow-up time after the blood draw as of December 31, 2024 were considered for selection in the Galleri Analyzable Set.
- Of the 22,698 participants included in selection, 26 were not eligible, primarily because there was no frozen plasma sample available for these participants.
- Frozen plasma samples from 7,766 participants were selected for testing and yielded valid Galleri test results, which included the following groups: 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 during 12 months of follow-up time. The Galleri Analyzable Set represented 34.2% (7,766/22,698) of the participants with 12 months of follow-up time who were included in the MCED-V2 Analyzable Set.

7.1.6 PATHFINDER 2 Population Demographics

The demographic and clinical characteristics for the subjects in the MCED-V2 analyzable set are presented in Table 3. The demographic and clinical characteristics of the MCED-V2 Analyzable Set are highly similar to the Galleri Analyzable Set.

Table 3. Demographic and Baseline Characteristics of Participants in the PATHFINDER 2 MCED-V2 Analyzable Set

MCED-V2 Analyzable Set	
Characteristic	**Participants with 12M follow-up time as of December 31, 2024 (N = 25,125)**
Age (years)	
Mean (SD)	64.7 (8.2)
Median (Q1, Q3)	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%)

Table 3. Demographic and Baseline Characteristics of Participants in the PATHFINDER 2 MCED-V2 Analyzable Set

MCED-V2 Analyzable Set	
Characteristic	**Participants with 12M follow-up time as of December 31, 2024 (N = 25,125)**
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%)
Missing	288 (1.1%)
BMI 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%)
Alcohol Use (past 12-months)	
Heavy	1693 (6.7%)
Moderate	5995 (23.9%)

Table 3. Demographic and Baseline Characteristics of Participants in the PATHFINDER 2 MCED-V2 Analyzable Set

MCED-V2 Analyzable Set	
Characteristic	**Participants with 12M follow-up time as of December 31, 2024 (N = 25,125)**
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 was truncated at 90 years.
[2]Non-metastatic basal cell carcinoma and squamous cell carcinoma of the skin are not included.

7.1.7 PATHFINDER 2 Primary Safety Analysis

This section describes the data supporting the PATHFINDER 2 primary safety objective, which was to evaluate the safety of the test in terms of the number and type of diagnostic testing triggered by a positive test result, and a summary of the AEs. These data were generated by MCED-V2 (investigational device). These safety objectives cannot be assessed with the Galleri test because Galleri results were not returned to study subjects or their providers. FDA has reviewed the concordance assessment between MCED-V2 and Galleri. In the absence of direct Galleri safety data, FDA considers the primary safety analysis for PATHFINDER 2 using MCED-V2 to be an approximate estimate of the safety profile for Galleri. FDA does not have outstanding questions for the Panel on the primary safety analysis.

The primary safety objective for PATHFINDER 2 was to evaluate the safety of the MCED test in terms of the number and type of diagnostic testing triggered by the MCED test result.

There were 229 participants in the MCED-V2 Cancer Signal Detected Analysis Set with 12 months follow-up time as of December 31, 2024. Of these, 218 (95.2%) were eligible to be included in the primary safety analysis. These participants had at least one diagnostic evaluation performed and all of their diagnostic evaluations were initiated after communication of their MCED-V2 test result. There were 9 participants excluded from the primary safety analysis due to initiation of diagnostic evaluation prior to communication of MCED-V2 test results. In addition, 2 participants had no diagnostic evaluations performed and so were also excluded from the primary safety analysis.

Of 218 participants who underwent diagnostic evaluation for positive MCED-V2 results, 159 (72.9%) had at least one invasive procedure performed. The proportion of participants who had at least one invasive procedure performed was approximately two times higher among participants who were diagnosed with cancer (90.6%) compared to participants who were not diagnosed with cancer (47.8%), as shown in Table 4, below.

Table 4. Number of MCED-V2 Analyzable 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	47 (36.7%)	33 (36.7%)	80 (36.7%)
Biopsy	68 (53.1%)	10 (11.1%)	78 (35.8%)
Other[1]	2 (1.6%)	2 (2.2%)	4 (1.8%)
No invasive procedures	12 (9.4%)	47 (52.2%)	59 (27.1%)

[1]All four (4) "other" non-surgical invasive procedures were Pap smears.

A total of 227 invasive procedures were performed in 159 participants with MCED-V2 Cancer Signal Detected test results and 12 months follow-up time as of December 31, 2024 who had at least one invasive procedure during diagnostic evaluation initiated after an MCED-V2 Cancer Signal Detected result. Of these, 89.4% (203 of 227) of invasive procedures were non-surgical. A greater proportion of invasive procedures were surgical among participants who were diagnosed with cancer (12.5%; 20 of 160) compared to those who were not diagnosed with cancer (6.0%, 4 of 67).

The number of participants who experienced an AE during diagnostic evaluation after receiving an MCED-V2 Cancer Signal Detected result is presented in Table 5. Nine participants (9 of 218, 4.1%) in the MCED-V2 Cancer Signal Detected Analysis Set with 12 months of follow-up time as of December 31, 2024 experienced a total of 10 AEs during the time of diagnostic evaluation. There were 4 participants with a total of 5 study-related[1] AEs during the time of diagnostic evaluation, all of whom were diagnosed with cancer. None of the study-related AEs were serious. None of the AEs were related to the device, and all occurred during the targeted diagnostic evaluation.

[1] "Study-related" is defined as related to a study activity listed in the protocol Schedule of Activities, and includes complications from procedures performed as part of a diagnostic evaluation following a "cancer signal detected" test result.

Table 5. Adverse Events During the Time of Diagnostic Evaluation in PATHFINDER 2 MCED-V2 Cancer Signal Detected Analysis Set

Number of Participants with[1]	Diagnostic resolution achieved in 12 months		All other participants[2] (N = 13)	Total (N = 218)
	Participants with a cancer diagnosis (N = 127)	Participants with no cancer diagnosis (N = 78)		
No AE	119 (93.7%)	77 (98.7%)	13 (100.0%)	209 (95.9%)
1 AE	7 (5.5%)	1 (1.3%)	0	8 (3.7%)
> 1 AE	1 (0.8%)	0	0	1 (0.5%)
Serious AE (SAE)	1 (0.8%)	0	0	1 (0.5%)
AE severity				
Mild	6 (4.7%)	1 (1.3%)	0	7 (3.2%)
Moderate	1 (0.8%)	0	0	1 (0.5%)
Severe	1 (0.8%)	0	0	1 (0.5%)
AE setting				
Diagnostic procedure prompted by a Cancer Signal Detected test result	5 (3.9%)	1 (1.3%)	0	6 (2.8%)
Other	3 (2.4%)	0	0	3 (1.4%)
AE outcome				
Recovered/Resolved	6 (4.7%)	1 (1.3%)	0	7 (3.2%)
Missing	3 (2.4%)	0	0	3 (1.4%)
AE related to study or device				
Study-related	4 (3.1%)	0	0	4 (1.8%)
Device-related	0	0	0	0

[1]Participants may report multiple AEs or the same AE in multiple settings; therefore, column totals may exceed the number of unique participants and do not sum to the overall total.
[2]Participants who did not reach diagnostic resolution within 12 months.

7.1.8 PATHFINDER 2 Primary Effectiveness Analysis

This section describes the data supporting the PATHFINDER 2 primary effectiveness objective, which was to evaluate the performance of the test in individuals eligible for cancer screening. **The data presented in this section were generated by the Galleri test** based on retrospective testing of frozen plasma samples, as previously described. FDA seeks input from the Panel on the clinical significance of Galleri performance results i) overall, ii) per cancer type, iii) for cancer types with current guideline-recommended screening (i.e., breast, colorectal, lung, cervical, and prostate), and iv) for cancer types without current guideline-recommended screening. FDA also seeks input from the Panel on the clinical significance of the inter-study variability observed on the test's performance estimates. Finally, FDA requests the Panel discuss whether there are cancer types for which Galleri performance presents new risks (e.g., due to uncertainty in performance estimates) and for which risk mitigations may be needed. Where applicable, the Panel should discuss what types of mitigations may be effective.

In total, there were 303 participants diagnosed with cancer who were included in the Galleri Analyzable Set with 12 months follow-up time as of December 31, 2024. Overall, the Galleri 12-month episode sensitivity was 35.0% (95% CI: 29.8%, 40.5%), specificity was 99.85% (95% CI: 99.75%, 99.91%), positive predictive value (PPV) was 77.0% (95% CI: 65.8%, 85.4%), and negative predictive value (NPV) was 99.07% (98.93%, 99.20%). Data are presented in Table 6.

Table 6. PATHFINDER 2 Summary of Galleri Performance Measures

	Galleri Analyzable Set			
	Cancer diagnosis within 12M (N = 303)	**No cancer diagnosis within 12 months (Weighted N* = 21115)**	**Total (Weighted N* = 21418)**	
Cancer Signal Detected	106	32	138	**PPV = 77.0%** (65.8%, 85.4%)
No Cancer Signal Detected	197	21084	21281	**NPV = 99.07%** (98.93%, 99.20%)
	12-month Episode Sensitivity = 35.0% (29.8%, 40.5%)	**Specificity = 99.85%** (99.75%, 99.91%)		

* Weighted counts are rounded to the nearest whole number and therefore may not sum exactly to the displayed row or column totals. Weights were calculated for participants with no cancer diagnosis and MCED-V2 No Cancer Signal Detected group based on Statistical Analysis Plan (SAP)-defined sampling strata. 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, NPV).

The Galleri test false positive rate was 0.15% (95% CI: 0.09%, 0.25%), cancer detection rate (CDR) was 0.49% (95% CI: 0.41%, 0.60%), the number needed to screen (NNTS) was 202 (95% CI: 167, 245), the positive likelihood ratio (PLR) was 233.7 (95% CI: 135.6, 402.7), and the negative likelihood ratio (NLR) was 0.65 (95% CI: 0.60, 0.71). Data are presented in Table 7 (also see Appendix 3).

Table 7. PATHFINDER 2 Summary of Additional Galleri Performance Measures

Galleri Analyzable Set with 12M assessment completed	
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)
Cancer Detection Rate (n/N) (95% CI)	0.49% (106/21418) (0.41%, 0.60%)
Number Needed to Screen (n/N) (95% CI)	202

Table 7. PATHFINDER 2 Summary of Additional Galleri Performance Measures

Galleri Analyzable Set with 12M assessment completed	
	(21418/106) (167, 245)

*Weights were calculated for participants with no cancer diagnosis and MCED-V2 No Cancer Signal Detected group based on SAP-defined sampling strata. 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 (FPR, cancer detection rate, number needed to screen); and Delta method for PLR and NLR.

Table 8 shows the Galleri 12-month episode sensitivity by cancer type using the first cancer diagnosed if multiple cancers (also see Appendix 4). 12-month episode sensitivity by cancer type ranged from 0.0% for Myeloid Lineage (95% CI: 0.0%, 39.0%), Skin (excluding BCC/SCC; 95% CI: 0.0%, 21.5%), and Thyroid cancers to 81.2% (95% CI: 57.0%, 93.4%) for Head and Neck and Liver, Intrahepatic Bile Duct cancers. Point estimates and confidence intervals are not shown for cancers with fewer than five (5) cases. Fewer than five (5) cases of Anus, Bone or Soft Tissue Sarcoma, Esophagus, Stomach, Thyroid, and Uterus cancers were observed in PATHFINDER 2. Galleri 12-month episode sensitivity was also assessed for a pre-specified subgroup of 12 cancers responsible for two-thirds of U.S. cancer deaths[2], which was 61.3% (95% CI: 52.4%, 69.6%) in PATHFINDER 2.

Table 8. Galleri 12-Month Episode Sensitivity by Cancer Type in PATHFINDER 2

Cancer Type	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)
Cancer Types With Guideline-Recommended Screening	
Colon/Rectum	62.5% (5/8) (30.6%, 86.3%)
Lung	47.1% (8/17) (26.2%, 69.0%)
Breast	26.4% (14/53) (16.4%, 39.6%)
Prostate	10.7% (8/75) (5.5%, 19.7%)
All Combined	22.9% (35/153) (16.9%, 30.1%)
Cancer Types Without Guideline-Recommended Screening	
Head and Neck	81.2% (13/16) (57.0%, 93.4%)
Liver, Intrahepatic Bile Duct	81.2% (13/16) (57.0%, 93.4%)
Pancreas, Extrahepatic Bile-Duct, Gallbladder	66.7% (6/9) (35.4%, 87.9%)

[2] 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.

Table 8. Galleri 12-Month Episode Sensitivity by Cancer Type in PATHFINDER 2

Cancer Type	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)
Lymphoid Lineage	63.0% (17/27) (44.2%, 78.5%)
Ovary or Fallopian Tubes	60.0% (3/5) (23.1%, 88.2%)
Plasma Cell Lineage	60.0% (3/5) (23.1%, 88.2%)
Bladder, Urothelial Tract	28.6% (2/7) (8.2%, 64.1%)
Kidney	18.8% (3/16) (6.6%, 43.0%)
Skin (excluding BCC/SCC)	0.0% (0/14) (0.0%, 21.5%)
Myeloid Lineage	0.0% (0/6) (0.0%, 39.0%)
Anus	2/4
Esophagus	1/2
Bone or Soft Tissue Sarcoma	1/4
Stomach	1/4
Uterus	1/4
Thyroid	0/4
Other[1]	71.4% (5/7) (35.9%, 91.8%)
All Combined	47.3% (71/150) (39.5%, 55.3%)

[1]Other cancer types include Thymus (2), Ampulla of Vater (1), Brain and Spinal Cord (1), Unknown Primary Site (1), Small Intestine (1), Testis (1).
CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity)
Episode sensitivity and 95% CIs for cancer with <5 observations were not calculated

Table 9 shows the Galleri 12-month episode sensitivity for cancers with guideline-recommended screening, by whether cancers were diagnosed in participants eligible or not eligible for screening per USPSTF guidelines. In general, for each cancer type with guideline recommended screening, the Galleri 12-month episode sensitivity was higher in individuals not eligible for screening than those eligible for screening.

Table 9. Galleri 12-Month Episode Sensitivity for Cancer Types with Guideline-Recommended Screening by Screening Eligibility in PATHFINDER 2

Cancer Type[1]	Eligible[2] (n/N) (95% CI)	Not Eligible (n/N) (95% CI)	Overall (n/N) (95% CI)
Colon/Rectum	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%)

Table 9. Galleri 12-Month Episode Sensitivity for Cancer Types with Guideline-Recommended Screening by Screening Eligibility in PATHFINDER 2

Cancer Type[1]	Eligible[2] (n/N) (95% CI)	Not Eligible (n/N) (95% CI)	Overall (n/N) (95% CI)
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%)
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%)
Combined	17.7% (17/96) (11.4%, 26.5%)	31.6% (18/57) (21.0%, 44.5%)	22.9% (35/153) (16.9%, 30.1%)

[1]First cancer diagnosed was used in the analysis. No cervical cancers were diagnosed during the 12-month follow-up period.
[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.
Episode sensitivity and 95% CIs for cancer with <5 observations were not calculated

This section describes the distribution of Galleri detected new and recurrent cancers by stage (i.e., I, II, III, and IV) or extent of disease (i.e., local, regional, distant) in PATHFINDER 2 participants within the 12-month follow-up period. FDA seeks input from the Panel on whether the performance of Galleri by stage (overall and per cancer type) supports claims related to "early detection" (e.g., compared to claims such as "cancer detection") in the proposed indications for use statement, specifically *"Galleri is intended for screening for the early detection of multiple types of cancer, in adults aged 50 years or older."*

There were 268 out of 303 (88.4%) participants diagnosed with new primary cancers. Of the 268 participants diagnosed with new primary cancer, 90 (33.6%) were detected by Galleri. Of the 177 participants diagnosed with stage I-II cancer, 44 (24.9%) were detected by Galleri. Of the 208 participants diagnosed with stage I-III cancer, 62 (29.8%) were detected by Galleri. (Table 10). In the Galleri Cancer Signal Detected group, 44 (48.9%, 44/90) new cancers were detected at stages I-II and included Head and Neck (13), Liver (9), Colon/Rectum (3), Lymphoid Lineage (5), Breast (4), Pancreas (2), Lung (2), Plasma Cell Lineage (2), Anus (1), Kidney (1), Bladder, Urothelial Tract (1) and Other (1). In the Galleri Cancer Signal Detected group, 62 (68.9%, 62/90) new cancers were detected at stages I-III. The Galleri 12-month episode sensitivity for new cancers per stage by cancer type is shown in Appendix 5.

Table 10. Distribution of Stage for Participants with Galleri Detected New Cancers in PATHFINDER 2

Participants with given cancer stage[1,2]	Galleri Detected (N = 90)	Galleri Not Detected (N = 178)	Total (N = 268)	12-Month Episode Sensitivity[3] (95% CI)
Stage I	27	99	126	21.4% (15.2%, 29.4%)
Stage II	17	34	51	33.3% (22.0%, 47.0%)
Stage III	18	13	31	58.1% (40.8%, 73.6%)

Table 10. Distribution of Stage for Participants with Galleri Detected New Cancers in PATHFINDER 2

Participants with given cancer stage[1,2]	Galleri Detected (N = 90)	Galleri Not Detected (N = 178)	Total (N = 268)	12-Month Episode Sensitivity[3] (95% CI)
Stage IV	24	14	38	63.2% (47.3%, 76.6%)
Stage I-II	44	133	177	24.9% (19.1%, 31.7%)
Stage I-III	62	146	208	29.8% (24.0%, 36.3%)
Stage III-IV	42	27	69	60.9% (49.1%, 71.5%)
No TNM stage expected[4]	4	11	15	26.7% (10.9%, 51.9%)
Missing	0	7	7	0% (0%, 35.4%)

[1]A participant with both a new primary colon cancer and a distant recurrent colon cancer during the study is counted in both the distribution of new and recurrent cancers
[2]For participants with multiple primary cancers, only information from the first diagnosed cancer is included in the participant-level summary.
[3]Differential bias can exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw.
[4]No TNM stage is expected for cancers such as brain and spinal cord, leukemia, myeloma and plasma cell disorders, polycythemia vera, and cancer of unknown primary.

Thirty-five (35) participants were diagnosed with recurrent cancer. Of these, 16 (45.7%) were detected by Galleri. Of the 8 participants with local recurrent cancer, 1 was detected by Galleri. Of the 6 participants with regional recurrent cancer, 4 were detected by Galleri. Nineteen participants with recurrent cancers had distant (metastatic) disease, 10 of which were detected by Galleri (Table 11). One additional participant had missing information regarding whether the cancer was a new primary or recurrent.

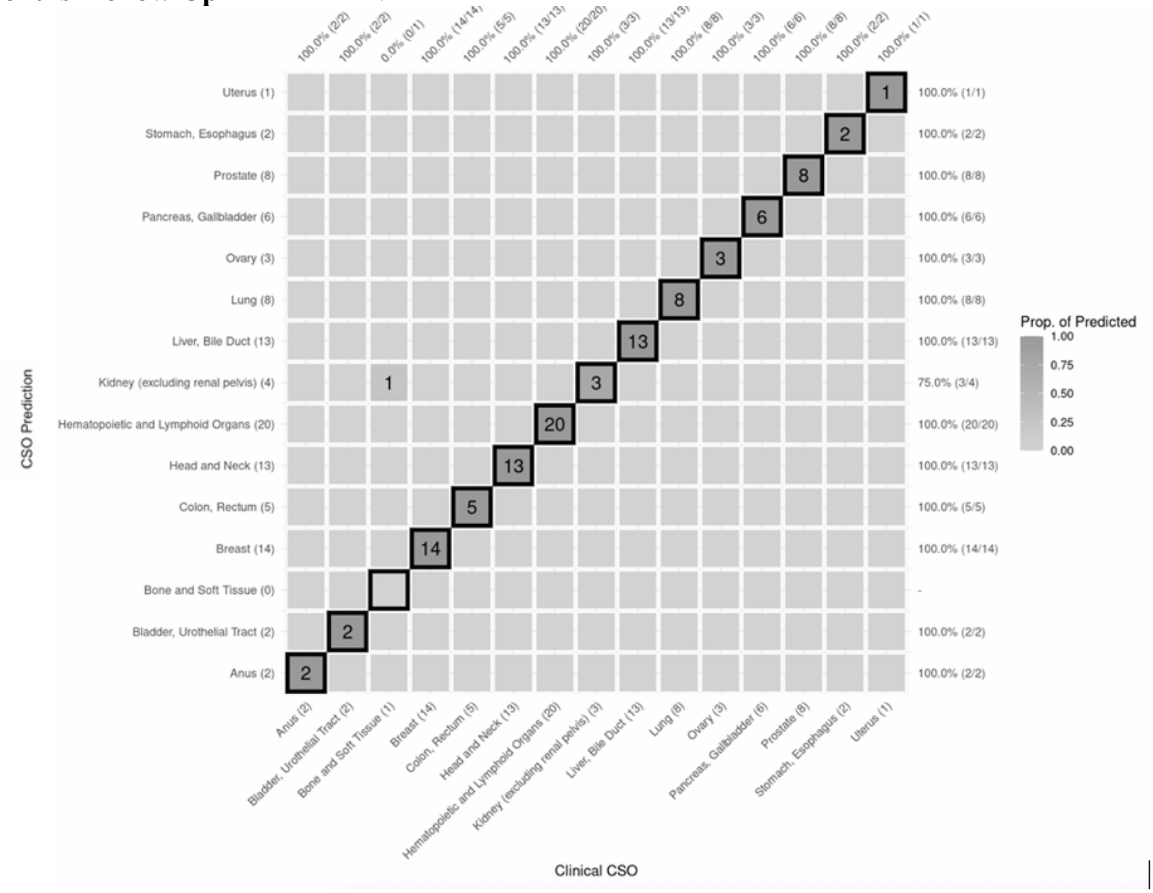
Table 11. Extent of Disease for Participants with Galleri Detected Recurrent Cancers in PATHFINDER 2

Participants with recurrent cancer[1]	Galleri Detected (N = 16)	Galleri Not Detected (N = 19)	Total (N = 35)	12-Month Episode Sensitivity[2] (95% CI)
Local	1	7	8	12.5% (2.2%, 47.1%)
Lymph nodes (regional)	4	2	6	66.7% (30%, 90.3%)
Distant (metastatic)	10	9	19	52.6% (31.7%, 72.7%)
Missing	1	1	2	1/2

[1]A participant with both a new primary colon cancer and a distant recurrent colon cancer during the study is counted in both the distribution of new and recurrent cancers
[2]Differential bias can exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw.

Overall accuracy of Galleri CSO prediction for participants with true positive results based on a cancer diagnosis within 12 months of follow-up time as of December 31, 2024, was **94.3%** (100/106; 95% CI: 88.2%, 97.4%). (Figure 1).

Figure 1. Cancer Signal Origin (CSO) Confusion Matrix for Galleri Prediction at 12 Months' Follow-Up in PATHFINDER 2



There were 6 participants whose Galleri CSO did not accurately predict their cancer diagnosis. Of these, 4 participants were diagnosed with a cancer that did not have a defined clinical CSO (small intestine, testis, and 2 thymus cancers) and 1 participant with a cancer of unknown primary site. There was 1 participant who was diagnosed with cancer of the bone and soft tissue whose Galleri CSO prediction was Kidney.

In addition to a CSO prediction, the Galleri test provided a supplemental CSO (CSO-S) prediction in 44/106 (41.5%) participants. Of these, 42 participants had an assigned clinical CSO-S and two (2) had unknown or unassigned clinical CSO-S. The accuracy of CSO-S prediction in participants with true positive results, with assigned clinical CSO-S was 97.6% (41/42; 95% CI: 87.7%, 99.6%). One participant had a CSO-S prediction of an HPV associated methylation signal and an assigned clinical CSO-S of squamous cell signal of head and neck, lung and esophagus. However, HPV status was not determined for this participant.

Galleri 12-month episode sensitivity accounting for CSO accuracy was 33.0% (95% CI:28.0%, 38.5%). Galleri 12-month episode sensitivity estimates accounting for CSO accuracy by clinical CSO were generally consistent with Galleri 12-month episode sensitivity estimates by cancer type.

Galleri performance for detecting cancers in participants who were up to date with their USPSTF Grade A and B recommended cancer screening was assessed. It should be noted, however, that guideline-recommended screening was not performed concurrently with the MCED blood draw; therefore, it is unknown whether these cancers would have been detected by guideline-recommended screening if performed at the same time. Galleri detected 5 of 20 breast cancers in eligible women who were up to date with their breast cancer screening at the time of diagnosis (interval cancers). Galleri detected 2 of 4 colorectal cancers in participants who were up to date with colorectal cancer screening at the time of diagnosis (interval cancers). No lung cancers were diagnosed in participants who were up to date with their lung cancer screening at the time of their cancer diagnosis. Eight (8) of 13 Galleri-detected lung cancers were diagnosed in participants who were not eligible for lung cancer screening.

7.1.9 PATHFINDER 2 Select Secondary Endpoints Results

Time to Diagnostic Resolution

The median time to diagnostic resolution among all participants with a positive **MCED-V2** test result was 46 days (95% CI: 42, 59); 74% of participants achieved diagnostic resolution within 90 days after their MCED-V2 test result communication. Participants with true positive results had a shorter median time to diagnostic resolution (36 days) compared to those who did not have a cancer diagnosed (false positives, 75 days).

Participant-Reported Outcomes

This section describes the assessment of participant-reported state (situational) anxiety after receiving results from **MCED-V2**. FDA determined the measure of anxiety, the State-Trait Anxiety Inventory-6 (STAI-6), was fit-for-purpose and can be considered in the overall benefit-risk assessment. This study also administered a 3-item adapted version of the STAI-6 measuring anxiety due to the MCED test, the MCED-STAI. FDA also found this to be fit-for-purpose. In addition, this study also measured "attitude towards adherence to guideline-recommended screening," after use of MCED-V2 by asking participants how likely they were to follow cancer screening recommendations. However, this measure had a weak correlation with cancer screening behavior, indicating little to no relationship between attitude towards adherence to guideline-recommended screening and actual cancer screening behavior. FDA determined the attitude measure was not fit-for-purpose. Therefore, FDA does not intend to consider it in the overall benefit-risk assessment and it is not presented in the executive summary.

Participant-reported state (situational) anxiety measured by the State Trait Anxiety Inventory-6 (STAI-6) questionnaire showed that baseline levels of 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 et. al., 1983, 2015). Participants with an

MCED-V2 Cancer Signal Detected test result reported a temporary increase in anxiety after test results were returned, which decreased towards pre-test levels by 12 months. This temporary increase in anxiety levels is comparable to that experienced by patients undergoing general, medical and surgical procedures (Spielberger et. al., 1983, 2015). Participant-reported state (situational) anxiety was also measured by the MCED STAI questionnaire. From pre-MCED-V2 test to post-MCED-V2 test, the proportion of participants who responded feeling worried, tense, or upset due to their MCED test increased among participants with a Cancer Signal Detected result and decreased slightly in participants with a No Cancer Signal Detected result.

Galleri Test Performance in Selected Subgroups

Galleri performance was evaluated in selected subgroups in the Galleri Analyzable Set with 12 months follow-up time as of December 31, 2024. PATHFINDER 2 was not powered for subgroups analyses, and these analyses should be interpreted descriptively. Results are presented in Appendix 6.

7.2 NHS-Galleri

The NHS-Galleri study is a prospective, randomized controlled trial in which participants aged 50-77 with no clinical suspicion of cancer were enrolled to assess the performance of the GRAIL MCED test for population screening in the United Kingdom (UK) when added to standard of care. Participants were randomized 1:1 to either the intervention arm where their blood samples were analyzed using the MCED test or the control arm where blood samples were stored for potential future use in research following blood collection.

Only those results with a finding of Cancer Signal Detected were reported to the participants and their general practitioner. Patients with a positive test were referred to an NHS Urgent Suspected Cancer Referral pathway (two week wait [TWW]) for diagnostic assessment. At the point of the referral, the participant was transferred from the research study to the NHS standard of care. 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.

7.2.1 NHS-Galleri Study Objectives

Sections 7.2.1 through 7.2.6 describe the NHS-Galleri study design (i.e., study objectives, enrollment criteria, follow-up schedule), accountability, and population demographics. FDA has reviewed this information and does not have outstanding questions for the Panel on these aspects of the study.

The primary objective for the PMA submission is to evaluate performance of the MCED test in the intervention arm in the first screening round (12 months follow-up time analysis period). There are several secondary objectives of NHS-Galleri, including assessment of the reduction of stage IV cancers in the first screening round, the number

and type of adverse events in the first screening round, test performance in predefined subgroups, participant-reported anxiety among those receiving a positive MCED test result, and self-reported adherence to current cancer screening guidelines.

7.2.2 NHS-Galleri Enrollment Criteria

7.2.2.1 Inclusion Criteria

- Participants must be 50-77 years of age, inclusive, at the time of data extraction from NHS datasets or general practitioner records used to identify potential participants; and
- Capable of giving signed and legally effective informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and the NHS-Galleri protocol.

7.2.2.2 Exclusion Criteria

- 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 (RDC) or other clinic with a stated suspicion of cancer
- Personal history of invasive cancer or hematological malignancy, diagnosed within the three years prior to expected enrolment date
- Note: Individuals with a diagnosis of non-melanoma skin cancer and prostate cancer patients whose only treatment is active surveillance are NOT excluded
- Definitive treatment for invasive cancer or hematological malignancy within the three (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
- Currently on a palliative care pathway
- Previous or current participation in another GRAIL-sponsored study

7.2.3 NHS-Galleri Target Clinical Outcome Definitions

Section 7.2.3 describes how the target clinical outcome of cancer and non-cancer status were defined in NHS-Galleri. For the PMA submission, cancer/non-cancer status was determined after approximately 12-months follow-up time. Thus, the sensitivity of the Galleri test is reported as 12-month episode sensitivity, which is defined as the ability of Galleri to identify cancer diagnosed during a 12-month follow-up period after testing (i.e., a 12-month episode duration). True cancer status, including disease stage, at the time of the Galleri test is unknown for cancer patients not detected by the Galleri test, and there is uncertainty in the extent to which 12-month episode sensitivity is representative of true test sensitivity. Differential bias can also exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw. The Panel should take these uncertainties into consideration during discussions of test performance.

In NHS-Galleri, cancer status was determined through passive follow-up via linkage to NHS datasets, including the National Cancer Registration and Analysis Service (NCRAS) database, which records all cancer diagnoses made through the NHS in England. A participant was considered to have cancer if a qualifying cancer diagnosis was recorded in the NCRAS dataset within 12 months of their blood draw. Cancer stage was assigned based on the staging system relevant to each cancer type, as submitted to NCRAS as part of the cancer registration process. NCRAS requires that the specific staging system used be identified when staging data are submitted. A cancer was considered stageable if an internationally recognized staging system exists for that cancer's histologic type and anatomic site; cancers for which no such system exists were considered unstageable. An important limitation of the NCRAS dataset is that recurrent cancers are not registered if there is sufficient evidence that the tumor represents a recurrence of a previously diagnosed cancer rather than a new primary cancer. As a result, test-positive recurrent cancers were categorized as “non-cancer” and were not captured in the cancer outcome definition for NHS-Galleri.

The clinical outcome of non-cancer is defined as absence of the diagnosis of cancer in the NCRAS dataset. A participant without cancer is defined as a participant for whom the diagnosis of cancer is absent within 12 months of follow-up.

7.2.4 NHS-Galleri Cancer Status Assessments and Loss to Follow-up

Participants received three rounds of testing with MCED-V2 (investigational device) approximately every 12 months. Cancer status was assessed at each screening round, with approximately 12 months follow-up after the MCED testing. For the PMA analysis, test performance measures were based on retrospective testing with Galleri and data from the first screening round (Y0) with 12 months of follow-up time from blood draw.

Loss to follow-up is defined as withdrawal of consent for passive data collection in the NCRAS cancer registry and linked datasets, or permanent emigration outside of England.

7.2.5 Accountability of NHS-Galleri

A total of 142,250 participants out of 142,826 consented participants were randomized

- Of the randomized participants, 71,128 and 71,112 participants were randomized to the control arm and intervention arm, respectively.
- Of the 71,128 participants randomized to the control arm, 71,033 were clinically eligible and evaluable. Of the 71,112 participants randomized to the intervention arm, 71,032 participants were clinically eligible and evaluable.
- Of the 71,032 participants clinically eligible and evaluable in the intervention arm, 70,323 had evaluable MCED-V2 results.
- 70,323 participants were included in the MCED-V2 Analyzable Set.
- Of these, 61,043 participants consented for future testing and were eligible for selection in the Galleri Analyzable Set.

- Frozen plasma samples from 7,926 participants were selected for testing and yielded valid Galleri results, which included the following groups: 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 during 12 months of follow-up time. The Galleri Analyzable Set represented 11.3% (7,926/70,323) of the participants with 12 months of follow-up time who were included in the MCED-V2 Analyzable Set.

7.2.6 NHS-Galleri Population Demographics

The demographic and clinical characteristics for the subjects in the MCED-V2 analyzable set are presented in Table 12. The demographic and clinical characteristics of the MCED-V2 Analyzable Set are highly similar to the Galleri Analyzable Set (weighted).

Table 12. Demographic and Baseline Characteristics of Participants in the NHS-Galleri MCED-V2 Analyzable Set

MCED-V2 Analyzable Set	
Characteristic	**First Screening Round (N = 70,323)**
Age (years)	
Mean (SD)	65.0 (7.6)
Median (Q1, Q3)	66.0 (59.0, 71.0)
Min, Max	50.0, 78.0
Age group	
50-59 years	18592 (26.4%)
60-69 years	28245 (40.2%)
70-79 years	23486 (33.4%)
Biological Sex	
Female	35332 (50.2%)
Male	34991 (49.8%)
Race/ethnicity (UK)	
White	65825 (93.6%)
Mixed of Multiple ethnic groups	765 (1.1%)
Black, African, Caribbean or Black British	1003 (1.4%)

Table 12. Demographic and Baseline Characteristics of Participants in the NHS-Galleri MCED-V2 Analyzable Set

MCED-V2 Analyzable Set	
Characteristic	**First Screening Round (N = 70,323)**
Asian or Asian British	2334 (3.3%)
Other ethnic group	311 (0.4%)
Missing	85 (0.1%)
BMI Category	
<25 kg/m^2	22824 (32.5%)
25 to <30 kg/m^2	27707 (39.4%)
≥30 kg/m^2	19492 (27.7%)
Missing	300 (0.4%)
Smoking Status	
Current smoker	4679 (6.7%)
Former smoker	26984 (38.4%)
Never smoker	38573 (54.9%)
Missing	87 (0.1%)
Alcohol Use (past 12-months)	
Heavy	8726 (12.4%)
Moderate	22838 (32.5%)
Light	23694 (33.7%)
Former	10771 (15.3%)
None	4004 (5.7%)
Missing	290 (0.4%)
Prior cancer history[1]	
Yes	5227 (7.4%)
No	65096 (92.6%)

[1]Prior cancer history was based on participants either having a prior cancer registration in NCRAS or a self-reported prior cancer. NCRAS registers cancer in England only. Prior cancers diagnosed in trial participants while living in another country are not captured.

7.2.7 NHS-Galleri Safety Analysis

This section describes the data supporting the NHS-Galleri safety objective, which was to evaluate the number and type of AEs in the first screening round (Y0 round). These data were generated by MCED-V2 (investigational device). The primary safety objective cannot be assessed by the Galleri test because Galleri results were not returned to study subjects or their providers. FDA has reviewed the concordance assessment between MCED-V2 and Galleri. In the absence of direct Galleri safety data, FDA considers the primary safety analysis for NHS-Galleri using MCED-V2 to be an approximate estimate of the safety profile for Galleri. FDA does not have outstanding questions for the Panel on the primary safety analysis.

A safety objective for NHS-Galleri was to evaluate the number and type of AEs in the first screening round (Y0 round). AEs were captured as study procedure related or device related. 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 (after the end of the study procedures) were assessed for their relationship to the device, and were classified as device related AEs. The term device related was used in this study to indicate an AE that was reported outside of protocol-defined study procedures in order to identify AEs that may have occurred in the setting of subsequent evaluations after MCED-V2 testing.

Among 71,122 participants in the intervention arm, there were 273 study-procedure-related and/or device-related AEs, while among 71,128 participants in the control arm, there were 263 study-procedure-related AEs, and among the 576 non-randomized participants, there were 33 study-procedure-related AEs, for a total of 569 study-procedure-related and/or device-related AEs (Table 13).

Most study-procedure-related AEs (495) were associated with phlebotomy. The number of related AEs during the blood draw visit was similar between the intervention and control arms. Most related AEs were mild or moderate in severity. No serious study-procedure-related or device-AEs occurred.

Table 13. Adverse Events Related to Study Procedures or Device in all Consented NHS-Galleri Participants (n = 142,826)

	Intervention arm (N = 71122)			Control arm (N = 71128)			Not randomized (N = 576)	Y0 Total
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**	
AE Relatedness								
Study-procedure-related[3]	211	40	251	257	6	263	33	547
Phlebotomy	205	6	211	246	5	251	33	495

Table 13. Adverse Events Related to Study Procedures or Device in all Consented NHS-Galleri Participants (n = 142,826)

	Intervention arm (N = 71122)			Control arm (N = 71128)			Not randomized (N = 576)	Y0 Total
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**	
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 percentages were calculated, given that this is AE-level summary, not participant-level summary.

7.2.8 NHS-Galleri Primary Effectiveness Analysis

This section describes the data supporting the NHS-Galleri primary effectiveness objective, which was to evaluate performance of the MCED test in the intervention arm in the first screening round (12 months follow-up time analysis period). **The data presented in this section were generated by the Galleri test** based on retrospective testing of frozen plasma samples, as previously described. FDA seeks input from the Panel on the clinical significance of Galleri performance results i) overall, ii) per cancer type, iii) for cancer types with current guideline-recommended screening (i.e., breast, colorectal, lung, cervical, and prostate), and iv) for cancer types without current guideline recommended screening. FDA also seeks input from the Panel on the clinical significance of the inter-study variability observed on the test's performance estimates. Finally, FDA requests the Panel discuss whether there are cancer types for which Galleri performance presents new risks (e.g., due to uncertainty in performance estimates) and for which risk mitigations may be needed. Where applicable, the Panel should discuss what types of mitigations may be effective.

In total, there were 820 participants diagnosed with cancer in the intervention arm who were included in the Galleri Analyzable Set with 12 months follow-up time. Overall Galleri 12-month episode sensitivity was 31.6% (95% CI: 28.5%, 34.8%), specificity was 99.74% (95% CI: 99.61%, 99.82%), PPV was 66.2% (95% CI: 56.7%, 74.6%), and NPV was 98.89% (95% CI: 98.78%, 98.98%). Data are presented in Table 14.

Table 14. NHS-Galleri Summary of Galleri Performance Measures

	Galleri Analyzable Set			
	Cancer diagnosis by 12 months (N = 820)	**No cancer diagnosis within 12 months (Weighted N* = 49919)**	**Total (Weighted N* = 50739)**	
Galleri Cancer Signal Detected	259	132	391	**PPV = 66.2%** (56.7%, 74.6%)
Galleri No Cancer Signal Detected	561	49786	50347	**NPV = 98.89%** (98.78%, 98.98%)
	12-Month Episode Sensitivity = 31.6% (28.5%, 34.8%)	**Specificity = 99.74%** (99.61%, 99.82%)		

* Weighted counts are rounded to the nearest whole number and therefore may not sum exactly to the displayed row or column totals. Weights were calculated for participants with no cancer diagnosis and MCED-V2 No Cancer Signal Detected group based on SAP-defined sampling strata. 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, NPV).

The Galleri test false positive rate was 0.26% (95% CI: 0.18%, 0.39%), cancer detection rate (CDR) was 0.51% (95% CI: 0.45%, 0.58%), the number needed to screen (NNTS) was 196 (95% CI: 173, 222), the PLR was 119.2 (95% CI: 80.1, 177.4), and the NLR was 0.69 (95% CI: 0.65, 0.72). Data are presented in Table 15 (also see Appendix 3).

Table 15. NHS-Galleri Summary of Additional Galleri Performance Measures

Galleri Analyzable Set with 12M assessment completed	
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)
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)

*Weights were calculated for participants with no cancer diagnosis and MCED-V2 No Cancer Signal Detected group based on pre-defined sampling strata. 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 (FPR, cancer detection rate, number needed to screen); and Delta method for PLR and NLR.

Table 16 shows the Galleri 12-month episode sensitivity by cancer type using the first cancer diagnosed if multiple cancers (also see Appendix 4). 12-month episode sensitivity by cancer type ranged from 0.0% for Thyroid, 3.4% (95% CI: 0.6%, 17.2%) for Skin, and 8.3% (95% CI: 1.5%, 35.4%) for Myeloid Lineage to 75.0% (95% CI: 50.5%, 89.8%) for Ovary or Fallopian Tubes and 80.0% (95% CI: 54.8%, 93.0%) for Liver, Intrahepatic Bile Duct. Point estimates and confidence intervals are not shown for cancers with fewer than five (5) cases. Fewer than five (5) cases of Anus, Cervix, and Thyroid cancers were observed in NHS-Galleri. Galleri 12-month episode sensitivity was also assessed for a pre-specified subgroup of 12 cancers responsible for two-thirds of U.S. cancer deaths, which was 52.1% (95% CI: 46.9%, 57.2%) in NHS-Galleri.

Table 16. Galleri 12-Month Episode Sensitivity by Cancer Type in NHS-Galleri

Cancer Type	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)
Cancer Types With Guideline-Recommended Screening	
Lung	63.8% (37/58) (50.9%, 74.9%)
Colon/Rectum	53.3% (49/92) (43.1%, 63.1%)
Breast	19.1% (21/110) (12.8%, 27.4%)
Prostate	10.7% (23/215) (7.2%, 15.5%)
Cervix	1/2
All Combined	27.5% (131/477) (23.6%, 31.6%)
Cancer Types Without Guideline-Recommended Screening	
Liver, Intrahepatic Bile Duct	80.0% (12/15) (54.8%, 93.0%)
Ovary or Fallopian Tubes	75.0% (12/16) (50.5%, 89.8%)
Esophagus	65.4% (17/26) (46.2%, 80.6%)
Stomach	57.1% (4/7) (25.0%, 84.2%)
Lymphoid Lineage	46.6% (27/58) (34.3%, 59.2%)
Head and Neck	42.9% (9/21) (24.5%, 63.5%)
Kidney	41.7% (10/24) (24.5%, 61.2%)
Pancreas, Extrahepatic Bile-Duct, Gallbladder	38.7% (12/31) (23.7%, 56.2%)

Table 16. Galleri 12-Month Episode Sensitivity by Cancer Type in NHS-Galleri

Cancer Type	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)
Bladder, Urothelial Tract	38.5% (5/13) (17.7%, 64.5%)
Plasma Cell Lineage	24.0% (6/25) (11.5%, 43.4%)
Bone or Soft Tissue Sarcoma	20.0% (1/5) (3.6%, 62.4%)
Uterus	18.5% (5/27) (8.2%, 36.7%)
Myeloid Lineage	8.3% (1/12) (1.5%, 35.4%)
Skin (excluding BCC/SCC)	3.4% (1/29) (0.6%, 17.2%)
Anus	1/3
Thyroid	0/3
Other[1]	17.9% (5/28) (7.9%, 35.6%)
All Combined	37.3% (128/343) (32.4%, 42.5%)

[1]Other cancer types include Brain and Spinal Cord (N = 8), Unknown Primary Site (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), Uveal Melanoma (N = 1).

Table 17 shows the Galleri 12-month episode sensitivity for cancers with guideline-recommended screening, by whether cancers were diagnosed in participants eligible or not eligible for screening per USPSTF guidelines. For breast and colorectal cancer, the Galleri 12-month episode sensitivity was higher in individuals not eligible for screening than those eligible for screening. For lung and prostate cancer, the Galleri 12-month episode sensitivity was approximately the same in individuals eligible and not eligible for screening. It should be noted that during the first screening round of NHS-Galleri, there were no population level screening recommendations for prostate and lung cancer in the UK.

Table 17. Galleri 12-Month Episode Sensitivity for Cancer Types with Guideline-Recommended Screening by Screening Eligibility in NHS-Galleri

Cancer Type[1]	Eligible[2] (n/N) (95% CI)	Not Eligible (n/N) (95% CI)	Overall (n/N) (95% CI)
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%)
Colon/Rectum	51.9% (40/77) (41.0%, 62.7%)	60.0% (9/15) (35.7%, 80.2%)	53.3% (49/92) (43.1%, 63.1%)
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%)
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%)
Cervix	1/1	0/1	1/2
Combined	28.8% (91/316) (24.1%, 34.0%)	24.8% (40/161) (18.8%, 32.0%)	27.5% (131/477) (23.6%, 31.6%)

[1]First cancer diagnosed was used in the 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.
Episode sensitivity and 95% CIs for cancer with <5 observations were not calculated

This section describes the distribution of Galleri detected new cancers by stage (i.e., I, II, III, and IV) in NHS-Galleri participants within the 12-month follow-up period. Data on recurrent cancers were not collected in the data source used for the NHS-Galleri study. FDA seeks input from the Panel on whether the performance of Galleri by stage (overall and per cancer type) supports claims related to "early detection" (e.g., compared to claims such as "cancer detection") in the proposed indications for use statement, specifically *"Galleri is intended for screening for the early detection of multiple types of cancer, in adults aged 50 years or older."*

There were 820 participants diagnosed with new primary cancers. Of these, 259 (31.6%) were detected by Galleri. Of the 474 participants diagnosed with stage I-II cancer, 97 (20.5%) were detected by Galleri. Of the 657 participants diagnosed with stage I-III cancer, 178 (27.1%) were detected by Galleri. The distribution of new cancers by stage is presented in Table 18. In the Galleri cancer signal detected group, 97 (37.4%) new cancers were detected at stages I-II and included Colon/Rectum (22), Breast (13), Lymphoid Lineage (13), Multiple Cancers (10), Liver (8), Prostate (6), Lung (5), Head and Neck (4), Pancreas (3), Uterus (3), Kidney (3), Esophagus (2), Stomach (2), Bladder/Urothelial Tract (1), Ovary (1), and Plasma Cell Lineage (1). In the Galleri cancer signal detected group, 178 (68.7%) new cancers were detected at stages I-III. The Galleri 12-month episode sensitivity for new cancers per stage by cancer type is shown in Appendix 5.

Table 18. Distribution of Stage for Participants with Galleri Detected New Cancers in NHS-Galleri

Participants with given cancer stage[1]	Galleri Detected (N = 259)	Galleri Not Detected (N = 561)	Total (N = 820)	12-Month Episode Sensitivity[2] (95% CI)
Stage I	43	274	317	13.6% (10.2%, 17.8%)
Stage II	54	103	157	34.4% (27.4%, 42.1%)
Stage III	81	102	183	44.3% (37.3%, 51.5%)
Stage IV	66	44	110	60.0% (50.7%, 68.7%)
Stage I-II	97	377	474	20.5% (17.1%, 24.3%)
Stage I-III	178	479	657	27.1% (23.8%, 30.6%)
Stage III-IV	147	146	293	50.2% (44.5%, 55.9%)
No stage expected[3]	4	21	25	16.0% (6.4%, 34.6%)
Missing	11	17	28	39.3% (23.6%, 57.6%)

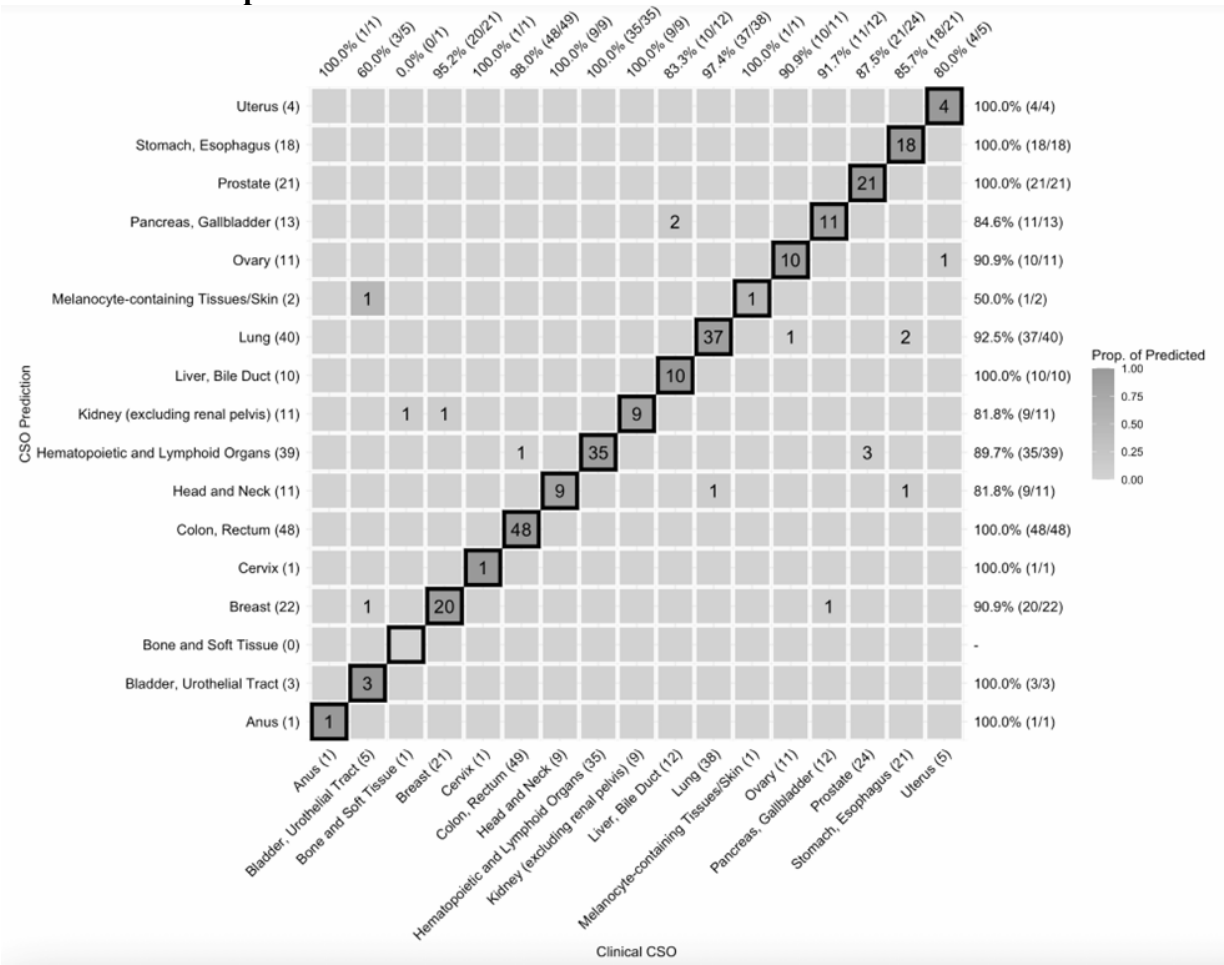
[1]For participants with multiple primary cancers, only information from the first diagnosed cancer is included in the participant-level summary.

[2]Differential bias can exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw.
[3]No TNM stage is expected for cancers such as brain and spinal cord, leukemia, myeloma and plasma cell disorders, polycythemia vera, and cancer of unknown primary.

Data on recurrent cancers were not collected in the data source used for the NHS-Galleri study. This is a known limitation of the NCRAS registration dataset.

Overall accuracy of Galleri CSO prediction for participants with true positive results based on a cancer diagnosis within 12 months of follow-up time was **91.9%** (238/259; 95% CI: 87.9%, 94.6%) (Figure 2)

Figure 2. Cancer Signal Origin (CSO) Confusion Matrix for Galleri Prediction at 12 Months' Follow-up in NHS-Galleri



There were 21 participants whose Galleri CSO did not accurately predict their cancer diagnosis. Of these, 2 participants were diagnosed with a cancer that did not have a defined clinical CSO and 2 participants with a cancer of unknown primary site.

In addition to a CSO prediction, Galleri provided a CSO-S prediction in 83 of 259 (32.0%) participants. Of these, 71 participants had an assigned clinical CSO-S and 12 had

unknown or unassigned clinical CSO-S. The accuracy of CSO-S prediction in participants with true positive results, with assigned clinical CSO-S was 97.2% (69/71; 95% CI: 90.3%, 99.2%).

Galleri 12-month episode sensitivity accounting for CSO accuracy was 29.0% (95% CI: 26.0%, 32.2%). Galleri 12-month episode sensitivity estimates accounting for CSO accuracy by clinical CSO were generally consistent with Galleri 12-month episode sensitivity estimates by cancer type.

7.2.9 NHS-Galleri Select Secondary Endpoints Results

This section describes results from select secondary endpoints in NHS-Galleri, including the reduction in stage IV cancers in the first screening round. The proposed indications for use for Galleri does not include a claim related to reduction in stage IV cancers and FDA is not requesting feedback from the Panel on whether Galleri may reduce stage IV cancers.

Reduction in Stage IV Cancers

A secondary objective for NHS-Galleri was to evaluate the reduction of stage IV cancers in the first screening round. **These data can only be obtained from MCED-V2 (investigational device) because Galleri test results were not returned to study subjects or their providers.** The results for reduction of stage IV routinely staged cancers for all routinely staged cancer and for the pre-specified subgroup of 12 cancers responsible for two-thirds of U.S. cancer deaths are summarized in Table 19. No formal statistical testing was conducted for this analysis. These data show a 3% or 13% reduction in the incidence of stage IV cancers in the intervention arm compared to the control arm for all routinely staged cancers or for the prespecified group of 12 cancer types, respectively (incidence rate ratio 0.97 [95% CI: 0.78, 1.21] and 0.87 [95% CI: 0.68, 1.13]).

Table 19. Reduction of Stage IV Routinely Staged Cancers in First Screening Round

	Intervention arm (N = 71,122)	**Control arm (N = 71,128)**
All Routinely Staged Cancers		
Number of Participants	71,122	71,128
Number of Participants with Stage IV Cancer	164 (0.23%)	169 (0.24%)
Follow-up in Person-Years	70,227	70,241
Incidence Rate (95% CI) per 100,000 person-years	233.5 (199.2, 272.1)	240.6 (205.7, 279.7)
Incidence Rate Ratio (95% CI)	0.97 (0.78, 1.21)	
Prespecified Group of 12 Cancer Types		

Table 19. Reduction of Stage IV Routinely Staged Cancers in First Screening Round

	Intervention arm (N = 71,122)	Control arm (N = 71,128)
Number of Participants	71,122	71,128
Number of Participants with Stage IV Cancer	118 (0.17%)	135 (0.19%)
Follow-up in Person-Years	70,253	70,256
Incidence Rate (95% CI) per 100,000 person-years	168.0 (139.0, 201.1)	192.2 (161.1, 227.4)
Incidence Rate Ratio (95% CI)	0.87 (0.68, 1.13)	

Participant-Reported Outcomes

Participant-reported state (situational) anxiety measured by the State Trait Anxiety Inventory-6 (STAI-6) questionnaire showed that levels of anxiety at the time of positive MCED-V2 test results were consistent with that reported in the STAI user manual for patients undergoing general, medical and surgical procedures (Spielberger et. al., 1983, 2015). Mean STAI scores 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) were comparable to scores for men and women aged 50-69 years (Spielberger et. al., 1983, 2015).

Galleri Test Performance in Selected Subgroups

Galleri performance was evaluated in selected subgroups in the Galleri Analyzable Set. NHS-Galleri was not powered for subgroups analyses, and these analyses should be interpreted descriptively. Results are presented in Appendix 7.

8. Summary

For many cancers, it is posited that earlier detection of cancer has the potential to improve patient outcomes by allowing for treatment initiation at a stage when curative treatment is more likely to be possible. A blood-based multi-cancer detection test may offer a valuable addition to existing screening approaches, particularly for cancer types for which few or no guideline-recommended screening options currently exist.

Galleri is a prescription, qualitative *in vitro* diagnostic test intended for screening for the early detection of multiple types of cancer in adults aged 50 years or older. The sponsor conducted two clinical studies to assess the performance of Galleri. The overall test performance across the two studies is shown in Table 20.

Table 20. Galleri Overall Performance in PATHFINDER 2 and NHS-Galleri

Performance Metric	PATHFINDER 2	NHS-Galleri
	% Estimate (n/N) (95% CI)	
12-Month Episode Sensitivity	35.0% (106/303) (29.8%, 40.5%)	31.6% (259/820) (28.5%, 34.8%)

Table 20. Galleri Overall Performance in PATHFINDER 2 and NHS-Galleri

Performance Metric	PATHFINDER 2	NHS-Galleri
	% Estimate (n/N) (95% CI)	
Specificity	99.85% (21,084/21,115) (99.75%, 99.91%)	99.74% (49,786/49,919) (99.61%, 99.82%)
PPV	77.0% (106/138) (65.8%, 85.4%)	66.2% (259/391) (56.7%, 74.6%)
NPV	99.07% (21,084/21,281) (98.93%, 99.20%)	98.89% (49,786/50,347) (98.78%, 98.98%)
CSO Prediction Accuracy	94.3% (100/106) (88.2%, 97.4%)	91.9% (238/259) (87.9%, 94.6%)

FDA seeks feedback from the Panel on the benefits and risks of Galleri performance for the proposed indications for use. In addition, FDA seeks advice on appropriate labeling for Galleri, including warnings and other risk mitigations, and how Galleri performance, benefits, risks, and limitations should be communicated to health care providers and patients to support shared decision-making in determining whether to use Galleri.

9. Questions for Panel Discussion

FDA is seeking input on the benefit-risk assessment for Galleri when indicated as the sponsor has proposed:

> *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 workup 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 only.*

We have the following discussion questions for the Panel to address during the Advisory Committee Meeting:

1. The FDA Executive Summary and panel presentation described Galleri performance by overall 12-month episode sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), 12-month episode sensitivity per cancer type, and 12-

month episode sensitivity by stage, as reported in the clinical studies (PATHFINDER 2 and NHS-Galleri).

a. Please discuss the clinical significance of the results for patients and providers in the intended use setting, considering Galleri performance:
    i. Overall
    ii. Per cancer type
    iii. For cancer types with current guideline-recommended screening (i.e., breast, colorectal, lung, cervical, and prostate)
    iv. For cancer types without current guideline-recommended screening.

    In your discussion, please also discuss the clinical significance of any inter-study variability observed between PATHFINDER 2 and NHS-Galleri on the test's performance estimates.

b. Please discuss whether Galleri performance by stage (overall and per cancer type) supports the proposed indications for use of "early" detection of multiple types of cancer.
    i. If no, please discuss whether Galleri performance supports an alternate indication for the detection of multiple types of cancer, absent the "early" characterization.
    ii. If yes, please identify the cancer types for which Galleri performance supports "early" detection, and discuss how "early" detection should be described in the test labeling (e.g., by cancer stage, intent for curative treatment available)

c. Please discuss whether there are any cancer types where Galleri's cancer type detection performance presents new risks (e.g., due to uncertainty in performance estimates) and for which risk mitigations may be needed. Where applicable, discuss what types of mitigations (e.g., labeling warnings or limitations) may be effective.

2. Taking into consideration current guideline-recommended screening methods and the demonstrated performance of Galleri to detect multiple cancer types, including cancers with and without guideline-recommended screening, please discuss how test performance and use, including benefits, risks, and limitations, should be communicated to providers and patients to support shared decision-making in determining whether to use Galleri?

   For reference, the following statement is currently proposed to be included in the Galleri Indications for Use:

   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.

   The following statements are proposed to be listed in the Precautions and Limitations section of the Galleri labeling:

- *The Galleri test is not a replacement for existing recommended single-cancer screening tests or diagnostic modalities for cancer.*
- *A result of No Cancer Signal Detected does not rule out the presence of cancer. Individuals should continue with guideline-recommended single-cancer screening*

3. If the device is approved based on existing data, please discuss whether one or multiple post-approval studies to gather additional information about benefits and risks of Galleri would be beneficial. Please discuss the types of information that would be important to collect during such studies.

10. Voting Questions

1. Is there reasonable assurance that Galleri is safe for use in patients who meet the criteria specified in the proposed indication?

2. Is there reasonable assurance that Galleri is effective for use in patients who meet the criteria specified in the proposed indication?

3. Do the benefits of Galleri outweigh the risk for use in patients who meet the criteria specified in the proposed indication?

11. References

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12. Appendix

Appendix 1. Reportable CSO and CSO-S Combinations

Appendix 2. Concordance Between MCED-V2 and Galleri

Appendix 3. Galleri Overall Performance in PATHFINDER 2 and NHS-Galleri

Appendix 4. Galleri 12-Month Episode Sensitivity by Cancer Type in PATHFINDER 2 and NHS-Galleri

Appendix 5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type in PATHFINDER 2 and NHS-Galleri

Appendix 6. Galleri Performance in Select Demographic Subgroups in PATHFINDER 2

Appendix 7. Galleri Performance in Select Demographic Subgroups in NHS-Galleri

Appendix 1. Possible Combinations of CSO and CSO-S Predictions

Table A1. Possible Combinations of CSO and CSO-S Predictions Reported by Galleri

CSO Predictions	CSO-S Predictions						
	HPV Associated Methylation Signal	Female Reproductive Tract Signal	Squamous Cell Signal	Neuro-Endocrine Signal	Lymphoid Lineage	Myeloid Lineage	Plasma Cell Lineage
Anus	■			■			
Bladder, Urothelial Tract				■			
Breast				■			
Cervix	■	■		■			
Colon, Rectum				■			
Head and Neck	■		■	■			
Kidney				■			
Liver, Bile Duct				■			
Lung			■	■			
Melanocyte-containing tissues/Skin				■			
Ovary		■		■			
Pancreas, Gallbladder				■			
Prostate				■			
Stomach, Esophagus			■	■			
Thyroid				■			
Uterus		■		■			
Bone and Soft Tissue							
Hematopoietic and Lymphoid Organs					■	■	■

Appendix 2. Concordance Between MCED-V2 and Galleri

For participants in both the MCED-V2 Analyzable Set and Galleri Analyzable Set, a 2x2 matrix of MCED-V2 and Galleri results were constructed separately for participants with a cancer diagnosis, participants without a cancer diagnosis, and all participants combined (Table A2-1).

Table A2-1. Concordance of MCED-V2 and Galleri test results for cancer signal detection

Category	Galleri positive	Galleri negative
MCED-V2 positive	A	B
MCED-V2 negative	C	D

Percent agreement between the two tests and corresponding confidence intervals were calculated as follows:

- Positive Percent Agreement (PPA) = 100% * A / (A+B)
- Negative Percent Agreement (NPA) = 100% * D / (C+D)

Table A2-2. PATHFINDER 2 Concordance Between MCED-V2 and Galleri

Participants	V2+/ G +	V2-/ G +	V2+/ G -	V2-/ G -	PPA (n/N) (95% CI)	NPA (n/N) (95% CI)
All	124	14	71	21210	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	21029	28.6% (22/77) (19.7%, 39.5%)	99.95% (21029/21038) (99.81%, 99.99%)

Note: MCED-V2 test results are used in the denominator for PPA and NPA calculations.
V2 = MCED-V2; G = Galleri

Table A2-3. NHS-Galleri Concordance Between MCED-V2 and Galleri

Participants	V2+/ G +	V2-/ G +	V2+/ G -	V2-/ G -	PPA (n/N) (95% CI)	NPA (n/N) (95% CI)
All	320	71	185	50162	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	49658	38.8% (81/209) (32.4%, 45.5%)	99.90% (49658/49710) (99.74%, 99.96%)

Note: MCED-V2 test results are used in the denominator for PPA and NPA calculations; V2 = MCED-V2; G = Galleri

Appendix 3. Galleri Overall Performance in PATHFINDER 2 and NHS-Galleri

Table A3. Galleri Overall Performance

Performance Metric	PATHFINDER 2	NHS-Galleri
	% Estimate (n/N) (95% CI)	
12-Month Episode Sensitivity	35.0% (106/303) (29.8%, 40.5%)	31.6% (259/820) (28.5%, 34.8%)
Specificity	99.85% (21,084/21,115) (99.75%, 99.91%)	99.74% (49,786/49,919) (99.61%, 99.82%)
PPV	77.0% (106/138) (65.8%, 85.4%)	66.2% (259/391) (56.7%, 74.6%)
NPV	99.07% (21,084/21,281) (98.93%, 99.20%)	98.89% (49,786/50,347) (98.78%, 98.98%)
False-Positive Rate	0.15% (32/21,115) (0.09%, 0.25%)	0.26% (132/49,918) (0.18%, 0.39%)
Positive Likelihood Ratio	233.7 (135.6, 402.7)	119.2 (80.1, 177.4)
Negative Likelihood Ratio	0.65 (0.60, 0.71)	0.69 (0.65, 0.72)
Cancer Detection Rate	0.49% (106/21,418) (0.41%, 0.60%)	0.51% (259/50,739) (0.45%, 0.58%)
Number Needed to Screen	202 (21,418/106) (167, 245)	196 (50,739/259) (173, 222)

Appendix 4. Galleri 12-Month Episode Sensitivity by Cancer Type in PATHFINDER 2 and NHS-Galleri (based on first cancer diagnosed in participants with multiple cancers)

Table A4. Galleri 12-Month Episode Sensitivity by Cancer Type

Cancer Type	PATHFINDER 2	NHS-Galleri
	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)	
Cancer Types <u>With</u> Guideline-Recommended Screening		
Colon/Rectum	62.5% (5/8) (30.6%, 86.3%)	53.3% (49/92) (43.1%, 63.1%)
Lung	47.1% (8/17) (26.2%, 69.0%)	63.8% (37/58) (50.9%, 74.9%)
Breast	26.4% (14/53) (16.4%, 39.6%)	19.1% (21/110) (12.8%, 27.4%)
Prostate	10.7% (8/75) (5.5%, 19.7%)	10.7% (23/215) (7.2%, 15.5%)
Cervix	0	1/2
Cancer Types <u>Without</u> Guideline-Recommended Screening		
Head and Neck	81.2% (13/16) (57.0%, 93.4%)	42.9% (9/21) (24.5%, 63.5%)
Liver, Intrahepatic Bile Duct	81.2% (13/16) (57.0%, 93.4%)	80.0% (12/15) (54.8%, 93.0%)
Pancreas, Extrahepatic Bile-Duct, Gallbladder	66.7% (6/9) (35.4%, 87.9%)	38.7% (12/31) (23.7%, 56.2%)
Lymphoid Lineage	63.0% (17/27) (44.2%, 78.5%)	46.6% (27/58) (34.3%, 59.2%)
Ovary or Fallopian Tubes	60.0% (3/5) (23.1%, 88.2%)	75.0% (12/16) (50.5%, 89.8%)
Plasma Cell Lineage	60.0% (3/5) (23.1%, 88.2%)	24.0% (6/25) (11.5%, 43.4%)
Bladder, Urothelial Tract	28.6% (2/7) (8.2%, 64.1%)	38.5% (5/13) (17.7%, 64.5%)
Kidney	18.8% (3/16) (6.6%, 43.0%)	41.7% (10/24) (24.5%, 61.2%)
Skin (excluding BCC/SCC)	0.0% (0/14) (0.0%, 21.5%)	3.4% (1/29) (0.6%, 17.2%)
Myeloid Lineage	0.0% (0/6) (0.0%, 39.0%)	8.3% (1/12) (1.5%, 35.4%)
Anus	2/4	1/3
Esophagus	1/2	65.4% (17/26) (46.2%, 80.6%)
Bone or Soft Tissue Sarcoma	1/4	20.0% (1/5) (3.6%, 62.4%)
Stomach	1/4	57.1% (4/7) (25.0%, 84.2%)
Uterus	1/4	18.5% (5/27) (8.2%, 36.7%)

Table A4. Galleri 12-Month Episode Sensitivity by Cancer Type

Cancer Type	PATHFINDER 2	NHS-Galleri
	Galleri 12-Month Episode Sensitivity (n/N) (95% CI)	
Thyroid	0/4	0/3
Other	71.4% (5/7) (35.9%, 91.8%)[1]	17.9% (5/28) (7.9%, 35.6%)[2]

[1]Other cancer types include Thymus (2), Ampulla of Vater (1), Brain and Spinal Cord (1), Unknown Primary Site (1), Small Intestine (1), Testis (1).
[2]Other cancer types include Brain and Spinal Cord (N = 8), Unknown Primary Site (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), Uveal Melanoma (N = 1).
CIs were calculated as follows: Wilson method for raw proportions (episode sensitivity)
Episode sensitivity and 95% CIs for cancer with <5 observations were not calculated

Appendix 5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type in PATHFINDER 2 and NHS-Galleri (based on first cancer diagnosed in participants with multiple cancers)

Table A5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type

	PATHFINDER 2				NHS-Galleri			
Cancer Type / Stage	**Galleri Signal Detected (N=90)**	**Galleri No Signal Detected (N=178)**	**Total (N=268)**	**12-Month Episode Sensitivity[1] (%)**	**Galleri Signal Detected (N=259)**	**Galleri No Signal Detected (N=561)**	**Total (N=820)**	**12-Month Episode Sensitivity[1] (%)**
Anus	**2**	**2**	**4**	**50.00%**	**1**	**2**	**3**	**33.33%**
Stage I	0	1	1	0.00%	0	0	0	*N/A*
Stage II	1	0	1	100.00%	0	0	0	*N/A*
Stage III	1	1	2	50.00%	1	2	3	33.33%
Stage IV	0	0	0	*N/A*	0	0	0	*N/A*
Bladder, Urothelial Tract	**2**	**5**	**7**	**28.57%**	**5**	**8**	**13**	**38.46%**
Stage I	1	5	6	16.67%	1	3	4	25.00%
Stage II	0	0	0	*N/A*	2	3	5	40.00%
Stage III	0	0	0	*N/A*	2	1	3	66.67%
Stage IV	1	0	1	100.00%	0	1	1	0.00%
Bone or Soft Tissue Sarcoma	**1**	**3**	**4**	**25.00%**	**1**	**4**	**5**	**20.00%**
Stage I	0	2	2	0.00%	0	1	1	0.00%
Stage II	0	0	0	*N/A*	0	0	0	*N/A*
Stage III	0	0	0	*N/A*	0	3	3	0.00%
Stage IV	1	1	2	50.00%	0	0	0	*N/A*
No stage expected	0	0	0	*N/A*	1	0	1	100.00%
Breast	**4**	**29**	**33**	**12.12%**	**21**	**89**	**110**	**19.09%**
Stage I	2	24	26	7.69%	3	46	49	6.12%
Stage II	2	3	5	40.00%	11	37	48	22.92%
Stage III	0	1	1	0.00%	4	4	8	50.00%
Stage IV	0	0	0	*N/A*	3	1	4	75.00%
Missing	0	1	1	0.00%	0	1	1	0.00%
Cervix	**0**	**0**	**0**	*N/A*	**1**	**1**	**2**	**50.00%**
Stage II	0	0	0	*N/A*	0	1	1	0.00%
Stage IV	0	0	0	*N/A*	1	0	1	100.00%
Colon/Rectum	**5**	**3**	**8**	**62.50%**	**49**	**43**	**92**	**53.26%**
Stage I	2	2	4	50.00%	8	25	33	24.24%
Stage II	1	0	1	100.00%	15	5	20	75.00%

Table A5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type

	PATHFINDER 2				NHS-Galleri			
Cancer Type / Stage	**Galleri Signal Detected (N=90)**	**Galleri No Signal Detected (N=178)**	**Total (N=268)**	**12-Month Episode Sensitivity[1] (%)**	**Galleri Signal Detected (N=259)**	**Galleri No Signal Detected (N=561)**	**Total (N=820)**	**12-Month Episode Sensitivity[1] (%)**
Stage III	2	0	2	100.00%	15	7	22	68.18%
Stage IV	0	0	0	*N/A*	9	6	15	60.00%
Missing	0	1	1	0.00%	2	0	2	100.00%
Esophagus	**1**	**0**	**1**	**100.00%**	**17**	**9**	**26**	**65.38%**
Stage I	0	0	0	*N/A*	0	1	1	0.00%
Stage II	0	0	0	*N/A*	2	1	3	66.67%
Stage III	1	0	1	100.00%	9	5	14	64.29%
Stage IV	0	0	0	*N/A*	5	2	7	71.43%
Missing	0	0	0	*N/A*	1	0	1	100.00%
Head and Neck	**13**	**3**	**16**	**81.25%**	**9**	**12**	**21**	**42.86%**
Stage I	11	2	13	84.62%	6	7	13	46.15%
Stage II	2	0	2	100.00%	0	1	1	0.00%
Stage III	0	0	0	*N/A*	2	2	4	50.00%
Stage IV	0	1	1	0.00%	1	2	3	33.33%
Kidney	**3**	**12**	**15**	**20.00%**	**10**	**14**	**24**	**41.67%**
Stage I	0	10	10	0.00%	1	6	7	14.29%
Stage II	1	1	2	50.00%	2	2	4	50.00%
Stage III	1	0	1	100.00%	2	6	8	25.00%
Stage IV	1	0	1	100.00%	4	0	4	100.00%
Missing	0	1	1	0.00%	1	0	1	100.00%
Liver, Intrahepatic Bile-Duct	**13**	**3**	**16**	**81.25%**	**12**	**3**	**15**	**80.00%**
Stage I	7	1	8	87.50%	4	1	5	80.00%
Stage II	2	0	2	100.00%	5	0	5	100.00%
Stage III	4	1	5	80.00%	1	0	1	100.00%
Stage IV	0	1	1	0.00%	2	1	3	66.67%
Missing	0	0	0	*N/A*	0	1	1	0.00%
Lung	**8**	**9**	**17**	**47.06%**	**37**	**21**	**58**	**63.79%**
Stage I	1	6	7	14.29%	2	9	11	18.18%
Stage II	1	0	1	100.00%	4	2	6	66.67%
Stage III	4	2	6	66.67%	18	4	22	81.82%
Stage IV	2	1	3	66.67%	13	6	19	68.42%

Table A5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type

	PATHFINDER 2				NHS-Galleri			
Cancer Type / Stage	**Galleri Signal Detected (N=90)**	**Galleri No Signal Detected (N=178)**	**Total (N=268)**	**12-Month Episode Sensitivity[1] (%)**	**Galleri Signal Detected (N=259)**	**Galleri No Signal Detected (N=561)**	**Total (N=820)**	**12-Month Episode Sensitivity[1] (%)**
Lymphoid Lineage	**15**	**9**	**24**	**62.50%**	**27**	**31**	**58**	**46.55%**
Stage I	1	1	2	50.00%	10	15	25	40.00%
Stage II	4	2	6	66.67%	4	1	5	80.00%
Stage III	0	0	0	*N/A*	7	5	12	58.33%
Stage IV	7	3	10	70.00%	5	10	15	33.33%
No TNM stage expected	3	3	6	50.00%	0	0	0	*N/A*
Missing	0	0	0	*N/A*	1	0	1	100.00%
Myeloid Lineage	**0**	**6**	**6**	**0.00%**	**1**	**11**	**12**	**8.33%**
No TNM/stage expected	0	6	6	0.00%	1	11	12	8.33%
Ovary or Fallopian Tubes	**2**	**1**	**3**	**66.67%**	**12**	**4**	**16**	**75.00%**
Stage I	0	1	1	0.00%	0	1	1	0.00%
Stage II	0	0	0	*N/A*	1	0	1	100.00%
Stage III	0	0	0	*N/A*	9	3	12	75.00%
Stage IV	2	0	2	100.00%	2	0	2	100.00%
Pancreas, Extrahepatic Bile-Duct, Gallbladder	**6**	**3**	**9**	**66.67%**	**12**	**19**	**31**	**38.71%**
Stage I	0	3	3	0.00%	1	5	6	16.67%
Stage II	2	0	2	100.00%	2	4	6	33.33%
Stage III	1	0	1	100.00%	1	4	5	20.00%
Stage IV	3	0	3	100.00%	7	6	13	53.85%
Missing	0	0	0	*N/A*	1	0	1	100.00%
Plasma Cell Lineage	**3**	**2**	**5**	**60.00%**	**6**	**19**	**25**	**24.00%**
Stage I	1	0	1	100.00%	0	5	5	0.00%
Stage II	1	1	2	50.00%	1	4	5	20.00%
Stage III	0	0	0	*N/A*	0	0	0	*N/A*
Stage IV	0	0	0	*N/A*	0	0	0	*N/A*
No TNM stage expected	1	1	2	50.00%	0	0	0	*N/A*
Missing	0	0	0	*N/A*	5	10	15	33.33%
Prostate	**7**	**63**	**70**	**10.00%**	**23**	**192**	**215**	**10.70%**
Stage I	0	19	19	0.00%	4	100	104	3.85%
Stage II	0	27	27	0.00%	2	36	38	5.26%

Table A5. Galleri 12-month Episode Sensitivity by Stage for New Cancers by Cancer Type

	PATHFINDER 2				NHS-Galleri			
Cancer Type / Stage	**Galleri Signal Detected (N=90)**	**Galleri No Signal Detected (N=178)**	**Total (N=268)**	**12-Month Episode Sensitivity[1] (%)**	**Galleri Signal Detected (N=259)**	**Galleri No Signal Detected (N=561)**	**Total (N=820)**	**12-Month Episode Sensitivity[1] (%)**
Stage III	3	8	11	27.27%	8	47	55	14.55%
Stage IV	4	6	10	40.00%	9	7	16	56.25%
Missing	0	3	3	0.00%	0	2	2	0.00%
Skin (exc BCC/SCC)	**0**	**13**	**13**	**0.00%**	**1**	**28**	**29**	**3.45%**
Stage I	0	13	13	0.00%	0	21	21	0.00%
Stage II	0	0	0	*N/A*	0	4	4	0.00%
Stage III	0	0	0	*N/A*	0	3	3	0.00%
Stage IV	0	0	0	*N/A*	1	0	1	100.00%
Stomach	**1**	**3**	**4**	**25.00%**	**4**	**3**	**7**	**57.14%**
Stage I	0	1	1	0.00%	0	0	0	*N/A*
Stage II	0	0	0	*N/A*	2	1	3	66.67%
Stage III	1	0	1	100.00%	1	1	2	50.00%
Stage IV	0	1	1	0.00%	1	1	2	50.00%
Missing	0	1	1	0.00%	0	0	0	*N/A*
Thyroid	**0**	**4**	**4**	**0.00%**	**0**	**3**	**3**	**0.00%**
Stage I	0	4	4	0.00%	0	3	3	0.00%
Uterus	**1**	**3**	**4**	**25.00%**	**5**	**22**	**27**	**18.52%**
Stage I	0	3	3	0.00%	2	21	23	8.70%
Stage II	0	0	0	*N/A*	1	0	1	100.00%
Stage III	0	0	0	*N/A*	0	1	1	0.00%
Stage IV	1	0	1	100.00%	2	0	2	100.00%
Other	**3**	**2**	**5**	**60.00%**	**5**	**23**	**28**	**17.86%**
Stage I	1	1	2	50.00%	1	4	5	20.00%
Stage II	0	0	0	*N/A*	0	1	1	0.00%
Stage III	0	0	0	*N/A*	1	4	5	20.00%
Stage IV	2	0	2	100.00%	1	1	2	50.00%
No TNM/stage expected	0	1	1	0.00%	2	10	12	16.67%
Missing	0	0	0	*N/A*	0	3	3	0.00%

[1]Differential bias can exist when evaluating episode sensitivity by stage, since the stage for a cancer not detected by the Galleri test would be determined at the time of clinical presentation, which may occur later than the time of blood draw.
N/A = not applicable

Appendix 6. Galleri Performance in Select Demographic Subgroups in PATHFINDER 2

Table A6-1. Galleri Test Performance at 12 Months by 10-year Age Intervals in PATHFINDER 2

	Galleri Analyzable Set with 12M assessment completed Participants with 12M follow up time as of December 31, 2024			
	Age 50-59 (Weighted N = 5647)	**Age 60-69 (Weighted N = 9579)**	**Age 70-79 (Weighted N = 5454)**	**Age 80+ (Weighted N = 738)**
PPV	80.0% (12/15) (53.0%, 93.4%)	90.6% (48/53) (79.3%, 96.0%)	68.4% (36/53) (45.8%, 84.7%)	58.8% (10/17) (35.2%, 79.0%)
NPV	99.49% (5603/5632) (99.26%, 99.64%)	98.99% (9430/9526) (98.77%, 99.18%)	98.83% (5339/5402) (98.50%, 99.09%)	98.75% (712/721) (97.61%, 99.35%)
12-month Episode Sensitivity	29.3% (12/41) (17.6%, 44.5%)	33.3% (48/144) (26.2%, 41.4%)	36.4% (36/99) (27.6%, 46.2%)	52.6% (10/19) (31.7%, 72.7%)
Specificity	99.95% (5603/5606) (99.83%, 99.98%)	99.95% (9430/9435) (99.87%, 99.98%)	99.69% (5339/5355) (99.25%, 99.87%)	99.03% (712/719) (97.96%, 99.54%)

Table A6-2. Galleri Test Performance at 12 Months by Biological Sex in PATHFINDER 2

	Galleri Analyzable Set with 12M assessment completed Participants with 12M follow up time as of December 31, 2024	
	Female (Weighted N = 12131)	**Male (Weighted N = 9287)**
PPV	82.5% (47/57) (70.4%, 90.3%)	73.2% (59/81) (56.3%, 85.3%)
NPV	99.32% (11992/12074) (99.16%, 99.45%)	98.75% (9092/9207) (98.50%, 98.96%)
12-month Episode Sensitivity	36.4% (47/129) (28.6%, 45.0%)	33.9% (59/174) (27.3%, 41.2%)
Specificity	99.92% (11992/12002) (99.85%, 99.96%)	99.76% (9092/9113) (99.52%, 99.88%)

Table A6-3. Galleri Test Performance at 12 Months Stratified by Race and Ethnicity in PATHFINDER 2

	Galleri Analyzable Set with 12M assessment completed Participants with 12M follow up time as of December 31, 2024				
	American Indian or Alaska Native (Weighted N = 292)	**Asian, Native Hawaiian or other Pacific Islander (Weighted N = 1360)**	**Black or African American (Weighted N = 1770)**	**White (Weighted N = 17757)**	**Hispanic or Latino (Weighted N = 1391)**
PPV	50.0% (1/2) (5.9%, 94.1%)	71.4% (5/7) (32.7%, 92.8%)	73.3% (11/15) (46.7%, 89.6%)	77.1% (86/112) (63.6%, 86.6%)	100.0% (9/9) (70.1%, 100.0%)

Table A6-3. Galleri Test Performance at 12 Months Stratified by Race and Ethnicity in PATHFINDER 2

	Galleri Analyzable Set with 12M assessment completed Participants with 12M follow up time as of December 31, 2024				
	American Indian or Alaska Native (Weighted N = 292)	**Asian, Native Hawaiian or other Pacific Islander (Weighted N = 1360)**	**Black or African American (Weighted N = 1770)**	**White (Weighted N = 17757)**	**Hispanic or Latino (Weighted N = 1391)**
NPV	98.97% (287/290) (96.84%, 99.67%)	99.19% (1342/1353) (98.54%, 99.55%)	99.15% (1740/1755) (98.59%, 99.48%)	99.07% (17481/17645) (98.91%, 99.20%)	99.35% (1373/1382) (98.75%, 99.66%)
12-month Episode Sensitivity	25.0% (1/4) (4.6%, 69.9%)	31.2% (5/16) (14.2%, 55.6%)	42.3% (11/26) (25.5%, 61.1%)	34.4% (86/250) (28.8%, 40.5%)	50.0% (9/18) (29.0%, 71.0%)
Specificity	99.65% (287/288) (97.58%, 99.95%)	99.85% (1342/1344) (99.41%, 99.96%)	99.77% (1740/1744) (99.39%, 99.91%)	99.85% (17481/17507) (99.73%, 99.92%)	100.00% (1373/1373) (99.72%, 100.00%)

Table A6-4. Galleri Test Performance at 12 Months by Prior Cancer History in PATHFINDER 2

	Galleri Analyzable Set with 12M assessment completed Participants with 12M follow up time as of December 31, 2024	
	Prior cancer history (Weighted N = 2137)	**No prior cancer history (Weighted N = 19281)**
PPV	80.6% (25/31) (63.1%, 91.0%)	76.0% (81/107) (62.2%, 85.9%)
NPV	98.20% (2068/2106) (97.51%, 98.70%)	99.17% (19016/19175) (99.03%, 99.29%)
12-month Episode Sensitivity	39.7% (25/63) (28.5%, 52.0%)	33.8% (81/240) (28.1%, 39.9%)
Specificity	99.71% (2068/2074) (99.36%, 99.87%)	99.87% (19016/19041) (99.75%, 99.93%)

Appendix 7. Galleri Performance in Select Demographic Subgroups in NHS-Galleri

Table A7-1. Galleri Test Performance at 12 Months by 10-year Age Intervals in NHS-Galleri

	Galleri Analyzable Set (First Screening Round)		
	Age 50-59 (Weighted N = 13166)	**Age 60-69 (Weighted N = 20382)**	**Age 70-79 (Weighted N = 17191)**
PPV	70.2% (29/41) (53.7%, 82.7%)	67.8% (93/137) (48.5%, 82.5%)	64.4% (137/213) (52.0%, 75.1%)
NPV	99.44% (13051/13124) (99.30%, 99.56%)	98.94% (20030/20245) (98.78%, 99.08%)	98.39% (16705/16978) (98.17%, 98.59%)
12-month Episode Sensitivity	28.4% (29/102) (20.6%, 37.8%)	30.2% (93/308) (25.3%, 35.5%)	33.4% (137/410) (29.0%, 38.1%)
Specificity	99.91% (13051/13064) (99.83%, 99.95%)	99.78% (20030/20074) (99.52%, 99.90%)	99.55% (16705/16781) (99.27%, 99.72%)

Table A7-2. Galleri Test Performance at 12 Months by Biological Sex in NHS-Galleri

	Galleri Analyzable Set (First Screening Round)	
	Female (Weighted N = 25084)	**Male (Weighted N = 25655)**
PPV	69.8% (107/153) (61.5%, 77.0%)	63.9% (152/238) (49.6%, 76.1%)
NPV	99.13% (24713/24931) (98.99%, 99.24%)	98.65% (25074/25417) (98.49%, 98.80%)
12-month Episode Sensitivity	32.9% (107/325) (28.0%, 38.2%)	30.7% (152/495) (26.8%, 34.9%)
Specificity	99.81% (24713/24759) (99.74%, 99.86%)	99.66% (25074/25160) (99.40%, 99.81%)

Table A7-3. Galleri Test Performance at 12 Months Stratified by Race and Ethnicity in NHS-Galleri

	Galleri Analyzable Set (First Screening Round)				
	White (Weighted N = 47849)	**Mixed or Multiple ethnic groups (Weighted N = 530)**	**Black, African, Caribbean or Black British (Weighted N = 650)**	**Asian or Asian British (Weighted N = 1430)**	**Other ethnic group (Weighted N = 229)**
PPV	66.9% (252/377) (56.9%, 75.5%)	66.7% (2/3) (15.4%, 95.7%)	23.2% (1/4) (2.7%, 76.9%)	57.1% (4/7) (23.0%, 85.6%)	0
NPV	98.89% (46944/47472) (98.78%, 98.98%)	98.48% (519/527) (96.99%, 99.24%)	98.61% (637/646) (97.34%, 99.27%)	98.95% (1408/1423) (98.25%, 99.37%)	99.56% (228/229) (96.97%, 99.94%)

Table A7-3. Galleri Test Performance at 12 Months Stratified by Race and Ethnicity in NHS-Galleri

	Galleri Analyzable Set (First Screening Round)				
	White (Weighted N = 47849)	**Mixed or Multiple ethnic groups (Weighted N = 530)**	**Black, African, Caribbean or Black British (Weighted N = 650)**	**Asian or Asian British (Weighted N = 1430)**	**Other ethnic group (Weighted N = 229)**
12-month Episode Sensitivity	32.3% (252/780) (29.1%, 35.7%)	20.0% (2/10) (5.7%, 51.0%)	10.0% (1/10) (1.8%, 40.4%)	21.1% (4/19) (8.5%, 43.3%)	0.0% (0/1) (0.0%, 79.3%)
Specificity	99.73% (46944/47069) (99.60%, 99.82%)	99.81% (519/520) (98.65%, 99.97%)	99.48% (637/640) (97.95%, 99.87%)	99.79% (1408/1411) (99.34%, 99.93%)	100.00% (228/228) (98.34%, 100.00%)

Table A7-4. Galleri Test Performance at 12 Months by Prior Cancer History in NHS-Galleri

	Galleri Analyzable Set (First Screening Round)	
	Prior cancer history (Weighted N = 3581)	**No prior cancer history (Weighted N = 47158)**
PPV	35.0% (21/60) (23.4%, 48.7%)	71.8% (238/331) (59.8%, 81.4%)
NPV	98.64% (3473/3521) (98.19%, 98.97%)	98.90% (46313/46826) (98.80%, 99.00%)
12-month Episode Sensitivity	30.4% (21/69) (20.8%, 42.1%)	31.7% (238/751) (28.5%, 35.1%)
Specificity	98.89% (3473/3512) (98.40%, 99.23%)	99.80% (46313/46407) (99.66%, 99.88%)