GRAIL Announces Final Results From the PATHFINDER Multi-Cancer Early Detection Screening Study at ESMO Congress 2022

September 11, 2022

Adding Multi-Cancer Early Detection (MCED) Screening to Standard of Care Screening More Than Doubled the Number of Cancers Detected

71% of Participants With MCED-Detected Cancers Had Cancer Types With No Routine Screening Tests Available

Approximately Half of the MCED-Detected New Cancers Were Stage I or II

MCED-Predicted Cancer Signal Origin Had 97.1% Accuracy and Enabled Targeted Diagnostic Evaluations

MCED Screening was Implemented in Adults With Elevated Cancer Risk Without Study-Related Serious Adverse Events

Participants Reported High Satisfaction and Low Negative Psychological Impact With MCED Screening

MENLO PARK, Calif., September 11, 2022–GRAIL, LLC, a healthcare company whose mission is to detect cancer early when it can be cured, today announced final results from the interventional PATHFINDER study, which evaluated multi-cancer early detection (MCED) screening using a blood test and the clinical care pathways following a “cancer signal detected” MCED test result in 6,662 individuals aged 50 years or older, an age group at elevated risk for cancer. Results were presented in a proffered paper session at the European Society for Medical Oncology (ESMO) Congress 2022 in Paris.

“The PATHFINDER study is an exciting first step towards fundamental change in the approach to cancer screening. The study found cancer in about 1% of participants including types for which there is no established screening method. The study demonstrated the feasibility of this paradigm and solid test performance,” said Deb Schrag, MD, MPH, chair, Department of Medicine at Memorial Sloan Kettering Cancer Center in New York. “Although continued public health efforts to optimize adherence to existing screening strategies that have been proven effective are critical, this study provides a glimpse of what the future may hold—the opportunity for screening using blood tests to detect various types of cancers at their earliest and most treatable stages.”

PATHFINDER was a single-arm study that measured the time required to achieve diagnostic resolution (i.e., healthcare provider-defined end to the diagnostic evaluation) following a “cancer signal detected” MCED blood test result and the number and types of diagnostic tests that were used (primary endpoint). MCED test performance was a key secondary endpoint, including positive predictive value (PPV, the percent of cancer signal detected results that were confirmed to be cancer) and the accuracy of the predicted cancer signal origin (CSO). Participants were followed for 12 months after enrollment. If a participant had a negative MCED test at enrollment but developed a cancer within the 12-month follow-up, it was counted as an MCED false negative.

Test performance was measured using both an earlier version of Galleri (MCED-E) and a refined version of Galleri (MCED-Scr). The earlier version of the test was refined to reduce the detection of pre-malignant hematologic conditions, which are fairly common, and improve prediction of the cancer signal origin. The study was completed with the earlier version of the test (MCED-E) and then the blood samples were retested in a pre-specified retrospective analysis using the refined Galleri test (MCED-Scr).

“When added to standard of care screening, MCED testing more than doubled the number of cancers detected compared to standard screening alone. In fact, Galleri detected more cancers than all U.S. Preventive Services Task Force-recommended standard single cancer screenings combined. These included Stage I cancers of the liver, small intestine, and uterus, and Stage II pancreatic, bone, and oropharyngeal cancers,” said Jeffrey Venstrom, MD, chief medical officer at GRAIL. “This is particularly notable given the PATHFINDER population was heavily screened with higher-than-average rates for mammography, colonoscopy, and low-dose CT lung scans.”

A cancer signal was detected in 92 participants, two of whom began workup prior to the return of their MCED test results. Of these, 35 participants were diagnosed with 36 cancers. Among the confirmed cancers, 71% (25/35) of participants had cancer types that have no routine cancer screening available. Nearly half (48%) of the non-recurrent cancers were found in early-stages (Stage I or II). Standard of care screening identified 29 cancers, and another 56 cancers were diagnosed because symptoms appeared or tumors were found incidentally or from monitoring for cancer recurrence.

The cancer signal origin prediction had a 97% accuracy and directed physician clinical workup, leading to resolution of the cancer diagnosis in less than three months for most participants with a true positive signal (73%), and in less than two months for half of them. The median time to diagnostic resolution was longer for false positive results (162 days); 44% of these participants had scheduled follow-up imaging or procedures three or more months later, contributing to the longer time to resolution.

Most participants underwent imaging procedures, such as scans or MRIs, following true and false-positive results. As expected, most true positive participants (82%) underwent an invasive procedure to confirm a cancer diagnosis. Three underwent endoscopies triggered by the predicted cancer signal origin, and 24 had procedures triggered only by abnormal imaging, physical, or laboratory findings, including three surgical biopsies. A smaller proportion of false positive participants had invasive procedures (30%). Five had procedures triggered by CSO predictions (five endoscopies, one endometrial biopsy and one pap smear), and 12 had procedures triggered only by abnormal imaging, physical, or laboratory findings, or by their medical history. No study-related serious adverse events were reported as a result of MCED testing in the study, and there were no adverse events reported from diagnostic workups.

The PPV was 43.1% with the refined test and 38.0% with the earlier version. Specificity, or the percentage of true negatives, of the refined test was 99.5%, and 99.1% with the earlier version, and the false positive rate for both versions was less than 1%. Test performance was consistent with the interim analysis and the previous case-controlled Circulating Cell-free Genome Atlas (CCGA) study.

“The refinements we made to the earlier version of Galleri resulted in clinically expected outcomes and had the intended result of reducing false

positives from hematological signals," added Venstrom. "While PATHFINDER was not designed to determine sensitivity or the number of cancer types detected by Galleri, 11 different cancer types were detected in this study that have no standard screening today, and the false positive rate was less than 1%. In the much larger CCGA case-control study, the Galleri test detected over 50 types of cancer."

An analysis of participant-reported outcomes of anxiety, distress, and satisfaction related to MCED testing from the study were also presented at the ESMO Congress 2022. PATHFINDER participants completed patient-reported outcomes assessments before MCED testing, after receiving MCED test results, and at the end of the study. The analysis found 97.1% of participants reported a high level of satisfaction with the test, including those who had both true positive (92%) and false-positive (82.3%) results. As expected, a higher level of anxiety was seen in participants following a positive result, but that resolved to pre-MCED test levels within 12 months.

Preliminary Real World Analysis Generally Consistent with PATHFINDER Results
GRAIL conducted an analysis of the first 38,154 Galleri commercial test results to monitor Galleri performance in a real world setting. The analysis showed a 1.1% cancer signal detection rate. As seen in clinical trials, the signal detection rate increases with age and male sex, consistent with the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) statistics. Among 326 patients with a positive cancer signal detected result and short-term follow up (as voluntarily reported by the ordering physicians), 108 cancers have been confirmed by the ordering providers to-date, representing 28 different cancer types. Of the 108 patients with a provider-confirmed cancer diagnosis, 64 had no recommended cancer screening test (59%). Provider-confirmed cancers include, among others, Stage I pancreatic, head and neck, endometrial, esophageal, and gastrointestinal stromal tumor (GIST) cancers and Stage II rectal, liver, and head and neck cancers.

"Every year, we lose more than 600,000 loved ones to cancer in the U.S. alone. Unfortunately, the burden of cancer will grow with the demographic tidal wave, as the absolute risk of developing any cancer increases as we get older," said Josh Ofman, MD, MSHS, president at GRAIL. "Bending the cancer mortality curve will require earlier detection of more cancer. However, a world with more single cancer screening tests is simply clinically and economically untenable as each single cancer screening test has a false positive rate of 5-10%. We need to expand from screening for individual cancers to also screening individuals for cancer. We believe MCED tests can enable this paradigm shift by finding more types of cancer at earlier stages with a single blood test."

About GRAIL's MCED Clinical Development Program
The Galleri clinical development program consists of studies that collectively include more than 335,000 participants—and what is believed to be the largest linked datasets of genomic and clinical data in the cancer field. GRAIL's program includes the foundational CCGA development and validation study, the interventional PATHFINDER and PATHFINDER 2 studies, the NHS-Galleri randomized, controlled clinical study, the STRIVE and SUMMIT observational studies, and the REFLECTION real-world registry. The largest of these, the NHS-Galleri trial, has enrolled 140,000 participants with the primary objective of a reduction in late-stage cancer diagnoses, thought to be a necessary prerequisite for a mortality reduction.

About GRAIL
GRAIL is a healthcare company whose mission is to detect cancer early, when it can be cured. GRAIL is focused on alleviating the global burden of cancer by developing pioneering technology to detect and identify multiple deadly cancer types early. The company is using the power of next-generation sequencing, population-scale clinical studies, and state-of-the-art computer science and data science to enhance the scientific understanding of cancer biology, and to develop its multi-cancer early detection blood test. GRAIL is headquartered in Menlo Park, CA with locations in Washington, D.C., North Carolina, and the United Kingdom. GRAIL, LLC, is a subsidiary of Illumina, Inc. (NASDAQ:ILMN) currently held separate from Illumina Inc. under the terms of the Interim Measures Order of the European Commission dated 29 October 2021.

For more information, visit grail.com.

About Galleri®
The earlier that cancer is detected, the higher the chance of successful outcomes. The Galleri multi-cancer early detection test can detect signals across more than 50 types of cancer, as defined by the American Joint Committee on Cancer Staging Manual, through a routine blood draw. When a cancer signal is detected, the Galleri test predicts the cancer signal origin, or where the cancer is located in the body, with high accuracy to help guide the next steps to diagnosis. The Galleri test is available in the U.S. and requires a prescription from a licensed healthcare provider. The Galleri test should be used in addition to recommended cancer screenings such as mammography, colonoscopy, prostate-specific antigen (PSA) test, or cervical cancer screening. It is intended for use in people with an elevated risk of cancer, such as those aged 50 or older.

All cells—cancer and healthy ones—shed DNA, which is called cell-free DNA, into the bloodstream. One of the "hallmarks of cancer" is when methyl groups are added to DNA. This does not alter the DNA code but it can alter gene expression. Methylation patterns on tumor-derived cell-free DNA carry cancer-specific signals and are therefore very helpful in detecting cancer and determining its origin. Galleri uses next-generation sequencing and machine learning algorithms to analyze these methylation patterns of cell-free DNA in the bloodstream.

For more information about Galleri, visit galleri.com.

Important Galleri Safety Information
The Galleri test is recommended for use in adults with an elevated risk for cancer, such as those aged 50 or older. The Galleri test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider. Galleri is intended to detect cancer signals and predict where in the body the cancer signal is located. Use of Galleri is not recommended in individuals who are pregnant, 21 years old or younger, or undergoing active cancer treatment.

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

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

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

FOR GRAIL

Media:
Trish Rowland

Cammy Duong
pr@grail.com

Investor Relations:
Alex Dobbin
ir@grail.com