Multi-cancer early detection test report

Patient

Name: Ima Sample
Patient ID: -
DOB: 01-AUG-1955
Bio Sex: Male
Email: robpf@usa.net

Sample

GRAIL ID: GAL8LYLG77
Report Date: 27-APR-2022 / 10:12 PT
Collection Date: 15-APR-2022 / 11:30 ET

Ordering Provider

Name: Robert M Pfoff MD
Location: Pittsburgh Functional and Longevity Medicine
Address: 125 Warren Road Warrendale, PA 15086
Phone: +14123344610
Fax: +17249336011

Results

Cancer Signal Not Detected

The Galleri® test did not detect DNA methylation signals associated with cancer in the analyzed cell-free DNA obtained from the patient sample. This does not exclude the presence of cancer.

Individuals should be advised to continue with all recommended cancer screening options at appropriate intervals. If signs or symptoms suggestive of cancer appear after a negative Galleri test result, timely clinical evaluation by a qualified health care professional is recommended.

Comments
No additional comment.

Laboratory Director: Rita Shaknovich, MD, PhD | CLIA #05D2154430 | CAP #8149563
1525 O'Brien Dr., Menlo Park, CA 94025 | 833-MY-GALLERI (833-694-2553) | FAX 650-999-9000 | customerservice@grail.com

Multi-cancer early detection test report

Method & Intended Use

GRAIL's Galleri test is a qualitative, next-generation sequencing (NGS)-based screening test for the detection of DNA methylation signals using cell-free DNA isolated from peripheral whole blood. GRAIL's Galleri test is a screening test used to complement existing single cancer screening tests and cannot be used to confirm a cancer diagnosis. The Galleri test is recommended for use in adults with an elevated risk of cancer such as those age 50 years and older. The test has been validated in the Circulating Cell-free Genome Atlas (CCGA) study and in the PATHFINDER study.[1] A test result of "Cancer Signal Detected" may indicate the presence of cancer. The predicted Cancer Signal Origin(s) can inform diagnostic evaluation recommended by a health care professional in accordance with professional guidelines. The Galleri test is a screening test, not a diagnostic test.

When a cancer signal is detected, one or two Cancer Signal Origins are reported. If the top Cancer Signal Origin score is equal to or greater than 9.0, then only one Cancer Signal Origin is reported; if the top Cancer Signal Origin score is less than 9.0, the two top Cancer Signal Origins are reported. The Galleri test has 21 possible Cancer Signal Origins: Anus; Bladder, Urothelial Tract; Bone and Soft Tissue; Breast; Cervix; Colon, Rectum; Head and Neck; Kidney; Liver, Bile Duct; Lung; Lymphoid Lineage; Melanocytic Lineage; Myeloid Lineage; Neuroendocrine Cells of Lung or other Organs; Ovary; Pancreas, Gallbladder; Plasma Cell Lineage; Prostate; Stomach, Esophagus; Thyroid Gland; and Uterus.

The Galleri test is for professional use only.

The Limit of Detection (LOD95) of Galleri test using abnormal coverage is 0.2.

[1] CCGA study (NCT02889978) and PATHFINDER study (NCT04241796); please see data at www.galleri.com/test-report.

Clinical Studie

Galleri Test Performance Characteristics in CCGA Sub-study: Results are reported from the case-control CCGA study (NCT02889978) where a pre-specified sub-study of 2,823 cancer participants (cases) and 1,254 non-cancer participants (controls) was analyzed. Participants were men and women age 20 years and older without prior history of cancer. Cancer participants were enrolled after diagnosis (or with a high suspicion of cancer) and prior to any cancer treatment. Cancer participants had stage I (30.1%), stage II (24.9%), stage III (20.0%), stage IV (21.9%) cancer, or cancer that does not have stages (2.4%).

In this CCGA sub-study, the Galleri test detected cancer signal or cancer signals across more than 50 cancer types (defined by American Joint Committee on Cancer)[1]. Results have been characterized across (i) solid tumors without common screening options[2], (ii) solid tumors with common screening options[2], and (iii) hematologic malignancies[2]. Sensitivities of cancer signal detection across cancer classes are shown below.

For more detailed study methods and results, and the subgroup analyses of participants age 50 years and older, please visit www.galleri.com/test-report.

False Positive Rate [3] (95% CI)	Specificity (95% CI)
0.5% (0.2-1.0%)	**99.5% (99.0-99.8%)**
6 (0.5%) non-cancer participants had false "Cancer Signal Detected" results among 1,254 non-cancer participants	1,248 (99.5%) non-cancer participants had accurate "Cancer Signal Not Detected" results among 1,254 non-cancer participants

[1] American Joint Committee on Cancer (AJCC) manual

[2] Solid tumors with common screening options include breast, cervix, colorectal, and prostate cancers. All other cancers found in this CCGA sub-study are grouped into "solid tumors without common screening options" or "hematologic malignancies" categories. Lung cancer is included in the category without common screening options because no broadly adopted guideline-recommended screening for the average risk population currently exists for lung cancer and only 10% of the 55-80 year old population meets current United States Preventive Services Task Force (USPSTF) high-risk criteria for lung cancer screening (Fedewa et al. State Variation in Low-Dose Computed Tomography Scanning for Lung Cancer Screening in the United States. JNCI 2020). It is estimated that about two-thirds of diagnosed lung cancers occur in patients who are not eligible for lung cancer screening (Pinsky et al. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Medical Screening 2012).

[3] False Positive Rate is calculated as (1-Specificity).

Clinical Studies continued on page 3

Multi-cancer early detection test report

Clinical Studies (Continued)

Cancer signal detection for various cancer classes in CCGA sub-study:
Sensitivities for cancer signal detection by cancer class and across cancer classes are shown below. Sensitivity or the true positive rate, is the proportion of study participants with "Cancer Signal Detected" test result among study participants with cancer stages I-IV. For sensitivity by stage, please visit www.galleri.com/test-report.

Cancers Responsible for ⅔ of All Cancer Deaths in the US[4]

Cancer Classes[5]	Sensitivity[6] (95% CI)
Anus, Bladder, Colon/Rectum, Esophagus, Head and Neck, Liver/Bile-duct, Lung, Lymphoma, Ovary, Pancreas, Plasma Cell Neoplasm, Stomach	**76.3% (74.0-78.5%)** 1,040 (76.3%) cancer participants had "Cancer Signal Detected" test result among 1,363 participants with cancers responsible for ⅔ of all cancer deaths in the US.

Solid Tumors without Common Screening Options[2]

Cancer Classes[5]	Sensitivity[6] (95% CI)
Overall	65.6% (63.0-68.1%)
Anus	81.8% (61.5-92.7%)
Bladder	34.8% (18.8-55.1%)
Esophagus	85.0% (76.7-90.7%)
Gallbladder	70.6% (46.9-86.7%)
Head and Neck	85.7% (77.8-91.1%)
Kidney	18.2% (11.8-26.9%)
Liver/Bile-duct	93.5% (82.5-97.8%)
Lung	74.8% (70.3-78.7%)
Melanoma	46.2% (23.2-70.9%)
Ovary	83.1% (72.2-90.3%)
Pancreas	83.7% (76.6-89.0%)
Sarcoma	60.0% (42.3-75.4%)
Stomach	66.7% (48.8-80.8%)
Thyroid	0.0% (0.0-21.5%)
Urothelial Tract	80.0% (49.0-94.3%)
Uterus	28.0% (21.6-35.5%)
Other[7]	50.8% (38.4-63.2%)

Solid Tumors with Common Screening Options[2]

Cancer Classes[5]	Sensitivity[6] (95% CI)
Overall	33.7% (31.1-36.5%)
Breast	30.5% (26.7-34.6%)
Cervix	80.0% (60.9-91.1%)
Colon/Rectum	82.0% (76.2-86.7%)
Prostate	11.2% (8.5-14.6%)

Hematologic Malignancies[2]

Cancer Classes[5]	Sensitivity[6] (95% CI)
Overall	55.1% (49.3-60.8%)
Lymphoid Leukemia	41.2% (28.8-54.8%)
Lymphoma	56.3% (48.9-63.5%)
Myeloid Neoplasm	20.0% (5.7-51.0%)
Plasma Cell Neoplasm	72.3% (58.2-83.1%)

4 American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021.

5 Sensitivity is calculated for 24 cancer classes (and additional Other class) that are aggregated into 21 Cancer Signal Origins when reported by the Galleri test.

6 Includes cancer participants with stage I-IV (96.9%), cancer participants with missing stage (0.7%), and cancer participants (2.4%) who had a cancer type which is not expected to have AJCC stage. To see sensitivity by clinical stage, please visit www.galleri.com/test-report.

7 Other cancers include Adrenal (N = 1), Ampulla of Vater (N = 1), Brain (N = 6), Choriocarcinoma (N = 1), Mesothelioma (N = 7), Non-melanoma Non-basal Cell Cancer/Squamous Cell Carcinoma Skin Cancer (N = 2), Penis (N = 1), Small Intestine (N = 13), Testis (N = 6), Thymus (N = 2), Vagina (N = 2), Vulva (N = 7), and Other/Unspecified (N = 10).

Clinical Studies continued on page 4

Multi-cancer early detection test report

Clinical Studies (Continued)

Galleri Test Performance Characteristics in PATHFINDER: Planned interim analysis results are reported from the interventional PATHFINDER study (NCT04241796)[8], which enrolled 6662 participants without clinical suspicion of cancer at time of enrollment. Participants were men and women age 50 years and older at varying levels of cancer risk including 25% with prior history of cancer, 38% with smoking history and 6% with genetic cancer predisposition. A total of 92 participants who received a "Cancer Signal Detected" result from an earlier version of the Galleri test underwent diagnostic evaluation to assess whether they had cancer: 29 of 65 participants who reached diagnostic resolution had a cancer diagnosis (PPV of 44.6% (95% CI 33.2-56.7%)).

All samples were later evaluated with the current version of the Galleri test, which returned "Cancer Signal Detected" results for 30 participants with diagnostic resolution[9] (19 with clinical cancer diagnosis, 11 without) and 17 participants who had no cancer signal detected by the earlier Galleri test and thus were not diagnostically evaluated. A conservative PPV estimate[10] for the current version of the Galleri test is 40.4% (95% CI 27.6-54.7%).

For more detailed results, please visit www.galleri.com/test-report.

Positive Predictive Value[11] (95% CI)
40.4% (27.6-54.7%)
19 (40.4%) participants had cancer diagnosed among 47 participants with "Cancer Signal Detected" results.

[8] Data on file 2021 GRAIL, LLC

[9] 10 participants with "Cancer Signal Detected" results by both earlier and current Galleri tests have not reached a diagnostic resolution yet and are being assessed for cancer. These participants will be included in the PPV calculations after diagnostic resolution.

[10] Conservative PPV estimate assumes that 17 participants who were "Cancer Signal Detected" by the current version of the test and "Cancer Signal Not Detected" by the earlier version of the test were all false positives.

[11] Proportion of participants with cancer diagnosis among those with a "Cancer Signal Detected" result on the current version of the Galleri test. Participants undergoing diagnostic evaluation who did not reach a resolution are excluded.

Cancer Signal Origin Accuracy: In this sub-study of the CCGA case-control study (NCT02889978), the Galleri test's top Cancer Signal Origin was accurate 88.7% (1273/1435 95% CI 87.0-90.2%) of the time for cancer participants with "Cancer Signal Detected". In cancer participants with a "Cancer Signal Detected" and two Cancer Signal Origins returned, the second Cancer Signal Origin was accurate 40.9% (56/137 95% CI 33.0-49.2%) of the time when the top Cancer Signal Origin was incorrect. When two Cancer Signal Origins were returned, one of the two was correct 92.6% (1329/1435 95% CI 91.1-93.9%) of the time.

Multi-cancer early detection test report

Warnings, Precautions, and Limitations

Galleri test performance may be subject to the collection, storage, and transportation of the blood samples. The test is not intended for other sample types. Any sample handling outside of the suggested procedures may affect test performance.

Use of Galleri is not recommended in individuals who are pregnant, 21 years old or younger, or undergoing active cancer treatment.

A "Cancer Signal Detected" result is not a diagnosis of cancer. The results of the Galleri test must be confirmed by diagnostic evaluation suggested by qualified health care professionals in accordance with standard medical practice. These results should be interpreted in the context of the individual's clinical risk factors. Diagnostic decisions are the responsibility of the treating physician.

A "Cancer Signal Not Detected" result does not eliminate the possibility that a cancer is present or will occur in the future. Individuals who receive a "Cancer Signal Not Detected" result should continue with all recommended cancer screening options at intervals appropriate for the individual. The use of the Galleri test should not replace, supersede, or otherwise alter the use or frequency of standard of care cancer screening or detection modalities.

The Galleri test may not detect a cancer signal in all cancers; cancers evaluated in the CCGA sub-study are listed at www.galleri.com/test-report. The test performance in cancer classes not observed in CCGA and PATHFINDER is unknown. If a cancer signal is detected, the Galleri test also reports one or two Cancer Signal Origins which must be confirmed by diagnostic evaluation.

In some cases, the Galleri test may produce a "Cancer Signal Detected" result, but follow-up diagnostic evaluation may not result in a cancer diagnosis. This could mean that the individual has a cancer that is difficult to identify by the selected follow-up diagnostic evaluation, that the individual has cancer but it is located elsewhere, or that the individual does not have cancer and the Galleri test result is a false positive.

Sensitivity and Cancer Signal Origin accuracy observed in cancer participants from the case-control CCGA sub-study may be higher than in the general screening population because cancer signals may be stronger in cancers that are detected by standard medical practice. The positive predictive value reported in the PATHFINDER study may be underestimated because only participants with "Cancer Signal Detected" results from the earlier version of the Galleri test had a diagnostic evaluation to establish clinical cancer status.

Performance of sequential Galleri tests has not been evaluated.

GRAIL's clinical laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and accredited by the College of American Pathologists (CAP). The Galleri test was developed, and its performance characteristics were determined by GRAIL. The Galleri test has not been cleared or approved by the 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.

The Galleri test can be ordered by a licensed practitioner only.

References

1. Liu MC, Oxnard GR, Klein EA, et al. CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol. 2020;31(6):745-759.

2. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol. 2021;32(9):1167-1177.

3. Beer TM, McDonnell CH III, Nadauld L, et al. A prespecified interim analysis of the PATHFINDER study: Performance of a multi-cancer early detection test in support of clinical implementation. Presented at: 2021 American Society of Clinical Oncology Annual Meeting; June 4-8, 2021. Abstract 3070.

4. Beer TM, McDonnell CH III, Nadauld L, et al. Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. Presented at: 2021 American Society of Clinical Oncology Annual Meeting; June 4-8, 2021. Abstract 3010.

