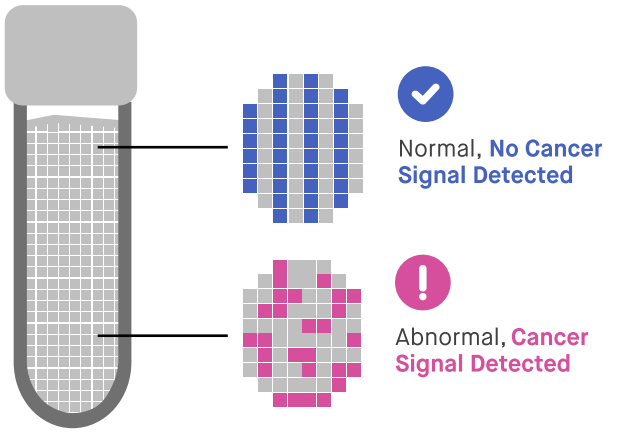
# About the Galleri® test

## How does the Galleri test work?

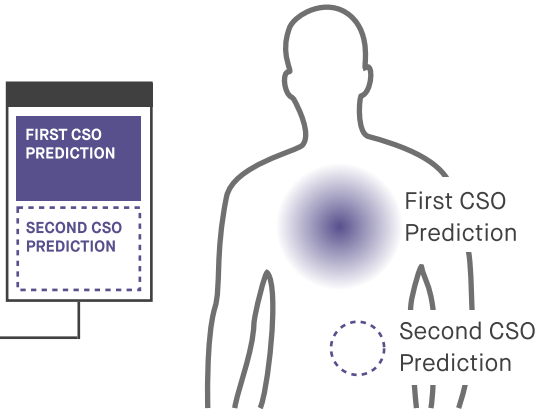
- **Galleri uses the latest scientific discoveries and DNA sequencing technology to analyze cell-free DNA that circulates in the blood.** All cells in your body, including cancer cells, release DNA fragments into the bloodstream. These fragments are called cell-free DNA.
- **The Galleri test screens your blood sample for cell-free DNA and identifies whether it comes from healthy or cancer cells.** DNA from cancer cells has specific methylation patterns that identify it as cancer. Methylation is a natural process that can change the activity of DNA. Methylation patterns also contain information about where in the body to look for cancer.
- **Galleri has been trained by the world's largest cancer methylation database, created by GRAIL.** The process uses advanced technology and pattern recognition to detect a Cancer Signal and predict the Cancer Signal Origin. This information helps guide healthcare providers to perform a diagnostic evaluation for cancer.

***The following is a visual explanation, not your Galleri test results.***

### 1 Cancer Signal Detection




### 2 Cancer Signal Origin Prediction




Galleri checks **more than one hundred thousand regions of DNA and over a million DNA methylation sites** in your blood sample. Galleri looks at methylation patterns in the DNA regions to determine whether it comes from healthy (normal) or cancer (abnormal) cells.

**If a cancer signal is detected, Galleri compares the patient's methylation pattern to the patterns of 21 possible CSO predictions.** If the CSO prediction has a very strong match to the patient's pattern, then only one CSO prediction is reported. Otherwise, the two best CSO predictions are returned.

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## Methods

**The Galleri test is a qualitative, next-generation sequencing screening test for detecting DNA methylation patterns using cell-free DNA isolated from peripheral whole blood.** The Limit of Detection (LOD95) of the Galleri test using abnormal coverage is 0.2 (abnormal coverage is the mean number of unique abnormal fragments observed per CpG in a sample). The test has been validated in the PATHFINDER[1,2] and Circulating Cell-free Genome Atlas (CCGA)[3,4] studies.

The Galleri test has 21 possible Cancer Signal Origin predictions: 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.

## Clinical Trials

**The following is data from clinical trials and is not your data.**

- **Galleri Test Performance Characteristics in the PATHFINDER Study**[1,2]
  The prospective PATHFINDER study enrolled 6,662 participants without clinical suspicion of cancer at enrollment. Participants were men and women at least 50 years old recruited into two cohorts. One cohort included participants with additional cancer risk (history of smoking, prior cancer with treatment completed > 3 years ago, or genetic cancer predisposition). The other cohort included participants without additional cancer risk. Participants who received a "Cancer Signal Detected" result from an early version of the Galleri test underwent a diagnostic evaluation to assess whether they had cancer. Later, blood samples were reanalyzed with the current version of the Galleri test: 58 of 6,578 participants had a "Cancer Signal Detected" result. All participants were followed for 12 months to assess cancer status.

  At the end of the study, 121 participants had a cancer diagnosis, including 73 with cancers detected by screening: 35 with a "Cancer Signal Detected" result from an early version of the Galleri test, 29 with cancers detected by recommended USPSTF screening, and 9 with cancers detected by other cancer screening. The early version of the Galleri test almost doubled the number of cancers detected by screening.

  For more detailed results, **galleri.com/test-report**

- **Galleri Test Performance Characteristics in the CCGA sub-study**[3,4]
  CCGA was a prospective, case-control, observational study, and CCGA3[3] a pre-specified sub-study of 2,823 cancer participants (cases) and 1,254 non-cancer participants (controls). Participants were men and women aged 20 years and older (81% 50 years or older) without a prior history of cancer. Cancer participants were enrolled after diagnosis (or with a high suspicion of cancer) before any cancer treatment.

  In this CCGA3 sub-study, the Galleri test detected a shared Cancer Signal shared across more than 50 types of cancer (defined by the American Joint Committee on Cancer[5]).

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


 

# About the Galleri® test

## Clinical Trials (Continued)

***Galleri test performance***

| Metrics | PATHFINDER[1,2] | | CCGA3[3,4] | |
|---|---|---|---|---|
| | Rate (95% CI) | Details | Rate (95% CI) | Details |
| **Positive Predictive Value (PPV)** | **43.1%** (31.2 - 55.9%) | 25 participants had cancer diagnosed among 58 participants with "Cancer Signal Detected" results. | **44.4%** (28.6 - 79.9%) | Projected estimate adjusted for SEER incidence and stage distribution in the 50-79 years age group.[6,d] |
| **Negative Predictive Value (NPV)** | **98.5%** (98.2 - 98.8%) | 6,216 participants had no cancer diagnosed among 6,311 participants with "No Cancer Signal Detected" results who completed a 12-month follow-up. | **99.4%** (99.4 - 99.5%) | Projected estimate adjusted for SEER incidence and stage distribution in the 50-79 years age group.[6,d] |
| **Accuracy: First Cancer Signal Origin (CSO) Prediction** | **84.0%** (65.3 - 93.6%) | 21 participants had correct first CSO prediction of 25 participants with "Cancer Signal Detected" results and cancer diagnosis. | **88.7%** (87.0 - 90.2%) | 1,273 cancer participants had correct first CSO prediction of 1,435 cancer participants with "Cancer Signal Detected" results. |
| **Accuracy: First or Second Cancer Signal Origin (CSO) Predictions** | **88.0%** (70.0 - 95.8%) | 22 participants had correct first or second CSO predictions of 25 participants with "Cancer Signal Detected" results and cancer diagnosis. | **92.6%** (91.1 - 93.9%) | 1,329 cancer participants had correct first or second CSO predictions of 1,435 cancer participants with "Cancer Signal Detected" results. |
| **Specificity (true negative rate)** | **99.5%** (99.3 - 99.6%) | 6,216 participants had accurate "No Cancer Signal Detected" results among 6,249 participants with no cancer diagnosis who completed a 12-month follow-up. | **99.5%** (99.0 - 99.8%) | 1,248 non-cancer participants had accurate "No Cancer Signal Detected" results among 1,254 non-cancer participants. |
| **False Positive Rate**[c] | **0.5%** (0.4 - 0.7%) | 33 participants had false "Cancer Signal Detected" results among 6,249 participants with no cancer diagnosis who completed a 12-month follow-up. | **0.5%** (0.2 - 1.0%) | 6 non-cancer participants had false "Cancer Signal Detected" results among 1,254 non-cancer participants. |

***Galleri test performance: Sensitivity***

| Metrics | CCGA3[3, 4] | |
|---|---|---|
| | Rate (95% CI) | Details |
| **Sensitivity: Cancers responsible for 2/3 of cancer deaths in the US**[e] | **76.3%** (74.0 - 78.5%) | 1,040 cancer participants received "Cancer Signal Detected" results among 1,363 participants with cancers responsible for 2/3 of all cancer deaths in the US. |

**Notes**

Sensitivity was not evaluated in the PATHFINDER study because the cancer status was unknown for all participants at the time of the blood draw.

CCGA3 enrolled participants with a cancer diagnosis. Therefore, the cancer status was known.

- **Positive Predictive Value:** The proportion of people with "Cancer Signal Detected" results diagnosed with cancer.
- **Negative Predictive Value:** The proportion of people with "No Cancer Signal Detected" results without a cancer diagnosis.
- **Accuracy: Cancer Signal Origin (CSO) Prediction:** The proportion of correctly predicted first (or second) CSO prediction(s) among study participants with cancer and "Cancer Signal Detected" results.
- **Specificity:** The proportion of people without cancer who received "No Cancer Signal Detected" results. True negative rate.
- **Sensitivity:** The proportion of people with cancer who received "Cancer Signal Detected" results. True positive rate.
- **False Positive Rate:** The proportion of people without cancer who received "Cancer Signal Detected" results.
- **95% Confidence Interval (CI):** A range of values that you can be 95% certain contains a true parameter of interest.

c. False Positive Rate is equal to (1 - Specificity).

d. Extrapolation of the positive predictive value (PPV) and negative predictive value (NPV). Results were adjusted by Surveillance, Epidemiology, and End Results Program (SEER) incidence rates and stage distribution for those aged 50-79 years to align with intended use population.[6]

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

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## Clinical Trials (Continued)

**The following is data from clinical trials and is not your data.**

***Cancer Signal detection for various cancer classes in the CCGA3 sub-study[3]***

| Cancer Classes[3] | Sensitivity[3], proportion of true positives | 95% Confidence Interval (CI) |
|---|---|---|
| Liver/Bile-duct | 93.5% | (82.5-97.8%) |
| Head and Neck | 85.7% | (77.8-91.1%) |
| Esophagus | 85.0% | (76.7-90.7%) |
| Pancreas | 83.7% | (76.6-89.0%) |
| Ovary | 83.1% | (72.2-90.3%) |
| Colon/Rectum | 82.0% | (76.2-86.7%) |
| Anus | 81.8% | (61.5-92.7%) |
| Cervix | 80.0% | (60.9-91.1%) |
| Urothelial Tract | 80.0% | (49.0-94.3%) |
| Lung | 74.8% | (70.3-78.7%) |
| Plasma Cell Neoplasm | 72.3% | (58.2-83.1%) |
| Gallbladder | 70.6% | (46.9-86.7%) |
| Stomach | 66.7% | (48.8-80.8%) |
| Sarcoma | 60.0% | (42.3-75.4%) |
| Lymphoma | 56.3% | (48.9-63.5%) |
| Other[f] | 50.8% | (38.4-63.2%) |
| Melanoma | 46.2% | (23.2-70.9%) |
| Lymphoid Leukemia | 41.2% | (28.8-54.8%) |
| Bladder | 34.8% | (18.8-55.1%) |
| Breast | 30.5% | (26.7-34.6%) |
| Uterus | 28.0% | (21.6-35.5%) |
| Myeloid Neoplasm | 20.0% | (5.7-51.0%) |
| Kidney | 18.2% | (11.8-26.9%) |
| Prostate | 11.2% | (8.5-14.6%) |
| Thyroid | 0.0% | (0.0-21.5%) |

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).

## Warnings, Precautions, and Limitations

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

The 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 healthcare professionals following 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 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 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 Origin predictions, 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 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 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. Schrag D, McDonnall CH III, Naduld L, et al. PATHFINDER: A Prospective Study of a Multi-Cancer Early Detection Blood Test. Ann Oncol. 2022;33(suppl_7; abstr 9030). 10.1016/annonc/annonc1061 Presentation at European Society of Medical Oncology (ESMO) Congress September 9-13, 2022; Paris, France.
2. The PATHFINDER Study: Assessment of the Implementation of an Investigational Multi-Cancer Early Detection Test Into Clinical Practice (NCT04241796).
3. 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.
4. The Circulating Cell-free Genome Atlas Study (NCT02889978).
5. Amin MB, et al. (Eds.). AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017.
6. SEER Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2017 Sub. Includes persons aged 50+ diagnosed 2006-2015. GRAIL. Data on file.


## Publications


- 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.
- 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.
- Schrag D, McDonnall CH III, Naduld L, et al. PATHFINDER: A Prospective Study of a Multi-Cancer Early Detection Blood Test. Ann Oncol. 2022;33(suppl_7; abstr 9030). 10.1016/annonc/annonc1061 - Presentation at European Society of Medical Oncology (ESMO) Congress September 9-13, 2022; Paris, France.



 