THE CURRENT STATE OF CANCER SCREENING & MULTI-CANCER EARLY DETECTION

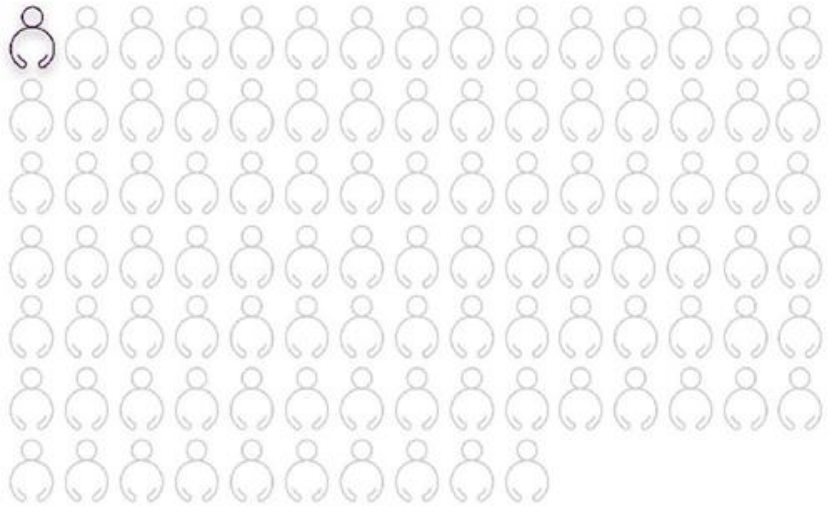
Agenda

1. Current State of Cancer Screening
2. Multi-Cancer Early Detection (MCED) Test
3. MCED Test Performance

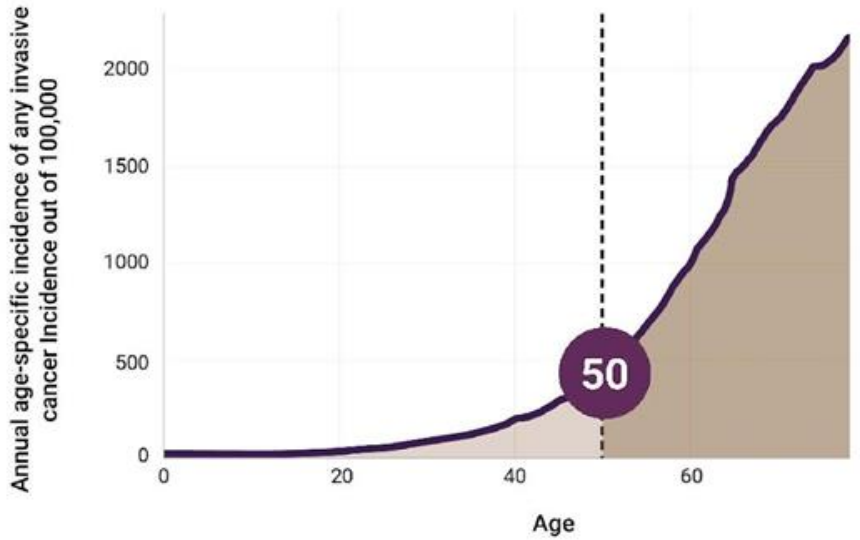
Cancer Risk Increases With Age

Highest Cancer Rates Are Over the Age of 50

1.2% Incidence per year in the population aged >50 years



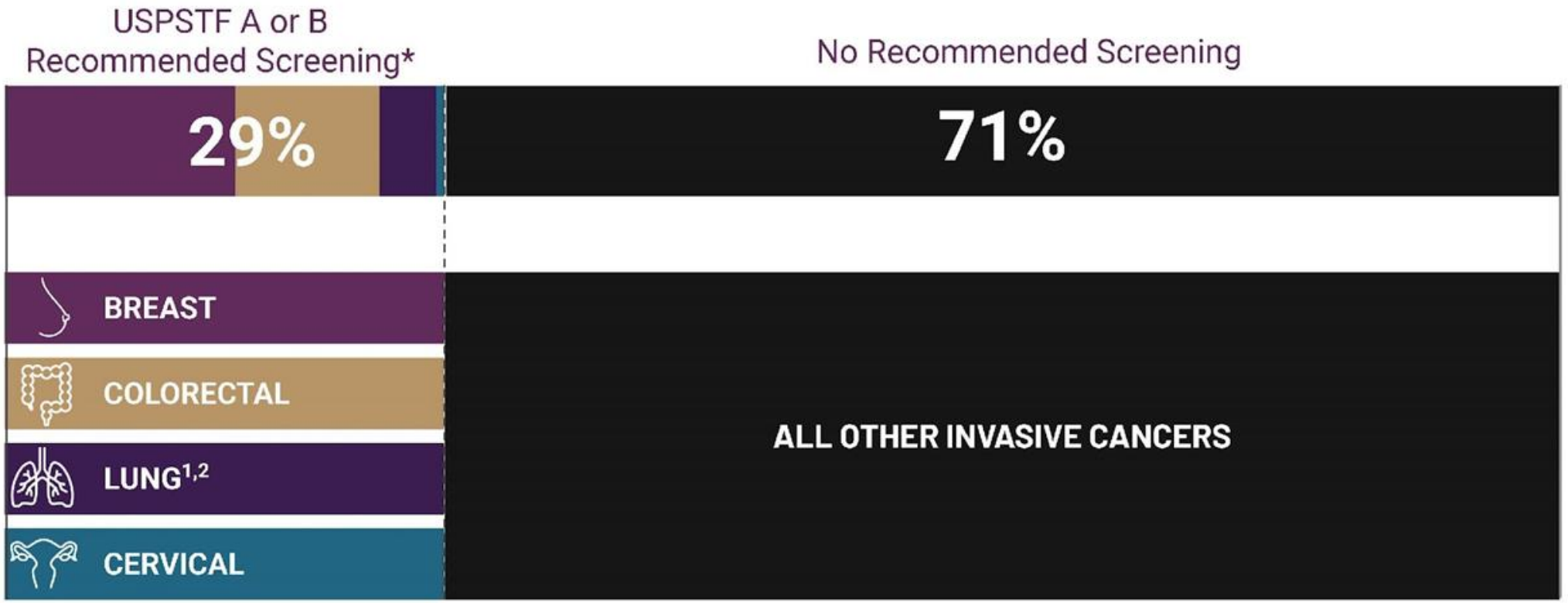
Average rate of cancer over age 50 is **13x** higher than under age 50



Data: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database Incidence - SEER Research Limited-Field Data, 21 Registries, Nov 2020 Sub (2000-2018) - Linked To County Attributes -Time Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission. Risk Factor Data on file: American Cancer Society Cancer Prevention Studies II/III

Most Cancers Lack Screening Options

1.2% Cancer Incidence in a population aged 50-79

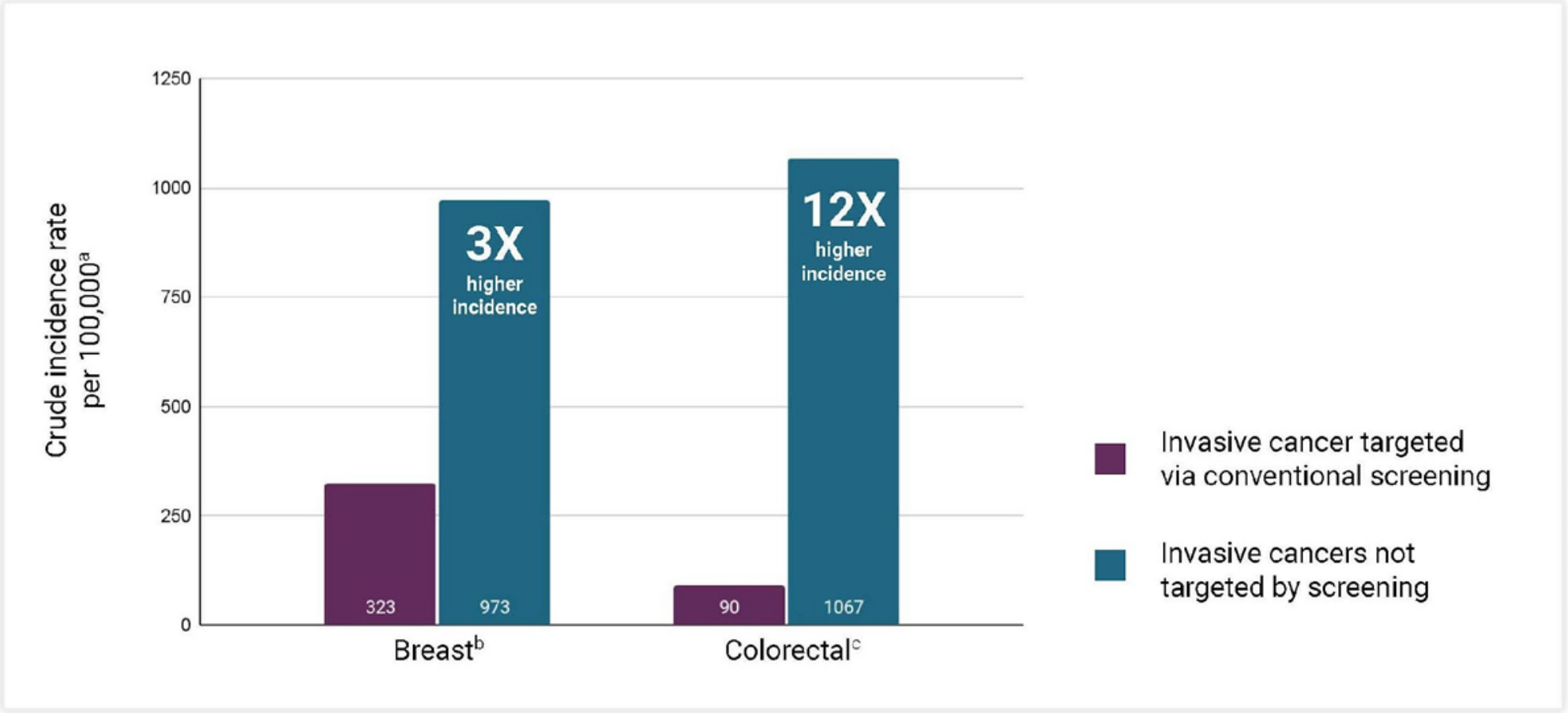


**Prostate cancer screening is recommended on an individual basis§*

§Calculated using rates per 100,000 person years in a population with same age/sex distribution as outlined by SEER18 2011-15. USPSTF, United States Preventive Services Task Force. *Assumes screening is available for all breast, cervical, and colorectal cancer cases and 43% of lung cancer cases (based on estimated proportion of lung cancers that occur in screen-eligible individuals older than 40 years). Source: SEER Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2017 Sub. Includes persons aged 50+ diagnosed 2006-2015. Data on file GA2021-0065. 1. Meza R, et al. JAMA. 2021;325(10):988-997. 2. Pinsky PF, et al. J Med Screen. 2012;19(3):154-156.

A Multi-Cancer Test Could Have a Significant Public Health Impact

Individuals Are More Likely to Have a Different Cancer Than the One That Is Being Screened



[a]All rates are crude per 100,000 from Surveillance, Epidemiology and End Results Program (SEER18; incidence of invasive cancers only) and National Center for Health Statistics (mortality). [b]Women aged 50-74 years (recommended biennial screening mammography). [c]Men and women aged 50 -74 years (choice of approved modality for screening). Clarke CA et al. Multi cancer early detection: A new paradigm for reducing cancer specific and all cause mortality. *Cancer Cell*. 2021 Apr 12;39(4):447-448. doi: 10.1016/j.ccell.2021.02.004. Data on File GA_2021_007.

Recommended Single-Cancer Screening

Optimize Sensitivity Over Specificity

CANCER	USPSTF RECOMMENDED SCREENING	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)
BREAST[1]	Mammography	87	89	4.4
COLORECTAL[2]	Decennial colonoscopy	*Reference Standard*	*Reference Standard*	***Reference Standard***
	Stool-based screening (sDNA)	92.3	86.6	3.7*
	Stool-based screening (FIT)	73.8	94.9	8.7
LUNG[3,4]	Low-dose CT	85†	87†	6.9†
CERVICAL[5]	Cytology / HPV Test	95	85.5	<1*

Shift from screening for individual cancers to screening individuals for cancers

CT, computed tomography; FIT, fecal immunochemical test; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force. *Pre-cancerous lesions were excluded. †Based on previous USPSTF recommendations of adults 55–80 years with a 30 pack/year smoking history. 1. USPSTF. 2016. Lehman, et al. Radiology. 2017;283(1):49-58. 2. USPSTF. 2017. United States Food and Drug Administration Premarket Approval P130017. 3. Pinsky PF, et al. J Med Screen. 2012;19(3):154-156. 4. Meza R, et al. JAMA. 2021;325(10):988–997. Recommendation for lung screening limited to high-risk smoking population, which accounts for less than 33% of all lung cancers. 5. Kim, et al. JAMA. 2018;320(7):706-714

Criteria for an Effective Multi-Cancer Early Detection (MCED) Test

Detect **many deadly cancers**, including unscreened cancers, using a single blood sample

Predict **signal origin** to assist with diagnostic workup

High **positive predictive value** and a low **false-positive rate** to limit unnecessary workups

Supported by large-scale clinical validation studies
Performance translates into an intended-use population

Hackshaw A, et al. *Cancer Cell*. 2022. doi.org/10.1016/j.ccell.2022.01.012.
Jamshidi A, et al. *Cancer Cell*. 2022. doi: 10.1016/j.ccell.2022.10.022.
Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. NPJ Precis Oncol. 2018;2:23. doi: 10.1038/s41698- 018-0066-x.
Chen X, et al. Clin Cancer Res. 2021;27(15):4221-4229. doi: 10.1158/1078- 0432.CCR-21-0417.

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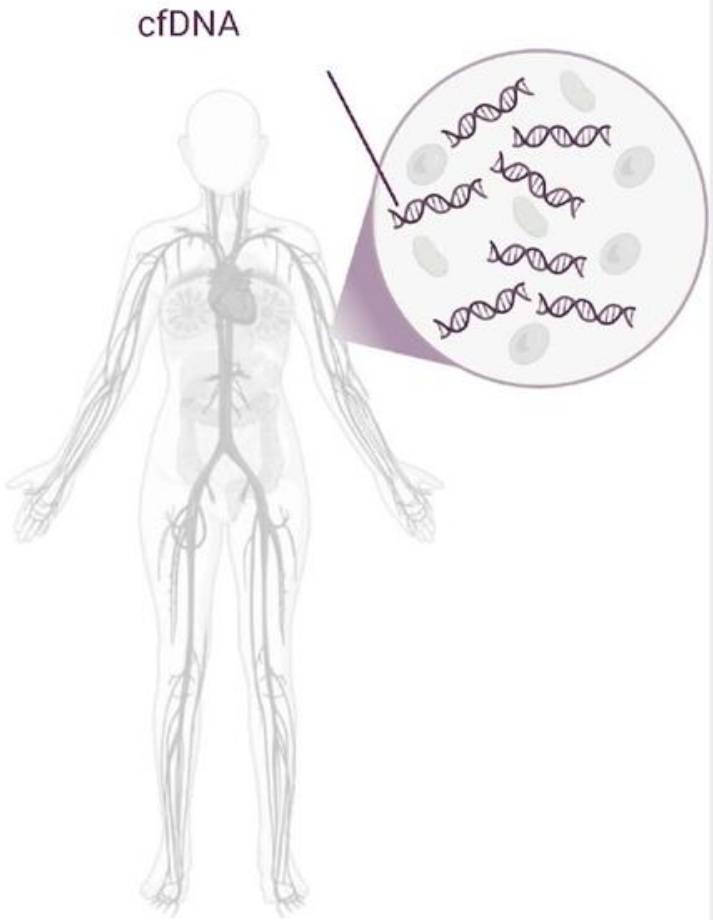
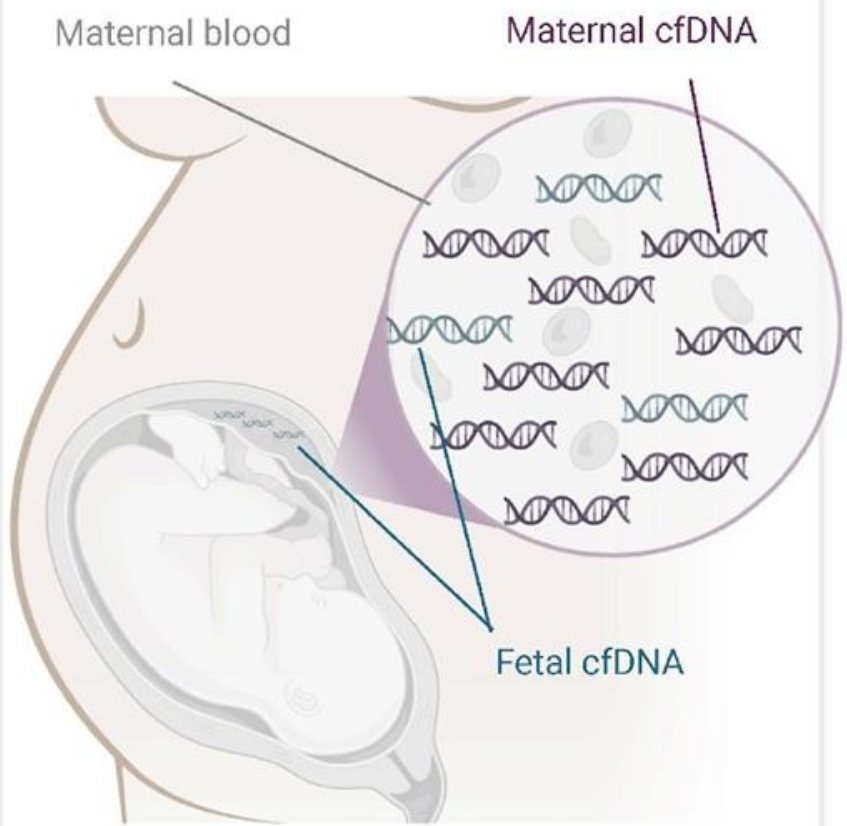
3. MCED Test Performance

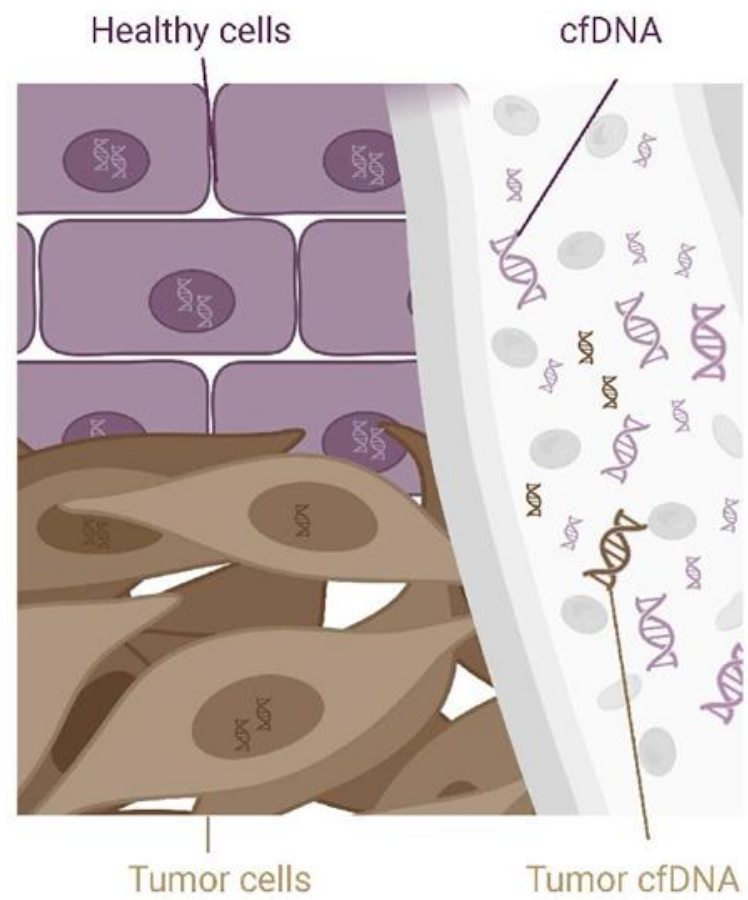
Cell-free DNA (cfDNA)

Cancer Signals Detected in cfDNA





10 cancer cases found in over 125K tests[1]



[1]Bianchi DW, et al. *JAMA*. 2015;314(2):162-169.

Circulating Cell-Free Genome Atlas (CCGA) Study

Prospective, observational, longitudinal, case-control study divided into 3 substudies with a total of 15,254 participants[1]

Substudy 1[2]	Substudy 2[3]	Substudy 3[4]
Discovery	**Training / Validation**	**Validation**
Methylation Patterns	Methylation Patterns	Methylation Patterns
Mutations	Machine-learning classifiers to differentiate cancer vs non-cancer and predict CSO	Clinical Validation supporting Multi-Cancer Early Detection Test launch
Chromosome Alterations		

CCGA, Circulating Cell-free Genome Atlas; CSO, cancer signal origin. 1.GRAIL, Inc. The Circulating Cell-Free Genome Atlas Study. Available from: https://clinicaltrials.gov/ct 2/show/NCT02889978. 2.Jamshidi A, et al. Cancer Cell. 2022;40(12):1537- 1549.e12. doi: 10.1016/j.ccell.2022.10.0 22. 3.Liu MC, et al. Ann Oncol. 2020;31(6):745- 759. doi: 10.1016/j.annonc.2020.0 2.011. 4.Klein EA, et al. Ann Oncol. 2021;32(9):1167- 1177. doi: 10.1016/j.annonc.2021.0 5.806.

Circulating Cell-Free Genome Atlas (CCGA)

CCGA substudy 1 was designed to compare cfDNA approaches among the same set of samples

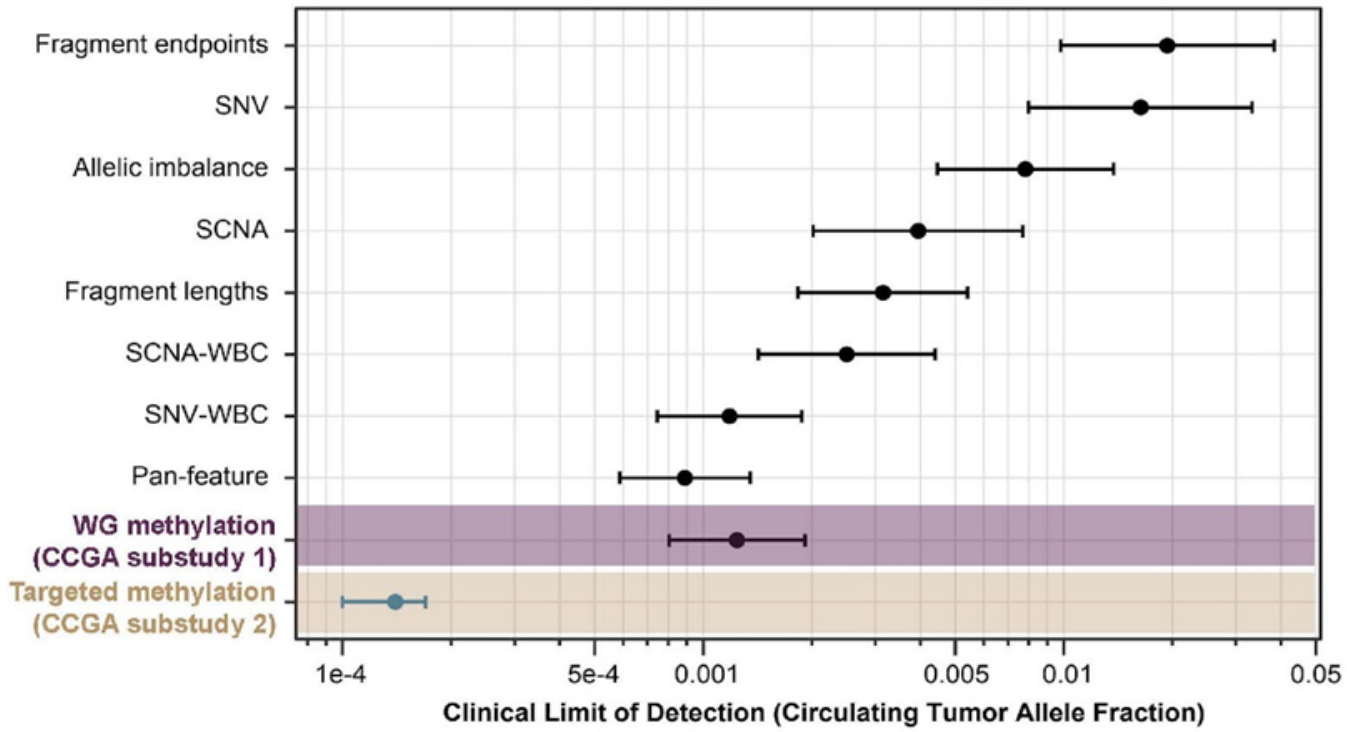
CCGA Substudy 1

Discovery

Methylation Patterns

Mutations

Chromosome Alterations

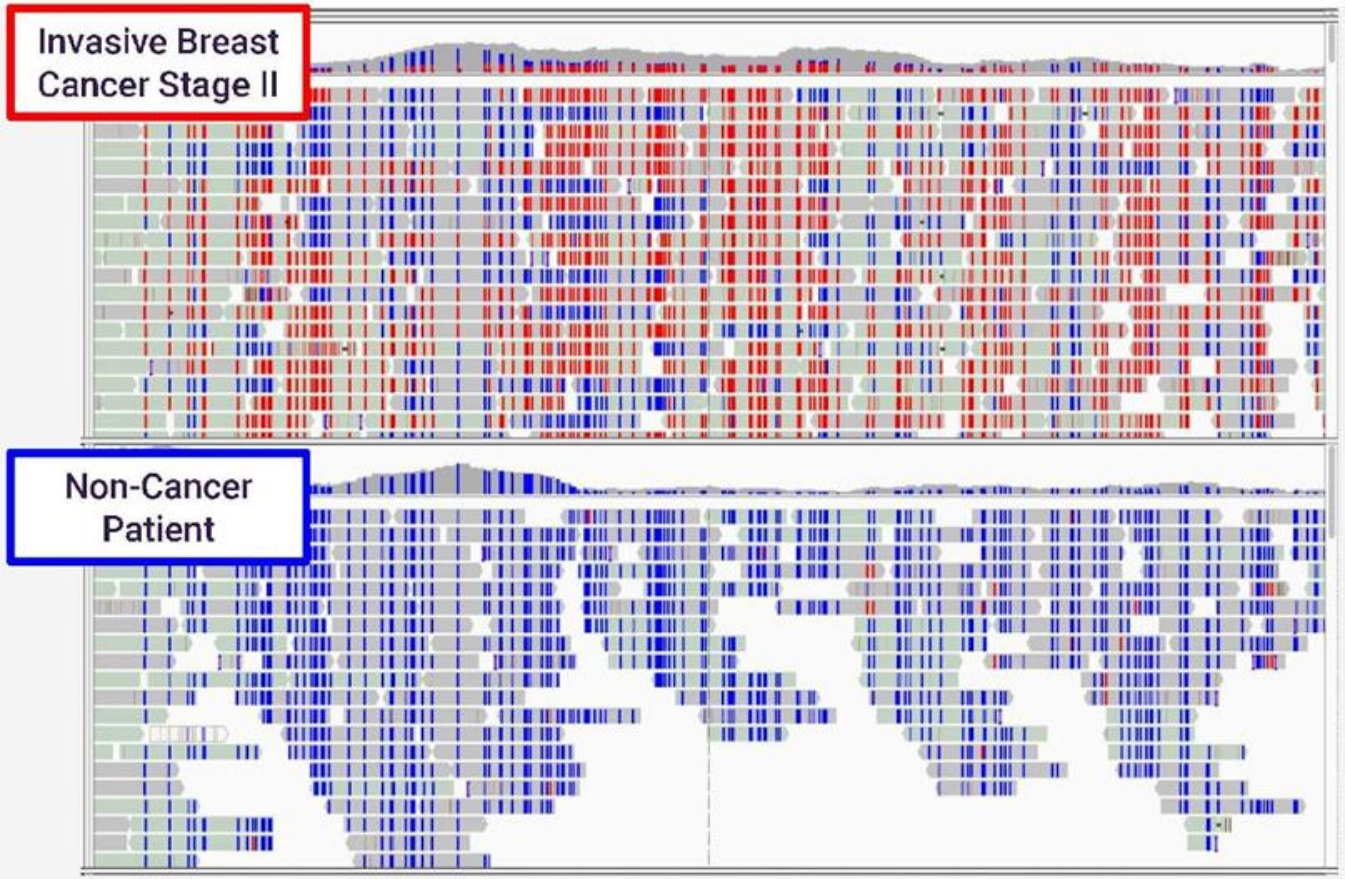


Combining other approaches did not increase methylation-only test performance

CCGA, Circulating Cell-free Genome Atlas; cfDNA, cell-free DNA; SNV, single nucleotide variants; SCNA, somatic copy number alterations; white blood cell; WG, whole-genome. Jamshidi A, et al. Cancer Cell. 2022. doi: 10.1016/j.ccell.2022.10.022.

DNA Methylation Patterns Distinguish Cancer from Non-Cancer

Shared Cancer Signal



cfDNA strand with methylated CpGs

Fragment-level CpG sites

Methylated CpG site

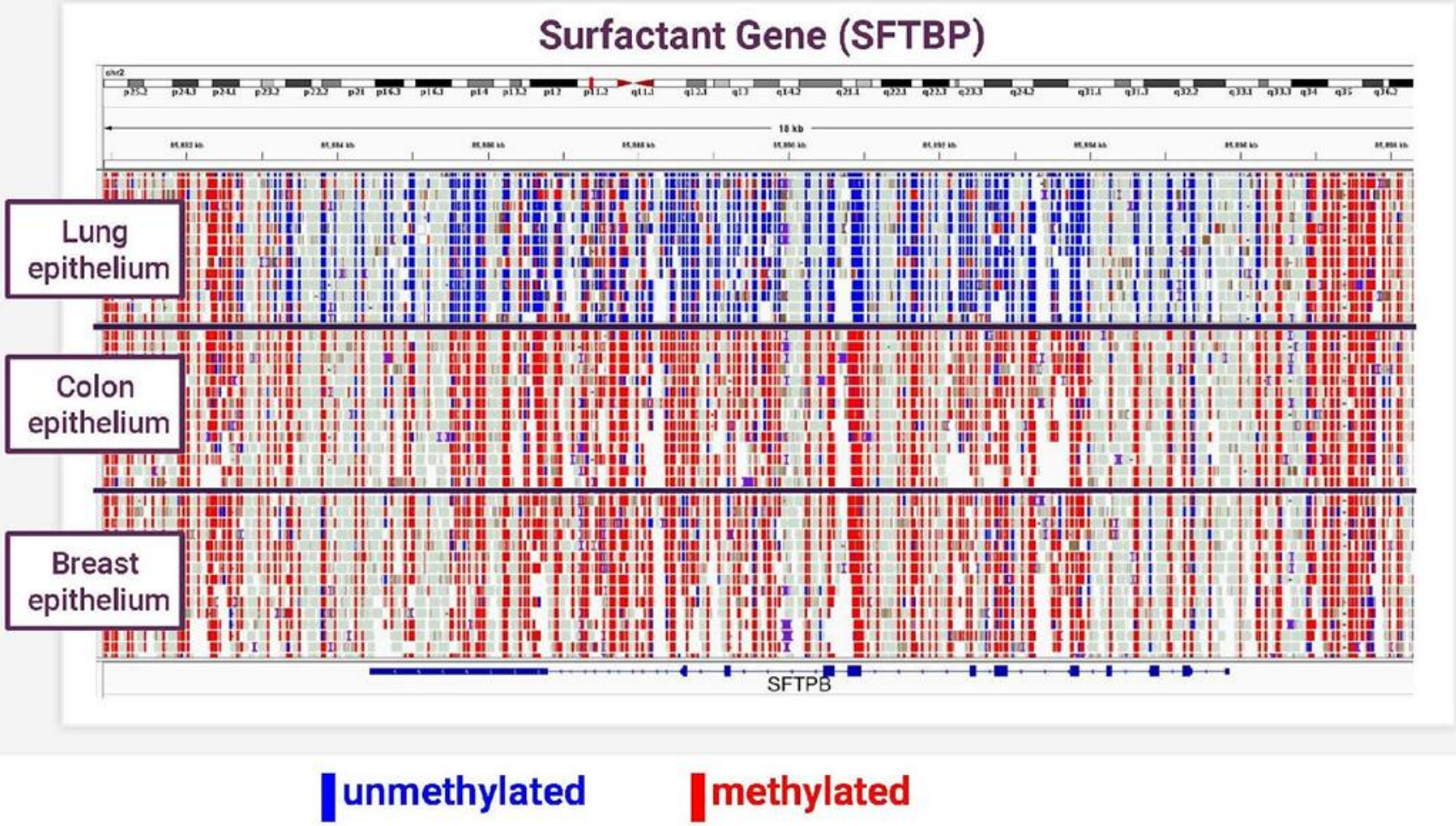
Unmethylated CpG site

unmethylated **methylated**

Aravanis AM, et al. Development of Plasma Cell-Free DNA Assays for Early Cancer Detection: First Insights from the Circulating Cell-Free Genome Atlas (CCGA) Study. Presentation at American Association for Cancer Research (AACR) Annual Meeting. Apr 14-18, 2018; Chicago, IL. Abstract nr LB-343.

DNA Methylation Patterns Are Tissue-Specific

Cancer Signal Origin (CSO)



Methylation patterns are established during development in a cell type–specific manner

Each cell type in the body has a unique pattern of methylation and tissue-specific gene expression

SFTPB, surfactant protein B.
GRAIL data on file GR-2023-0112.

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Circulating Cell-Free Genome Atlas (CCGA) Study

Prospective, observational, longitudinal, case-control study divided into 3 Substudies with a total of 15,254 participants[1]

Substudy 1[2]

Discovery

- Methylation Patterns
- Mutations
- Chromosome Alterations

Substudy 2[3]

Training / Validation

- Methylation Patterns
- Machine-learning classifiers to differentiate cancer vs non-cancer and predict CSO

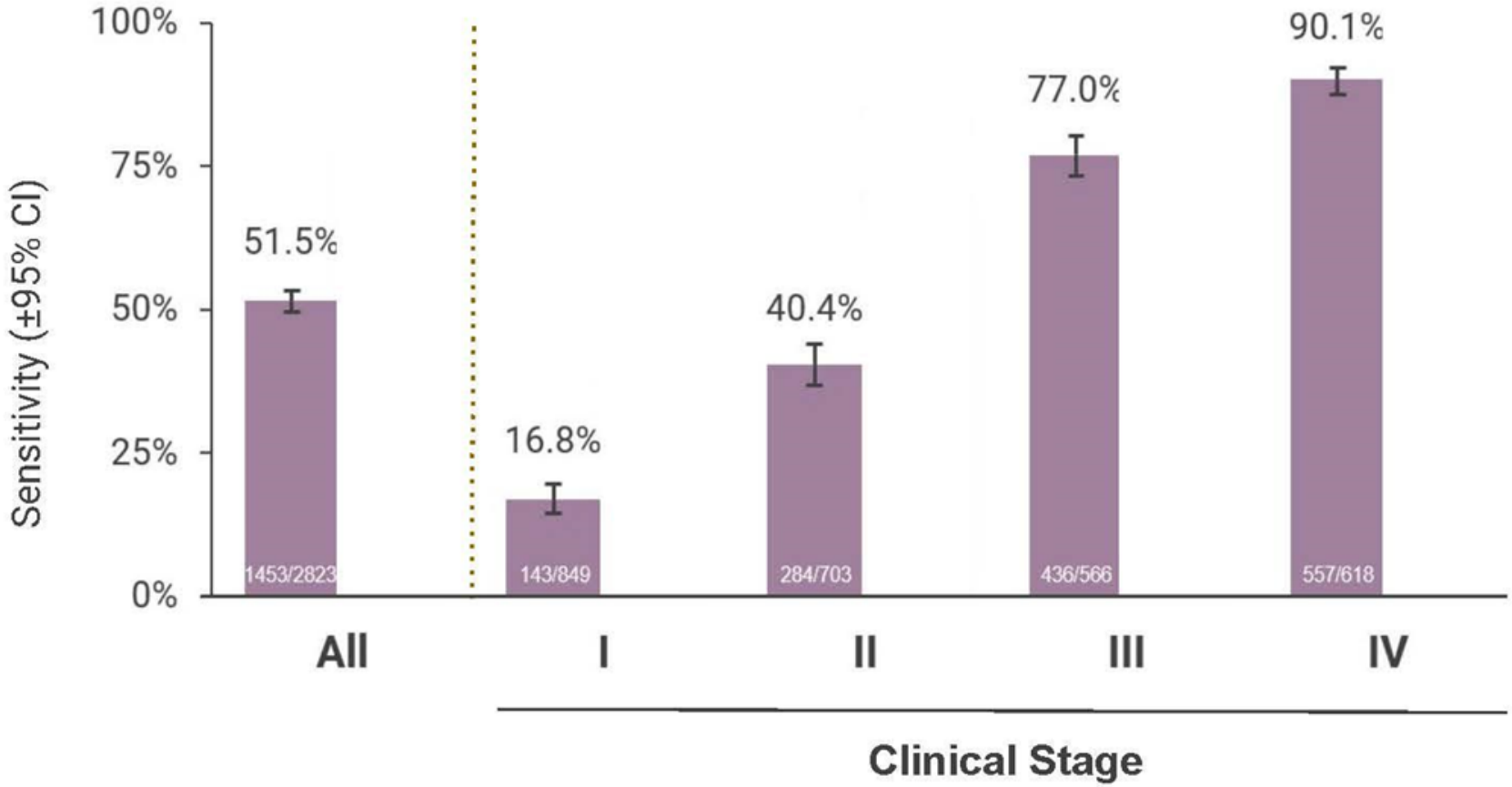
Substudy 3[4]

Validation

- Methylation Patterns
- Clinical Validation supporting Multi-Cancer Early Detection Test launch

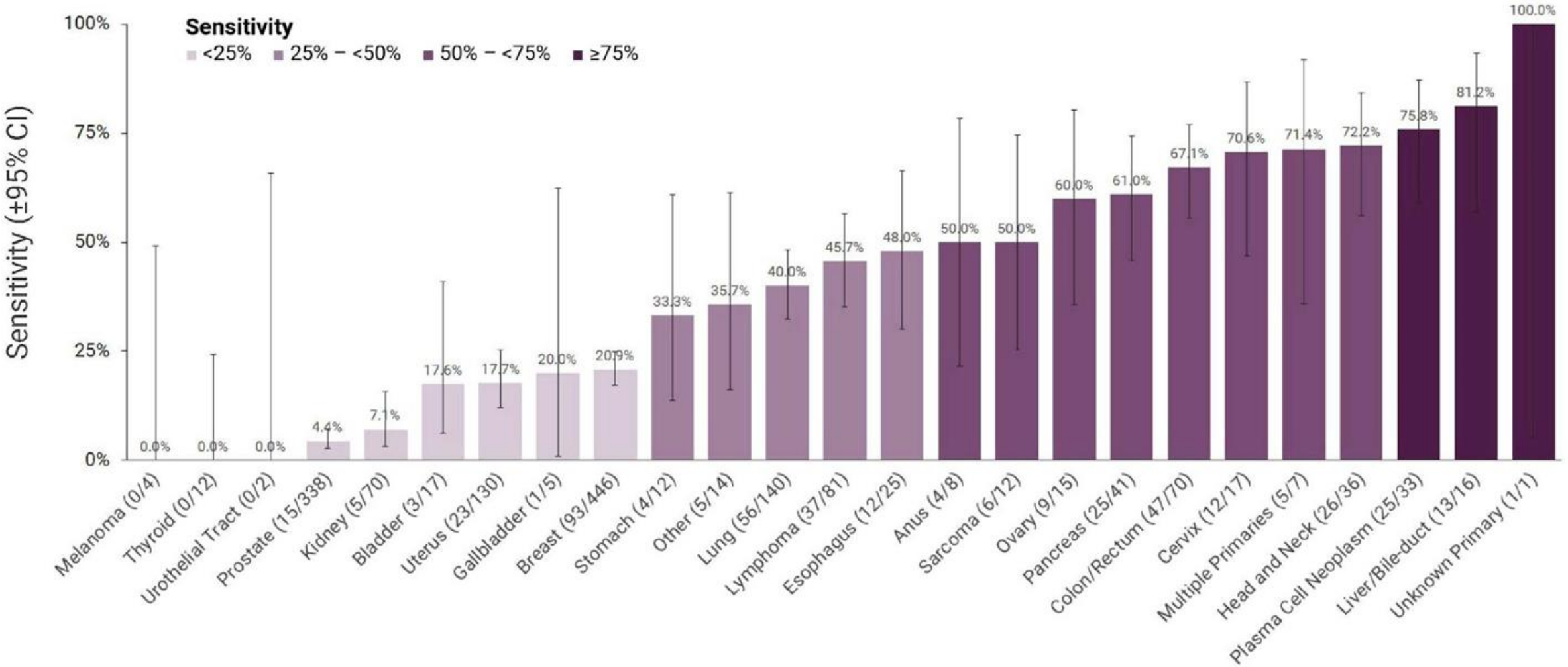
CCGA, Circulating Cell-free Genome Atlas; CSO, cancer signal origin. 1.GRAIL, Inc. The Circulating Cell-Free Genome Atlas Study. Available from: https://clinicaltrials.gov/ct 2/show/NCT02889978. 2.Jamshidi A, et al. Cancer Cell. 2022;40(12):1537- 1549.e12. doi: 10.1016/j.ccell.2022.10.0 22. 3.Liu MC, et al. Ann Oncol. 2020;31(6):745- 759. doi: 10.1016/j.annonc.2020.0 2.011. 4.Klein EA, et al. Ann Oncol. 2021;32(9):1167- 1177. doi: 10.1016/j.annonc.2021.0 5.806.

Sensitivity of Cancer Signal Detection by Clinical Stage



"All" comprises all cancer stages, including missing stage and cancer classes that do not have staging per American Joint Committee on Cancer (AJCC) staging manual. CI, confidence interval. Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806. Amin MB, et al. (Eds.). AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017.

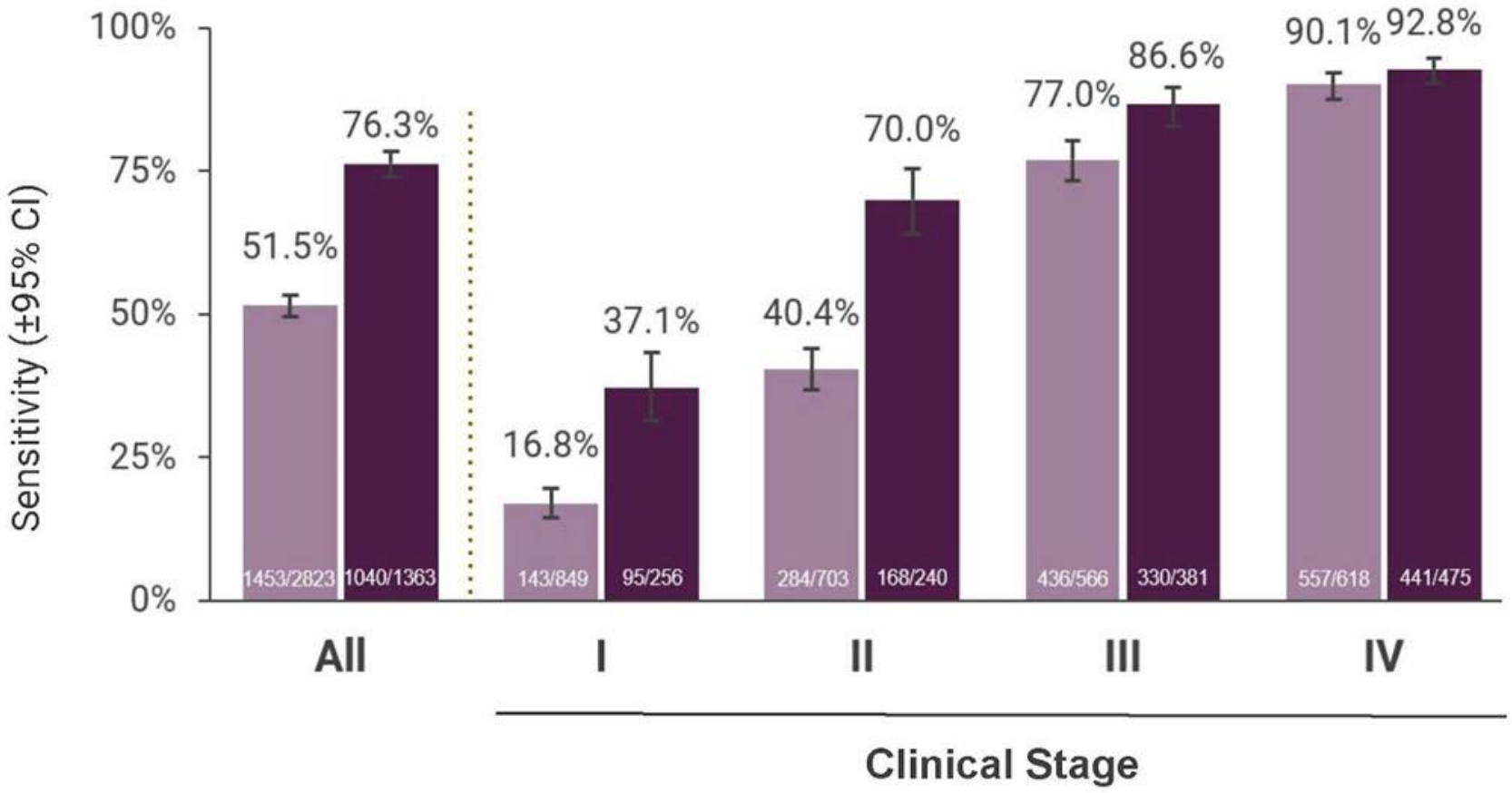
Sensitivity of Cancer Signal Detection by Cancer Class: **Stage I-II**



For multiple primaries, highest clinical stage was selected.
CI, confidence interval.
GRAIL data on file GA 2023 0113.

Sensitivity of Cancer Signal Detection by Clinical Stage

12 Pre-Specified Cancers Responsible for Two-Thirds of Cancer Deaths



12 cancers that account for 2/3 of US cancer deaths[1]

- Anus
- Bladder
- Colon/rectum
- Esophagus
- Head and neck
- Liver/bile duct
- Lung
- Lymphoma
- Ovary
- Pancreas
- Plasma cell neoplasm
- Stomach

"All" comprises all cancer stages, including missing stage and cancer classes that do not have staging per American Joint Committee on Cancer (AJCC) staging manual. CI, confidence interval. [1]American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society; 2022. Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/cancer-facts-and-figures-2022.pdf.

Methylation Predicts Cancer Signal Origin With High Accuracy

Cancer Signal Origin Assists Diagnostic Workup

89%

Rate of cancer signal origin predicted correctly[a]

Some cancer signal origins share biological features

Anus
Most common inaccuracy:
Head and Neck
(HPV-driven cancers)

Cervix
Most common inaccuracies:
Anus or Head and Neck
(HPV-driven cancers)

Ovary
Most common inaccuracy:
Uterus
(Müllerian cancers)

1. Klein EA, 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. doi:10.1016/j.annonc.2021.05.805. [a]For cancer participants with a positive cancer signal. Only CSOs with accuracy <85% and inaccurate call for a specific cancer occurred >15% of the time. CSO, cancer signal origin.

Methylation MCED Performance Characteristics

Largest Clinical Validation of an MCED Test

1 **Shared Cancer Signal**

89% **Cancer Signal Origin Accuracy[a]**

0.5% **False-Positive Rate**

>50 Types of Cancer

Anus
Breast
Cervix uteri
Corpus uteri (2 types[b])
Colon and rectum
Esophagus[c]
Exocrine pancreas
Gallbladder
Hodgkin and non-Hodgkin lymphoma
Bile duct (3 types[d])
Kidney
Larynx
Leukemia
Liver
Lung
Melanoma of the skin
Malignant pleural mesothelioma
Merkel cell carcinoma
Nasopharynx
Neuroendocrine (3 types[e])
Oral cavity
Oropharyngeal[f]
Oro- and hypo-pharynx[g]
Ovary[h]
Plasma cell myeloma[i]
Prostate
Renal pelvis and ureter
Soft tissue sarcoma (5 types[j])
Small intestine
Stomach
Testis
Urinary bladder
Vagina
Vulva

Bold indicates cancer with USPSTF screening guideline[k]

[a]For cancer participants with a positive cancer signal. [b]Corpus uteri carcinoma and carcinosarcoma; Corpus uteri sarcoma. [c]Esophagus and esophagogastric junction. [d]Distal bile duct; Perihiler ducts; Intrahepatic bile ducts. [e]Neuroendocrine tumors of the appendix; Neuroendocrine tumors of the colon and rectum; Neuroendocrine tumors of the pancreas. [f]HPV-mediated (p16+) oropharyngeal cancer. [g]Oropharynx (p16-) and hypopharynx. [h]Ovary, fallopian tube and primary peritoneal carcinoma. [i]Plasma cell myeloma and plasma cell disorders. [j]Soft tissue sarcoma: of the abdomen and thoracic visceral organs; of the head and neck; of the retroperitoneum; of the trunk and extremities; unusual histologies and sites. [k]USPSTF A, B, or C rating.
AJCC, American Joint Committee on Cancer; CCGA, Circulating Cell-free Genome Atlas; USPSTF, United States Preventive Services Task Force. GRAIL data on file GA_2021_008 and Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

Performance in an Intended-Use Population

Prospective, Multicenter, Interventional, Return-of-Results Study

6,662 PARTICIPANTS AGED ≥50 YEARS

QUESTIONNAIRE FOR PARTICIPANTS

DAY 1-15

BLOOD DRAWN, SHIPPED, PROCESSED, & TEST REPORT GENERATED

CANCER SIGNAL DETECTED

Test result communicated

Provider determines diagnostic follow-up procedures

DIAGNOSTIC RESOLUTION

Cancer or no cancer

CANCER STATUS

Assessed at 12 months

NO CANCER SIGNAL DETECTED

Participant to continue guideline-recommended screening

CANCER STATUS

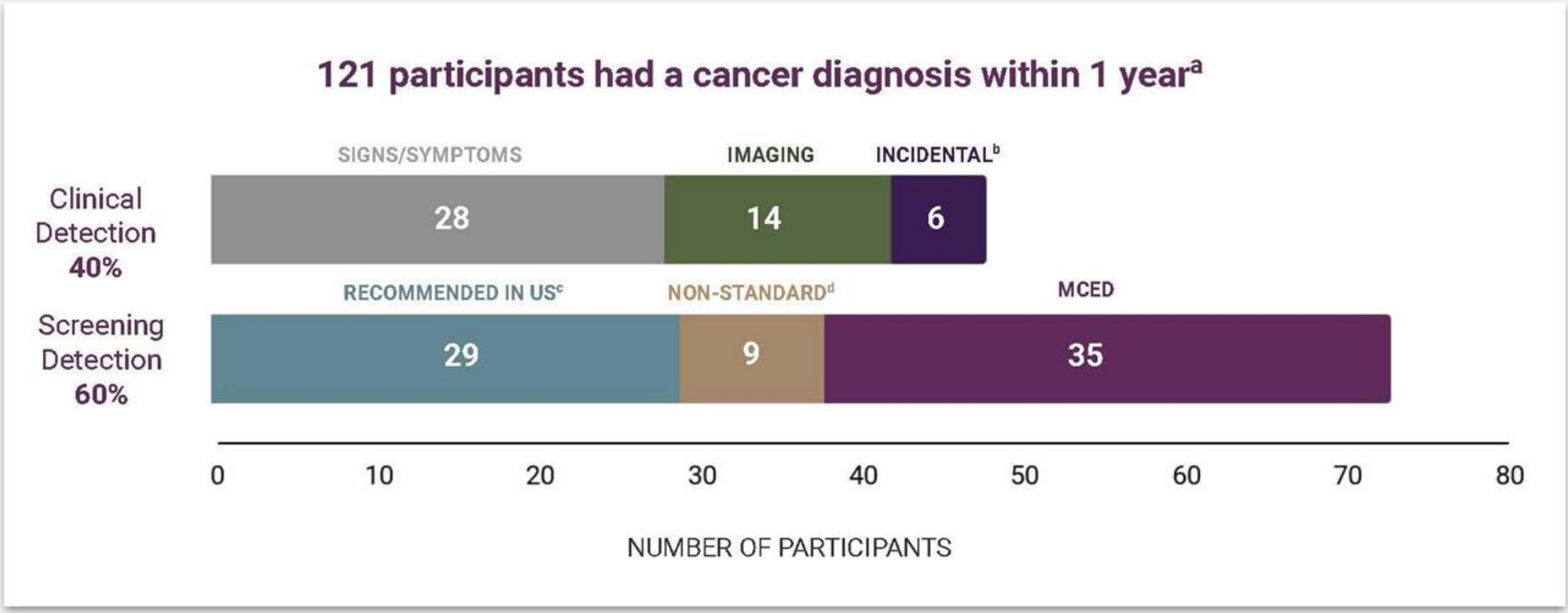
Assessed at 12 months

PRESPECIFIED REANALYSIS OF BLOOD SAMPLES WITH REFINED VERSION OF TEST

[a]Diagnostic resolution is defined as either (1) pathologic confirmation of an invasive or hematologic malignancy, or radiologic confirmation in the absence of pathology, or (2) completion of diagnostic evaluations without a cancer diagnosis.

Nadauld LD, et al. The PATHFINDER Study: Assessment of the Implementation of an Investigational Multicancer Early Detection Test into Clinical Practice. Cancers (Basel). 2021;13(14):3501. doi: 10.3390/cancers1314350

Early MCED Doubled the Number of Cancers Detected With SOC Screening



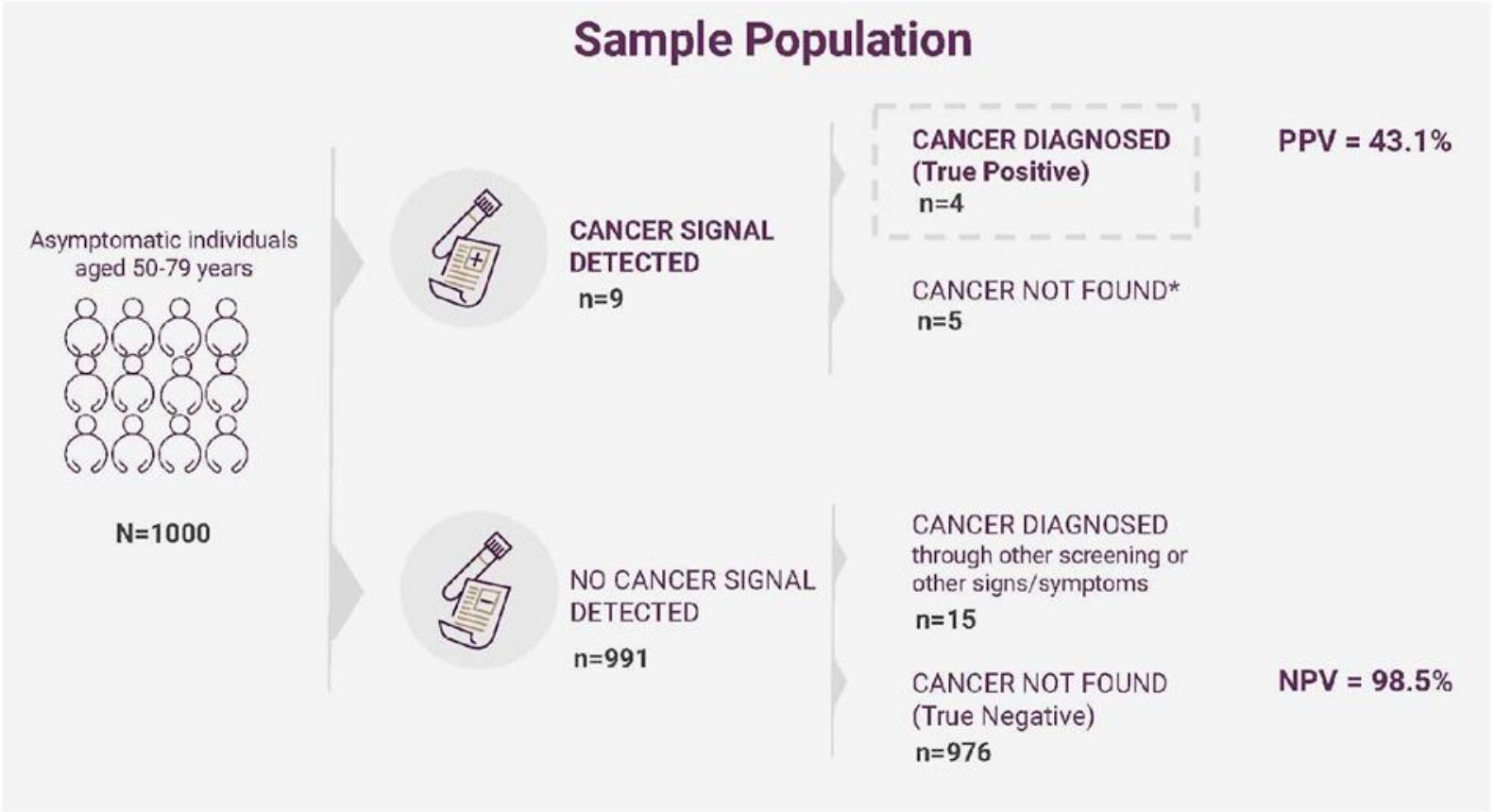
MCED, multi-cancer early detection. [a]Based on participants with cancer status assessment at the end of the study, [b]2 incidental findings, 2 change lab values, 1 surveillance of prior cancer, 1 follow-up after MGUS diagnosis. [c]breast, cervical, colorectal, lung, and prostate cancer, [d]3 thyroid and 6 melanoma. Schrag D, et al. Presentation at European Society for Medical Oncology (ESMO) Congress; September 9-13, 2022.

PATHFINDER Refined MCED Positive Predictive Value (PPV)

Probability that a person with a "Cancer Signal Detected" MCED test result has cancer.

PPV
Positive Predictive Value

43.1%



MCED, multi-cancer early detection. In the PATHFINDER study, out of 6,578 participants tested with Galleri, 58 had a Cancer Signal Detected result. Of these, 25 had a cancer diagnosed. 25/58 = 43.1%. Schrag D, et al. Presentation at European Society for Medical Oncology (ESMO) Congress; September 9-13, 2022. *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

Consistent Test Performance in an Intended-Use Population

CCGA3
Clinical Validation Study[1,2]

0.5%	44%	89%
False-positive rate	Positive predictive value (modeled)	Cancer signal origin accuracy[1,2]

PATHFINDER
Confirmatory Intended Use Population Study[3]

0.5%	43.1%	88%
False-positive rate	Positive predictive value	Cancer signal origin accuracy*

1. Based on tissue of origin class assigned in 96% of cases where cancer was detected accuracy of top Cancer Signal Origin for true positive cancer participants with a Cancer Signal Detected., 2. Klein EA 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. doi: 10.1016/j.annonc.2021.05.806., 3. Schrag D et al. PATHFINDER: A Prospective Study of a Multi-Cancer Early Detection Blood Test. Presentation at European Society of Medical Oncology (ESMO) Congress September 9-13, 2022, Paris, France. *Accuracy of top two cancer signal origin prediction for true positive patients, Based on prespecified reanalysis of blood samples with Galleri test.

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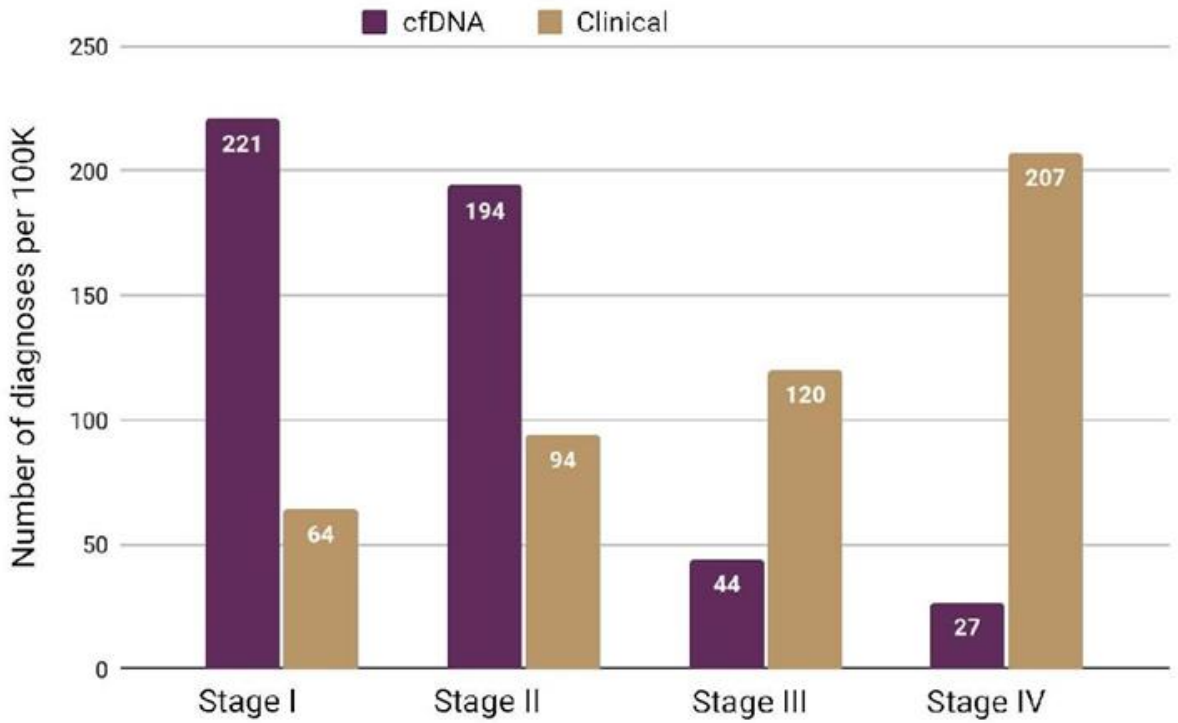
Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. NPJ Precis Oncol. 2018;2:23. doi: 10.1038/s41698- 018-0066-x.
Chen X, et al. Clin Cancer Res. 2021;27(15):4221-4229. doi: 10.1158/1078- 0432.CCR-21-0417.

Detect Cancer Early, When It Can Be Cured

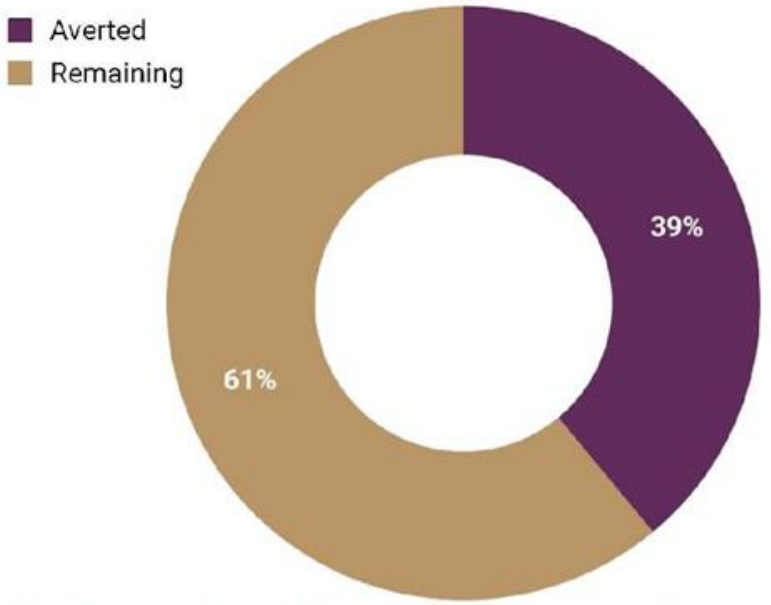
Expected Stage Shift in cfDNA-detectable Cancers

Modeled Data



Expected Proportion of Deaths Averted in Detected Cancers

Modeled Data



Resulting in a relative 26% mortality reduction in all-cancer mortality

Based on modeled data of MCED test in elevated risk population age 50–79 years.

Hubbell E et al. *Cancer Epidemiol Biomarkers Prev.* 2021;30:460-468. cfDNA, cell-free DNA; K, thousand; MCED, multi-cancer early detection; SEER, Surveillance, Epidemiology, and End Results. Based on data from SEER18 (2006-2017) in the United States, all cancer incidence. Adding the GRAIL's MCED test to usual care (based on modeled data). Assumes long-term screening results with optimized screening interval.

Important 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 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.