REFLECTION: Observational Study to Evaluate Real-World Performance of the Galleri™ Blood-Based Multi-Cancer Early Detection Test in Clinical Settings

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INTRODUCTION

- Screening recommendations exist for breast, colon, cervical, lung, and prostate cancer but unscreened cancers represent 68% of cancer deaths.[1]
- A particularly important factor in cancer patient survival is stage at diagnosis, suggesting advancements in early detection, when treatment is most effective, may lead to improved patient outcomes.[2-4]
- Galleri™ is a blood-based multi-cancer early detection (MCED) test that uses methylation-based cell-free DNA analysis to detect cancer signals across >50 cancer types, and to predict the cancer signal origin.[5,6]
- The Galleri test is intended to be used in patients at elevated risk of cancer (age 50+ or other behavioral, medical, or germ line risk factors) who do not currently exhibit signs or symptoms of cancer. This test can serve as a clinically important complement to existing guideline-recommended screening tests, which to date, only include tests for select single cancers.[7-11]
- The impact of MCED tests like Galleri on clinical practice has not been studied in the real-world setting.
- Here, we present the study design of the REFLECTION (Real-world Evidence For Learnings in Early Cancer detecTION) cohort study to assess the performance of the Galleri test in real-world clinical practice.

OBJECTIVE

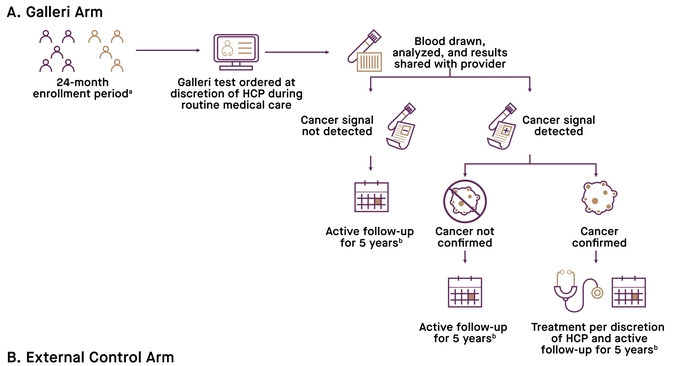
- To assess the performance of the Galleri MCED test in real-world clinical settings and identify factors to improve and optimize the test's incorporation into clinical practice.

METHODS

Study Design

- REFLECTION is a prospective, multicenter, observational cohort study that will include 2 study arms: a Galleri arm, and an external control arm (**Figure 1**).
- The Galleri arm will enroll approximately 35,000 participants.
  - Participants will be screened with the Galleri test during routine medical care at the discretion of their healthcare provider.
  - All participants will be actively followed for 5 years through questionnaires, electronic medical records, and administrative health databases, and passively followed for a longer period through cancer registries.
  - Patient-reported outcomes data will be collected at several time points with each Galleri test.
  - Healthcare providers will be asked to report on the incorporation and impact of the test in their clinical practice through annual questionnaires.
- The external control arm (propensity score-matched to the Galleri arm) will be constructed using data from participating health systems to assess the relative effectiveness of MCED testing.
  - Data will be gathered from sources such as electronic medical records and claims, and will include overall cancer detection, stage at diagnosis, and cancer screening behavior.

Figure 1: Study Design and Participant Workflow



[a]Participants will be enrolled from 20 integrated delivery networks and other health systems.
[b]Passive follow-up will be up to time of death, loss to follow-up, withdrawal of informed consent, or per institutional guidelines on duration of data collection, whichever occurs sooner. A subsequent Galleri test may be ordered.
HCP, health care professional.
End of study is defined as completion of the last active follow-up assessments or sooner, if the Sponsor ends the study early.

Participants and Healthcare Providers

- Participants will be recruited from participating healthcare delivery systems that offer the Galleri MCED test as part of routine care.
- Inclusion criteria for participants and healthcare providers are shown in **Figure 2**; there are no exclusions.

Figure 2. Inclusion Criteria

Participant Inclusion Criteria

- ≥18 years of age
- Eligible to receive the MCED test as determined by a healthcare provider
- Capable of providing signed and legally effective informed consent

HCP Inclusion Criteria

- Prescribed or participated in treatment associated with the MCED test for one or more patients
- Electronically signed completed healthcare provider questionnaires

HCP, health care professional; MCED, multi-cancer early detection test.

Study Endpoints

Figure 3. Study Endpoints

Primary Endpoint

- **To assess Galleri test performance in a real-world setting using the following metrics:**
  - **Cancer[a] detection rate in the study population**
  - **Sensitivity**
  - **Specificity**
  - **Positive predictive value**
  - **Negative predictive value**
  - **Number needed to screen**
- **Additional performance metrics include predicted cancer signal origin accuracy, distribution of cancer stage in those detected by the test, and sensitivity by cancer type and stage.**

Secondary Endpoints

- **Time from Galleri test result to diagnostic resolution**
- **Performance evaluation of subsequent Galleri tests**
- **Assessment of short-term HCRU stratified by test result and diagnosis**
- **Evaluation of participant adherence to existing screening guidelines, assessment of long term HCRU impact**
- **Assessment of the test's benefit by subpopulations**
- **Description of Galleri testing frequency and interval in a real-world setting**

Exploratory Endpoints

- **To assess the following in a real-world setting:**
  - **Feasibility and acceptability of Galleri from the participant perspective**
  - **Utility of Galleri retesting during the diagnostic journey of a participant with an initial signal detected test result**
  - **Representativeness of study participants**
  - **Overall survival in participants diagnosed with cancer**
  - **Safety of Galleri**

[a]Cancer diagnosis will be confirmed by pathology, or radiology in the absence of pathology. Cancers in the analyses will include but are not limited to invasive solid cancers and hematologic malignancies.
HCRU, health care resource utilization; MCED, multi-cancer early detection.

CONCLUSIONS

- The outcomes from the real-world REFLECTION study will help inform how incorporation of routine MCED testing into standard clinical practice can support early detection of many cancer types and complement existing guideline-recommended screening tests, with the aim of improving patient treatment, outcomes, and survival.

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ASSESSMENTS

Participant Questionnaires:

- Participants will complete paper or electronic questionnaires to assess their perceptions about the MCED test, including anxiety, health-related quality of life, satisfaction with the test, and potential impact of test results on attitude towards adherence to guideline-recommended screening and subsequent MCED testing.
  - Questionnaires will be administered at 4 different time-points, and participants will be required to complete the questionnaire within 14 days (**Table 1**).

Table 1. Time Points for Patient-Reported Outcome Measures

Instrument	Pre-Test	Post-Test[a]	6 Months Post-Test (Cancer Signal Detected Only)	12 Months Post-Test
SF-12v2 Health Survey	x	x	x	
Cancer Worry Scale	x	x	x	
Satisfaction with the MCED test (de novo)		x	x	
Attitude towards adherence to guideline-recommended screening (de novo)	x	x	x	
Attitude towards subsequent MCED test (de novo)		x	x	
Cancer status (de novo)			x	x

[a]Issued to every participant with a Galleri test result of cancer signal detected, and a random subset of participants with results of cancer signal not detected.
HCP, health care professional; SF-12v2, Short Form 12-Item (version 2) Health Survey.

Healthcare Professional Questionnaires

- Healthcare providers will be provided with an electronic questionnaire annually to assess healthcare provider perceptions about the Galleri test, including satisfaction with the test, feasibility and acceptability of the Galleri test at their institution, and impact on clinical decision-making for screening and diagnostic workup.
  - Questionnaires may be distributed to multiple healthcare providers involved with Galleri, such as primary care physicians, nurse practitioners, geneticists, oncologists, and case managers.

Clinical Data

- Clinical data to be captured include demographics, reasons for taking the Galleri test, personal and family medical history, test results, diagnostic resolution information, results from diagnostic workup, clinical stage of cancer, symptoms, and participant outcomes.
- Clinical endpoints, including cancer diagnosis, treatment, death, and health care resource utilization (HCRU) information, will be collected passively.

Healthcare Resource Utilization Data

- HCRU data collection will focus on participants with a cancer signal detected test result with regard to diagnostic workup and burden and will also include data on other cancer screening tests.
- HCRU data will also be collected annually post-test for participants with a signal not detected test result.
- The data collected may include the following:
  - Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
  - Number and type of further screening, diagnostic, or therapeutic tests and procedures.
  - Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).
  - Duration of hospitalization (total days or length of stay, including duration by wards, e.g., intensive care unit).

Safety

- Safety assessments will not include adverse events related to administration of the MCED test since participants received the test at the discretion of their healthcare provider.
- Adverse events such as anxiety associated with responses to study questionnaires will be assessed.

STATISTICAL ANALYSES

- For the primary objective, descriptive statistics including point estimates and confidence intervals will be provided to characterize the MCED test performance. These analyses will be conducted based on diagnostic resolution by 1 year of follow-up and by 2 years of follow-up post MCED test.
- For secondary and exploratory objectives, descriptive statistics will be used to summarize participant demographic and clinical characteristics.
  - The mean, standard deviation, median, interquartile range, minimum, and maximum will be reported for continuous variables, and counts and percentages for categorical variables.
  - If necessary, characteristics will be compared between groups using the appropriate statistical tests.
  - If the distribution of data suggests deviations from normality, an equivalent non-parametric test such as Wilcoxon or Kruskal-Wallis tests will be performed for continuous variables
  - For analysis of time-to-event (e.g., from Galleri test to diagnostic resolution or overall survival), the Kaplan Meier method will be used, stratified by Galleri test results and cancer diagnosis status.
- Analysis of HCRU, adherence to screening results, and participant and healthcare provider questionnaire data will be presented descriptively, and a series of multivariate models will be developed in efforts to control for potential confounding factors to produce the adjusted estimates of the parameters of interest for each endpoint.