Galleri®

Multi-cancer early detection test report

Patient

Name: John Doe
Patient ID: 123
DOB: 10-JAN-1972
Bio Sex: Male
Email: johndoe@abccompany.com

Sample

GRAIL ID: GAL31ASXQ7
Report Date: 26-MAR-2023 / 14:45 PT
Collection Date: 16-MAR-2023 / 07:30 CT

Ordering Provider

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Your Result

No Cancer Signal Detected

The Galleri® test did not detect DNA methylation patterns that are associated with cancer in your blood sample. In a clinical trial[a], fewer than 1% of individuals with this result were projected to have cancer.

What this result means

The Galleri test looked for a cancer signal in your blood sample and did not find one. Continue with routine cancer screening tests your healthcare provider recommends.

What this result does not mean

Although the Galleri test did not find a cancer signal in your blood, **this result does not completely rule out the possibility of cancer.** The Galleri test does not detect all cancers and not all cancers can be detected in the blood.

This result does not predict whether you will develop cancer in the future.

Talk to your healthcare provider about the following topics

Continue routine cancer screenings

Discuss which screening tests are right for you. Screening is recommended for colon/rectum, breast, cervix, lung (for those at risk), and prostate cancers.

Repeat testing with Galleri

Adding Galleri to annual wellness visits can improve the chances of finding cancer early when it is more treatable. Talk to your healthcare provider about whether annual testing with Galleri is appropriate for you.

a. The Circulating Cell-free Genome Atlas (CCGA) Study (NCT02889978) substudy 3 (CCGA3)[1] included cancer (n=2823) and non-cancer (n=1254) participants. It was estimated that 99.4% of participants with a 'no cancer signal detected' result would not have cancer based on Galleri test performance adjusted for SEER cancer incidence in the 50-79 years age group[2]

Multi-cancer early detection test report

What this screening test did

With the Galleri test, you took a step forward to better understand your health. The Galleri test allowed you to screen for a cancer signal shared by multiple cancers, many of which don't have recommended screening tests. Unlike single cancer screening, Galleri does not individually test for specific types of cancer. The Galleri test should be used in addition to routine cancer screening recommended by your healthcare provider.

- In order to deliver your result, the Galleri test studied **more than one hundred thousand regions of DNA and over a million DNA sites** from your blood sample to determine if any of it came from cancer cells.
- **The Galleri test development was supported by multiple rigorous trials involving over 20,000 patients.** In the CCGA clinical trial, the Galleri test was able to detect a signal shared across many cancers.[1] Among the cancers Galleri detected in this trial were cancers of the bladder, colon and rectum, esophagus, head and neck, liver, gallbladder, lung, lymphatic system, ovaries, pancreas, stomach and many others.

For a full list of cancers that Galleri was able to detect, visit: galleri.com/cancers

Intended use

The Galleri test is a qualitative, next-generation sequencing (NGS)-based screening test for the detection of DNA methylation patterns using cell-free DNA isolated from peripheral whole blood. When Galleri detects a cancer signal, diagnostic workup by a qualified healthcare provider is required to establish a cancer diagnosis.

The Galleri test is a screening test, it is not a diagnostic test. The Galleri test is intended to complement, not replace recommended single cancer screening tests such as colonoscopy or mammography.

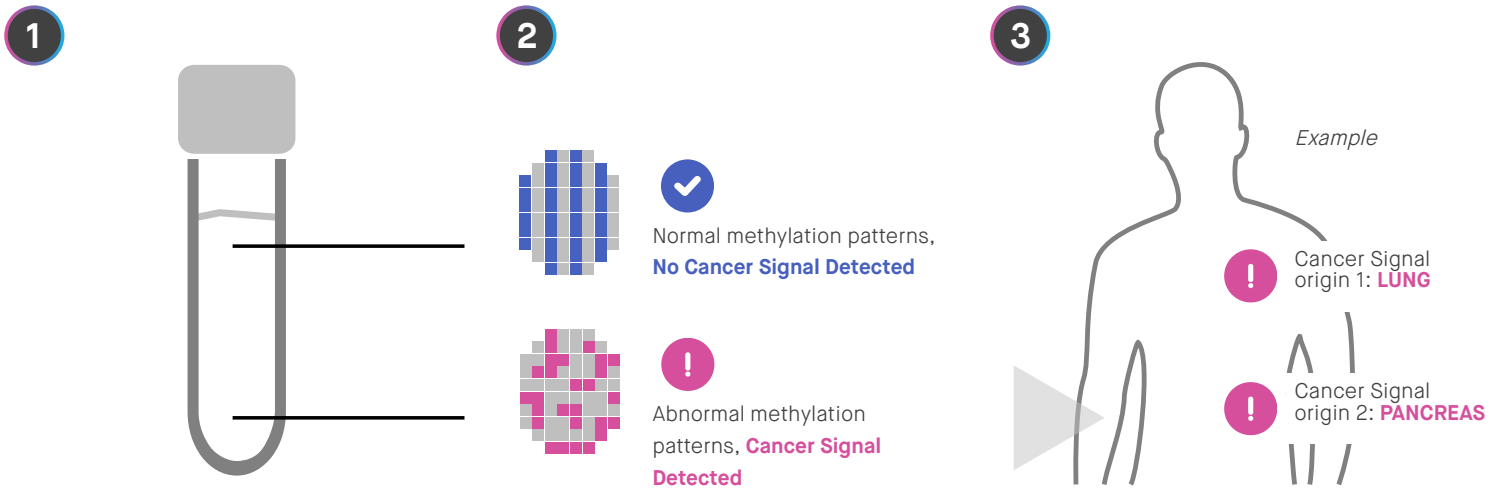
The Galleri test is recommended for use in adults with an elevated risk of cancer such as those age 50 years and older. The Galleri test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider.
The Galleri test is for professional use only.

Do you have more questions?
If you have questions about Galleri or your test result please contact the healthcare provider who ordered this test. We are also here to help! Give us a call at 833-694-2553 or email customerservice@grail.com.

About the Galleri® test

This and the following pages include additional information about the Galleri test. They do not include your own personal data and results.

How does the Galleri test work?



Galleri checks **more than one hundred thousand regions of DNA and over a million DNA sites** in your blood sample.

Galleri looks for **methylation patterns in the DNA regions** to detect abnormal ones.

If a cancer signal is detected, Galleri **predicts where in the body the cancer is likely coming from.**

Galleri uses the latest discoveries in science and DNA sequencing technology to analyze cell-free DNA that circulates in the blood. All cells in the body, including cancer cells, release DNA fragments into the bloodstream. These fragments are called cell-free DNA. The cell-free DNA from cancer cells is different from that of healthy cells. The Galleri test analyzes the abnormal DNA methylation patterns to identify a cancer signal.

When a cancer signal is detected, the Galleri test analyzes the DNA methylation patterns to predict where in the body the cancer signal is likely coming from (known as Cancer Signal Origin). The process uses machine learning and pattern recognition to predict the Cancer Signal Origin. The Cancer Signal Origin(s) help guide the diagnostic workup to confirm the presence of cancer by standard medical practice.

About the Galleri® test

Methods

The Galleri test is a qualitative, next-generation sequencing screening test for the detection of DNA methylation patterns using cell-free DNA isolated from peripheral whole blood. The Limit of Detection (LOD95) of Galleri test using abnormal coverage is 0.2. The test has been validated in the Circulating Cell-free Genome Atlas (CCGA)[3] and PATHFINDER clinical trials.[4]

Clinical Trials

The following is data from clinical trials and is not your own personal data

Galleri Test Performance Characteristics in CCGA Sub-study: Galleri was validated in the case-control CCGA3 study where a pre-specified sub-study of 2,823 cancer participants (cases) and 1,254 non-cancer participants (controls) was analyzed.[1] 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 a cancer signal shared across more than 50 cancer types (defined by American Joint Committee on Cancer[5]). Results have been characterized across (i) solid tumors without common screening options, (ii) solid tumors with common screening options, and (iii) hematologic malignancies.[b]

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[1c] (95% Confidence Interval)	Specificity[1], proportion of true negatives (95% Confidence Interval)
0.5% (0.2-1.0%) 6 (0.5%) non-cancer participants had false "Cancer Signal Detected" results among 1,254 non-cancer participants.	**99.5% (99.0-99.8%)** 1,248 (99.5%) non-cancer participants had accurate "No Cancer Signal Detected" results among 1,254 non-cancer participants.

b. 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 SA, et al. J Natl Cancer Inst. 2021;113(8):1044-1052. It is estimated that about two-thirds of diagnosed lung cancers occur in patients who are not eligible for lung cancer screening (Pinsky PF, et al. J Med Screen. 2012;19(3):154-156).

c. False Positive Rate is calculated as (1-Specificity).

About the Galleri® test

Clinical Trials (continued)

The following is data from clinical trials and is not your own personal data

Cancer signal detection for various cancer classes in CCGA3 sub-study[1]:
Sensitivities for cancer signal detection by cancer class and across cancer classes are shown below.[d] Sensitivity or the percentage of true positives, is the proportion of study participants with "Cancer Signal Detected" test result among study participants with cancer stages I-IV.[e] For sensitivity by stage or cancer type, please visit www.galleri.com/test-report

Cancer Classes[1]	Sensitivity[1], proportion of true positives
Cancers Responsible for 2/3 of All Cancer Deaths in the US[6e] 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 2/3 of all cancer deaths in the US.

Solid Tumors without Common Screening Options[1]

Cancer Classes[d]	Sensitivity[e] (95% Confidence Interval)
Overall	**65.6% (63.0-68.1%)** 876 (65.6%) cancer participants had "Cancer Signal Detected" test result among 1,336 participants with solid tumors without common screening options
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[f]	50.8% (38.4-63.2%)

Solid Tumors with Common Screening Options[1]

Cancer Classes[d]	Sensitivity[e] (95% Confidence Interval)
Overall	**33.7% (31.1-36.5%)** 396 (33.7%) cancer participants had "Cancer Signal Detected" test result among 1,175 participants with solid tumors with common screening options
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[1]

Cancer Classes[d]	Sensitivity[e] (95% Confidence Interval)
Overall	**55.1% (49.3-60.8%)** 156 (55.1%) cancer participants had "Cancer Signal Detected" test result among 283 participants with hematologic malignancies
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%)

d. 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.

e. 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 AJCC5 stage.

f. 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).

About the Galleri® test

Clinical Trials (continued)

The following is data from clinical trials and is not your own personal data

Negative Predictive Value projected based on CCGA sub-study:
Negative predictive value (NPV) is the probability that a study participant with a "No Cancer Signal Detected" Galleri test result is truly negative. Based on CCGA3[1] sub-study results, adjusted for the known distribution of cancers by stage in people who are 50-79 year old, the NPV was projected to be 99.4% (95% CI: 99.4-99.5%).[g] Meaning, it was projected that 0.6% of participants with "No Cancer Signal Detected" results would have cancer.

Galleri Test Performance Characteristics in PATHFINDER Study:
Planned interim analysis results are reported from the interventional PATHFINDER study[7], which enrolled 6,662 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[8], which returned "Cancer Signal Detected" results for 30 participants with diagnostic resolution[h] (including 19 with clinical cancer diagnosis) and 17 participants who had "No Cancer Signal Detected" by the earlier Galleri test and were not diagnostically evaluated. A conservative PPV estimate[i] 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[j], proportion of patients with cancer diagnosis among those with a "Cancer Signal Detected" result (95% Confidence Interval)
40.4% (27.6-54.7%)
19 (40.4%) participants had cancer diagnosed among 47 participants with "Cancer Signal Detected" results.

g. The Circulating Cell-free Genome Atlas (CCGA) Study (NCT02889978) substudy 3 (CCGA3)1 included cancer (n=2823) and non-cancer (n=1254) participants. It was estimated that 99.4% of participants with a 'No Cancer Signal Detected' result would not have cancer based on Galleri test performance adjusted for SEER cancer incidence in the 50-79 years age group.[2]

h. Not all participants with "Cancer Signal Detected" results by both earlier and current Galleri tests have reached a diagnostic resolution yet and are being assessed for cancer. These participants will be included in the PPV calculations after diagnostic resolution is achieved.

i. 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.

j. 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.

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 performances.

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 recommended 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 "No Cancer Signal Detected" result does not eliminate the possibility that a cancer is present or will occur in the future. Individuals who receive a "No Cancer Signal 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 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.

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

Laboratory Information

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.

References

1. 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.
2. SEER Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2017 Sub. Includes persons aged 50+ diagnosed 2006-2015. GA_2021_008.
3. The Circulating Cell-free Genome Atlas Study (NCT02889978). www.clinicaltrials.gov/ct2/show/NCT02889978
4. The PATHFINDER Study: Assessment of the Implementation of an Investigational Multi-Cancer Early Detection Test Into Clinical Practice (NCT04241796). www.clinicaltrials.gov/ct2/show/NCT04241796
5. Amin MB, et al. (Eds.). AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017.
6. American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021.
7. Beer TM, McDonnell CH, Nadauld L, et al. Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. J Clin Oncol. 2021;39(suppl 15;abstr 3010). Presentation at the American Society of Clinical Oncology (ASCO) Virtual Annual Meeting June 4-8, 2021.
8. Beer TM, McDonnell CH, 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. J Clin Oncol. 2021;39(suppl 15;abstr 3070). Presentation at the American Society of Clinical Oncology (ASCO) Virtual Annual Meeting June 4-8, 2021.

Publications

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- 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.
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