GRAIL CCGA Discovery Results Published in Cancer Cell Reveal Methylation as Promising DNA Hallmark for Multi-Cancer Early Detection

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Methylation Approach Had One of the Highest Cancer Signal Detection Sensitivities and Best Predicted Cancer Signal Origin of the Evaluated Technologies

Approach Informed Development of Galleri® Multi-Cancer Early Detection Blood Test

Analysis is Part of Extensive and Systematic Comparison of Cancer Specific

Cell-Free DNA Features for Multi-Cancer Early Detection

MENLO PARK, Calif., Nov. 17, 2022 – GRAIL, LLC, a healthcare company whose mission is to detect cancer early when it can be cured, today announced findings from a fundamental substudy of the Circulating Cell-free Genome Atlas (CCGA; NCT02889978) study, demonstrating that methylation had the most promising combination of cancer detection and prediction of cancer signal origin when compared with other evaluated approaches. This is the first rigorous and systematic comparison of various genomic measures from circulating cell-free DNA (cfDNA) for multi-cancer early detection (MCED) testing, and the largest comprehensive genome-wide comparison of cfDNA approaches. Findings were published online in *Cancer Cell* in a manuscript titled "Evaluation of Cell-Free DNA Approaches for Multi-Cancer Early Detection."

"Results from the CCGA study formed the basis for how we developed and refined the Galleri test—it's our origin story and the foundation of our work to transform cancer care with a simple blood test," said Amoolya Singh, Ph.D., Senior Vice President of Data Science and Chief Scientific Officer at GRAIL. "This defining study made it possible to carefully design a population screening test with a high specificity and low false-positive rate for cancer detection. When combined with standard screenings, this test has the potential to improve detection of cancer in asymptomatic individuals."

The CCGA Discovery Substudy, the first of three pre-planned substudies of the case-controlled CCGA study, evaluated multiple potential approaches to blood-based multi-cancer early detection (MCED) in a cohort of 2,800 individuals. These approaches included whole-genome sequencing, whole-genome methylation sequencing, and ultra deep targeted sequencing. Together this covered eight classifiers including methylation, somatic copy number alterations, somatic mutations, and a ninth pan-feature classifier. Criteria for evaluation included sensitivity (a test's ability to correctly identify people with cancer) at high (98%) specificity (a test's ability to correctly identify people without cancer) and cancer signal origin prediction (a test's ability to predict the anatomical localization or cell of origin of the detected cancer signal).

The CCGA Discovery Substudy showed that among the evaluated classifiers, those using whole-genome methylation had one of the highest cancer signal detection sensitivities at 98% specificity. Additionally, out of the evaluated approaches, whole-genome methylation had the best predicted cancer signal origin.

Findings from CCGA Discovery, along with the other substudies, were instrumental in developing, refining and validating the targeted methylation platform used in the Galleri® MCED test, which applies next-generation genomic sequencing, advanced data science and machine learning to detect a shared cancer signal across more than 50 types of cancer at 99.5% specificity and accurately predict where the signal originated in the body through a simple blood draw. Test performance was consistent in the interventional PATHFINDER study, which was recently presented at the European Society for Medical Oncology Congress 2022.

CCGA Discovery evaluated various cfDNA measures in three prototype assays and nine prototype machine learning classifiers to determine the most promising approach for an MCED test with a low false-positive rate and sufficient sensitivity to improve outcomes for individuals who undergo screening. The substudy included 2,800 participants—1,628 with cancer and 1,172 without cancer (non-cancer). Blood samples from individuals with cancer were demographically matched to non-cancer individuals to reduce statistical uncertainty. Patients with cancer diagnosed by screening or by clinical presentation were enrolled before starting definitive therapy.

The substudy implemented innovations in cancer detection evaluation, including study design, custom distributed and cloud computing, and the introduction of a novel measure: circulating tumor DNA allele fraction, defined as the fraction of tumor-distinguishing methylation marks in a cfDNA sample (i.e., the available signal). Furthermore, it introduced the metric of clinical limit of detection (cLOD) to measure cancer detection as a function of cfDNA tumor fraction — a more robust performance metric than sensitivity, which is highly dependent on study cancer type and stage composition.

"To be able to meaningfully compare ct-DNA assays in the future, the clinical limit of detection must be assessed," added Singh. "The CCGA Discovery analysis is the first direct head-to-head comparison of multiple approaches that we are aware of. Notably, CCGA Discovery identified methylation features in ct-DNA as having the leading combination of cancer detection and cancer signal origin performance. This motivated the development of an improved targeted methylation platform that underlies Galleri today with substantially improved performance."

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About the CCGA Study
The CCGA study is a prospective, multi-center, case-controlled, longitudinal study designed to characterize the landscape of genomic cancer signals in the blood of people with and without cancer.

The study is collecting de-identified biospecimens and clinical data from more than 15,000 participants across 142 sites in the U.S. and Canada, including both people who had cancer at the time of enrollment (newly diagnosed, and not yet received treatment) and people who did not have a known cancer diagnosis. Participants will be followed annually for up to five years. A separate pre-specified substudy from CCGA involving 4,077 participants was previously published in the *Annals of Oncology* in September, 2021.

About GRAIL's MCED Clinical Development Program
The Galleri clinical development program consists of studies that collectively include more than 335,000 participants together with what is believed to be the largest linked datasets of genomic and clinical data in the field of cancer research. 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 ascertaining 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.

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 requires a prescription from a licensed healthcare provider and 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.

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.

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