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GRAIL

Simultaneous Multi-Cancer Detection using a Cell-free Nucleic Acid Assay

Early Detection Research Network
June 2020

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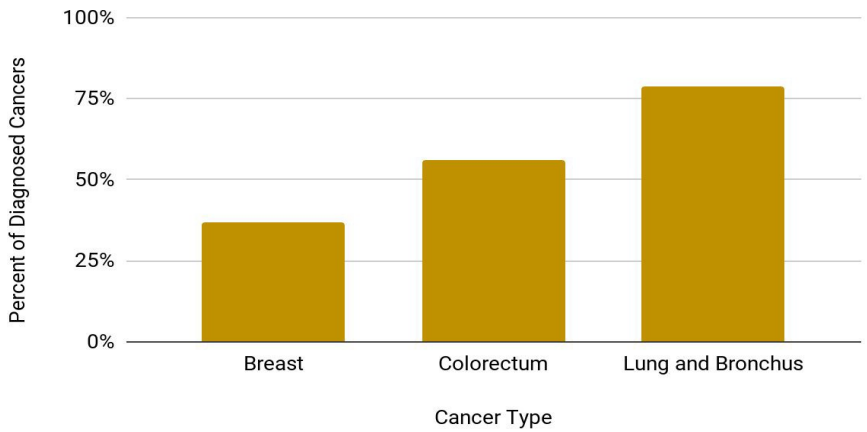
Many Cancers Are Detected Too Late

CANCERS WITH REGIONAL OR DISTANT METASTASES AT DIAGNOSIS[1]

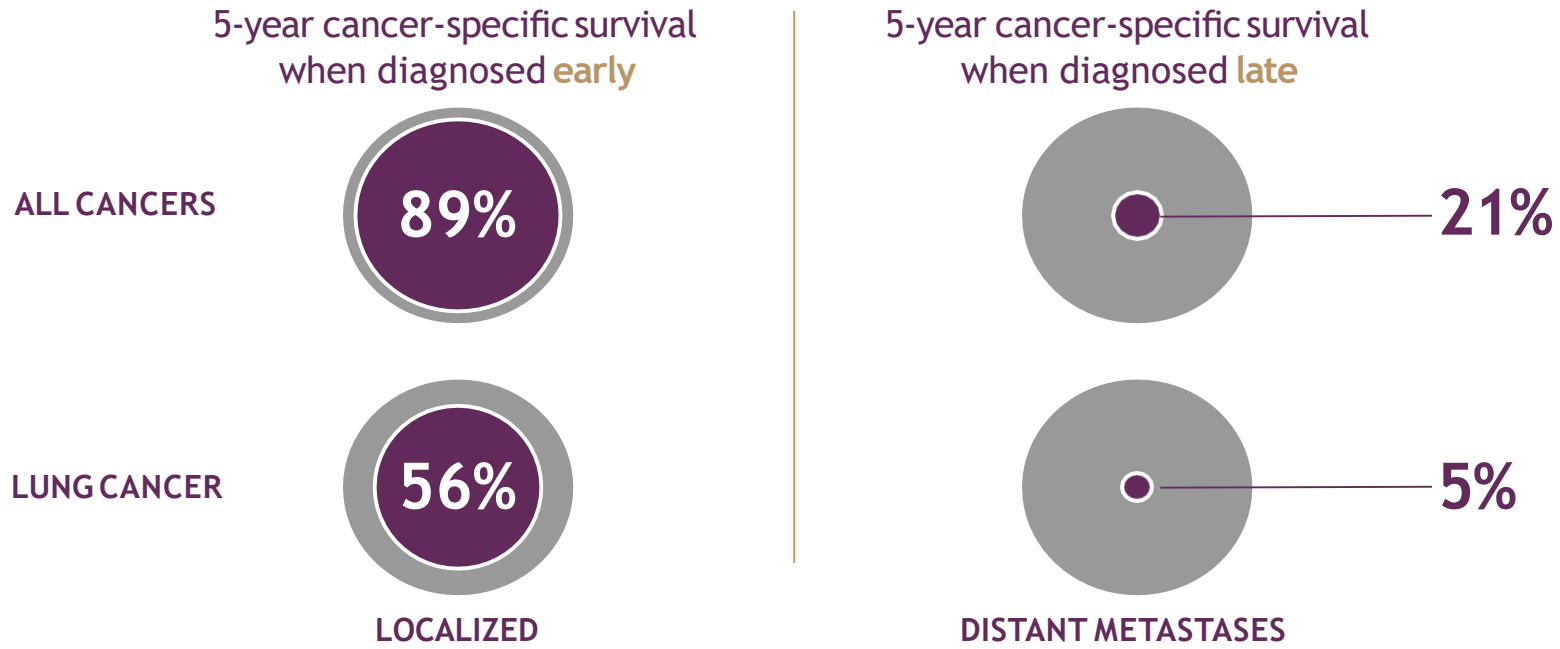


Treatment of metastatic cancer can be up to **2 times more costly** than treatment of nonmetastatic cancer[2]

[1]Siegel RL, et al. *CA Cancer J Clin*. 2018;68(1):7-30.

[2] Based on stage II and stage IV breast, colorectal, and lung cancer, and metastatic/non-metastatic pancreatic cancer: Banegas MO, et al. *J Natl Compr Canc Netw.* 2018;16(4):402-410, and Byfield S, et al. *J Med Econ.* 2013;16(12):1379-1386.

Early Diagnosis Can Dramatically Improve Cancer Survival



Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2018 Sub. Includes persons aged 50-79 diagnosed 2006-2015 "Early/Localized" includes invasive localized tumors that have not spread beyond organ of origin, "Late/Metastasized" includes invasive cancers that have metastasized beyond the organ of origin to other parts of the body. Noone AM, Howlader N, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER website April 2018.

Significant Challenges Exist for Single Cancer Screening

Cancer Type	Prevalence (%)	USPSTF Recommended Screening	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Compliance With Recommended Screening (%)
Breast[1]	0.35	Biennial mammography, women ages 55–79	87	89	4.4	72
Cervical[2]	1.5	Triennial cytology or quinquennial cytology/HPV test, women ages 21–65	93	94	19	83
Colorectal[3]	0.12	Colonoscopy	93	100	*Gold standard*	62
		Stool-based screening (FIT)	88	91	1.2	68
Lung[4]	0.18 (high risk: 1.1)	Annual low-dose CT for high-risk persons ages 55–80*	85	87	3.8	<5

*Recommendation for lung screening limited to high-risk smoking population, which accounts for less than 30% of all lung cancers.

CT, computed tomography; FIT, fecal immunochemical test; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.

[1]USPSTF. 2016. Lehman, et al. *Radiology.* 2017;283(1):49-58. White, et al. *Morbidity and Mortality Weekly Report.* 2017;66(8 [March]):201-206. [2]Polman, et al. *Lancet Oncology.* 2019;229-238. Cervical intraepithelial neoplasm 2 or greater (CIN2+). [3]USPSTF. 2017. United States Food and Drug Administration Premarket Approval P130017. Accessed March 26, 2019. White, et al. Morbidity and Mortality Weekly Report. 2017;66(8 [March]):201-206. United States Food and Drug Administration Premarket Approval P130017. Accessed March 26, 2019. Cologuard Test. Available from www.cologuardtest.com/hcp/crc-screening-redefined. Accessed March 26, 2019. [4]Humphrey, et al. *Ann Intern Med.* 159(6 [Sept]). Church, et al. *N Engl J Med.* 2013;368:1980-1991. Ahmedin, et al. *JAMA Oncol.* 2017;3(Sept):1278-1281.

Cumulative False Positive Rate From Single-Cancer Screening

Existing paradigms are associated with a high cumulative false positive rate

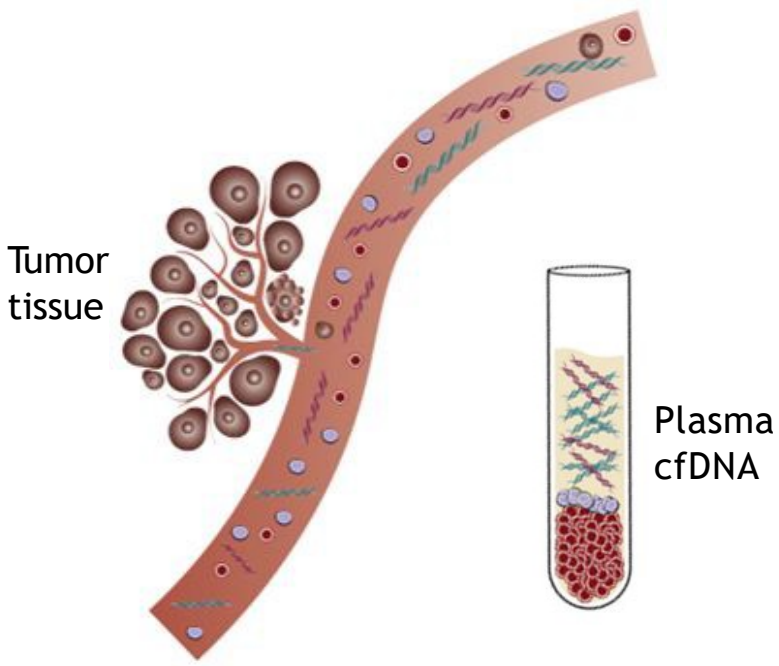
- FPRs of multiple single-cancer screening tests in an individual are additive
- A 60-year-old female with a history of smoking screened for 4 types of cancer would have a 37% false positive rate (FPR)
  - 10% FPR from mammography
  - 13.4% FPR from stool-based colon cancer screening
  - 7.4% FPR from cervical cancer screening
  - 12.8% FPR from low-dose computed tomography
- Each false positive would require follow-up tests or interventions with attendant risks
- These risks are not well understood at the population level because current paradigms only evaluate one cancer at a time
- These data underscore the need and rationale for a multi-cancer approach to early cancer detection

Evaluation Criteria for a Multi-Cancer Early Detection Test

- Identifies most types of cancer, the majority of which are deadly
- Localizes the tissue of origin to efficiently direct a diagnostic work-up
- Simple and easy access to maximize compliance
- Very low false positive rate leading to high positive predictive value to optimize safety
- Optimizes public health benefit by screening individuals >50 years old
- Balances sensitivity and specificity to optimize overall cancer detection and public health benefit
- Avoids overdiagnosis by preferentially detecting lethal cancers
- Validated by robust population-scale clinical studies

Tracking Down Cancer in Blood

Tumors shed nucleic acids into blood and other body fluids, carrying cancer-specific information



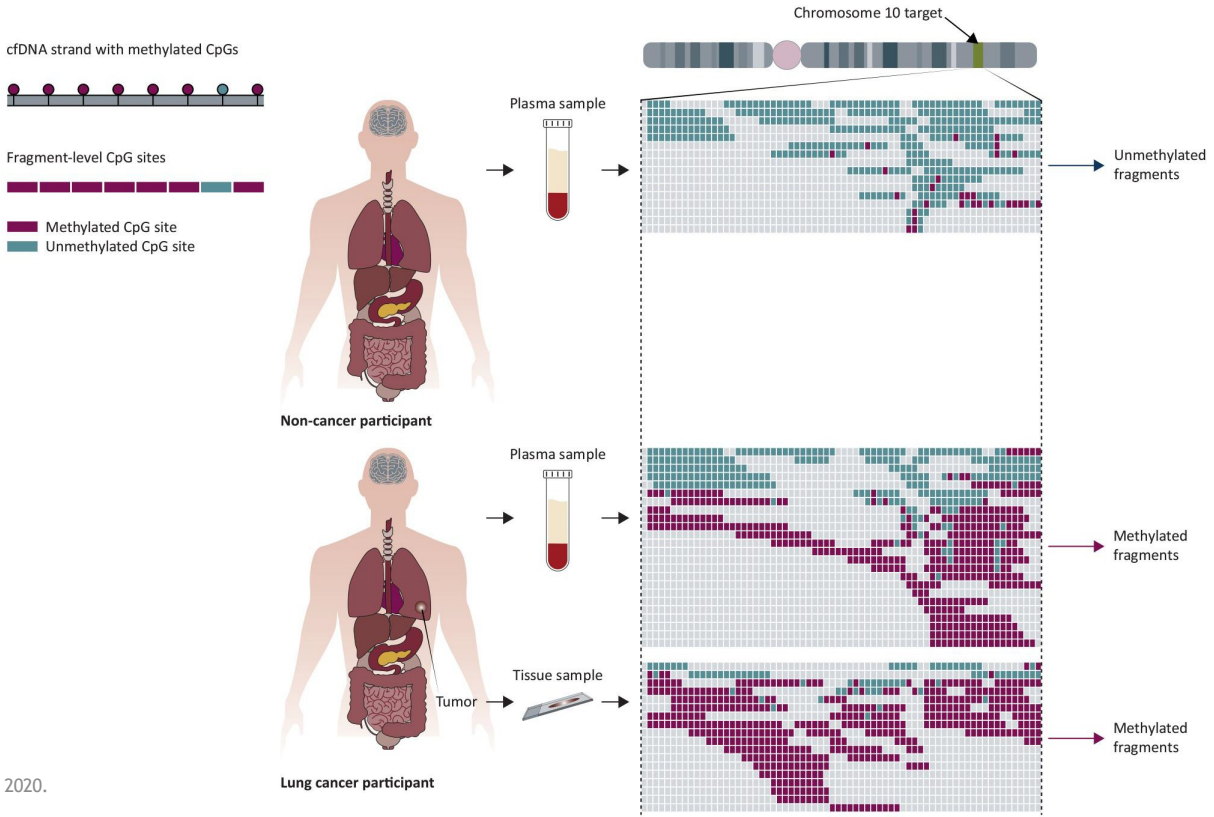
GRAIL compared test performance for 3 types of hallmarks of cancer in blood

- Mutations (single base changes)
- Chromosome alterations (copy number)
- DNA methylation patterns (chemical modification)

On the basis of results from CCGA substudy 1, DNA methylation analysis was selected for further development

cfDNA, cell-free DNA.
Figure from Liu MC, et al. *Ann Oncol*. 2020. DOI:10.1016/j.annonc.2020.02.011.

Methylation Biology Differentiates Cancer From Non-Cancer

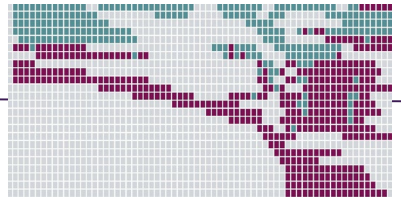


cfDNA, cell-free DNA.
Figure from Liu MC, et al. *Ann Oncol*. 2020.
DOI: 10.1016/j.annonc.2020.02.011.

Machine-Learning Classifiers Detect Cancer and Localize TOO

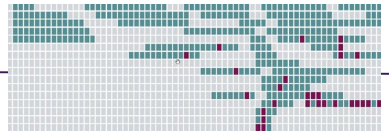
Largest known methylation sequencing database developed in CCGA study

~4,000 CCGA cancer samples
cfDNA methylation data from participants with cancer (20+ types, early + late stage)



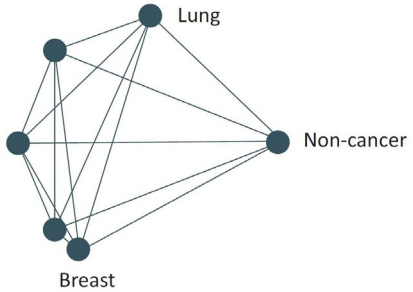
~2,000 CCGA non-cancer samples
cfDNA methylation data from healthy individuals and those with non-cancer conditions (eg, metabolic, hematologic, inflammatory, auto-immune diseases)

Frequency matched by age and gender in CCGA substudy 1



Public Sequence Data
Cancer (TCGA)
Oncoviruses

Machine-Learning Classifier



Target Regions (panel design)

Binary Classification (cancer/non-cancer)

Multi-class Classification (TOO localization)

CCGA, Circulating Cell-free Genome Atlas study (NCT02889978); cfDNA, cell-free DNA; TCGA, The Cancer Genome Atlas; TOO, tissue of origin..

Characteristics of Targeted Methylation Panel

Approximately 100,000 genomic regions

Panel Version 1.0

	Size/Count
Targeted regions (Mb)	17.1
Probe regions covering target regions (Mb)	31.3
Probes (n)	1,121,325
Probe size (bp)	120 (60 bp overlap)
CpGs (n)	1,116,720

Number of CpGs

Probe	CpGs (n)
Hypo	363,033
Hyper	585,181
Binary	218,506
Total	1,116,720

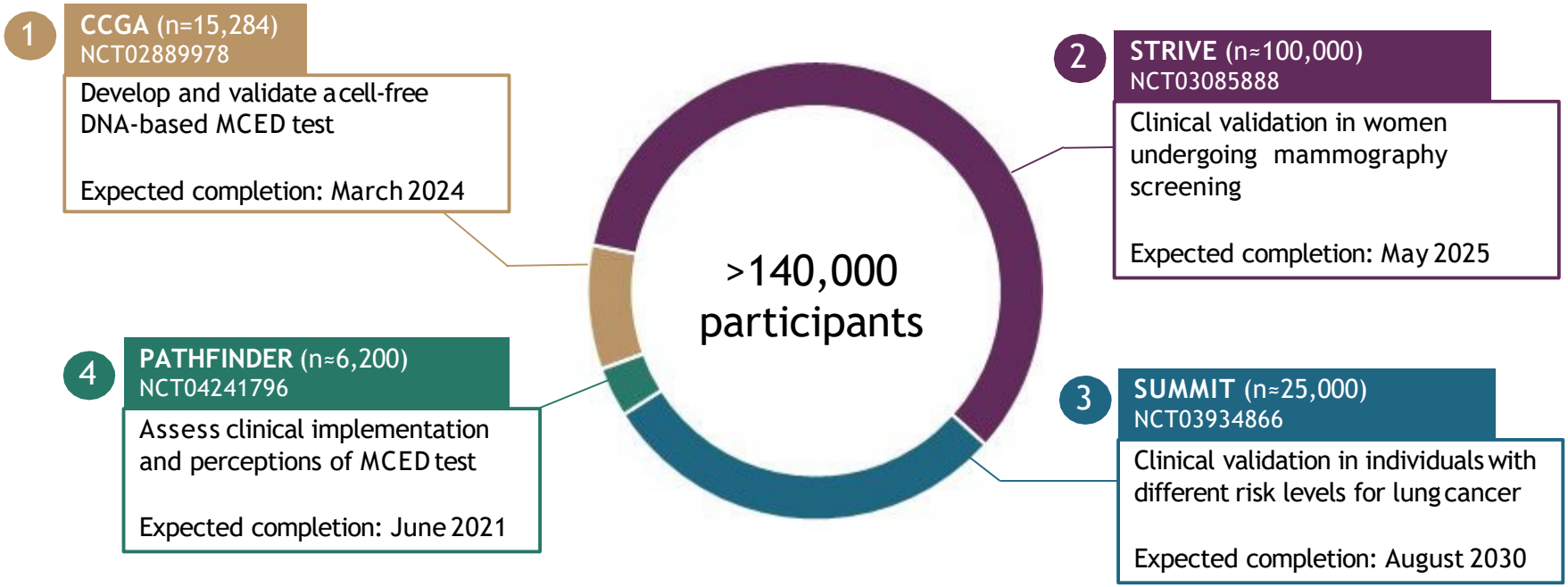
Type of Genomic Region

	CpGs (n)	%
1-5 kb upstream	193,818	17
Promoter	278,872	24
Introns	500,996	43
Exons	292,798	25
Intron/Exon Boundaries	247,752	21
5' UTR	134,144	11
Between genes	182,174	16
Not annotated	1,817	<1

UTR, untranslated region.

Clinical Development Program

Test development, validation, and implementation in population-scale studies



CCGA, Circulating Cell-free Genome Atlas; MCED, multi-cancer early detection.

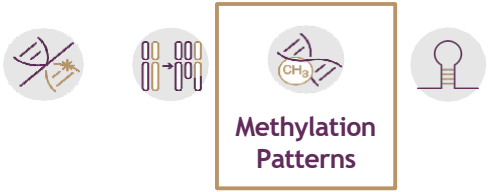
Circulating Cell-free Genome Atlas (CCGA) Study

Observational case-control study to develop and validate a cfDNA MCED test

CCGA

Study Objectives

Discovery



Training/Validation of machine-learning classifier to differentiate cancer vs non-cancer and localize TOO

Study Design

~15,000 participants
with/without cancer

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142 sites

Fully Enrolled

Blood samples
(all participants)

Tissue samples
(cancer only)

Follow-up for 5 years
(vital status, cancer status)

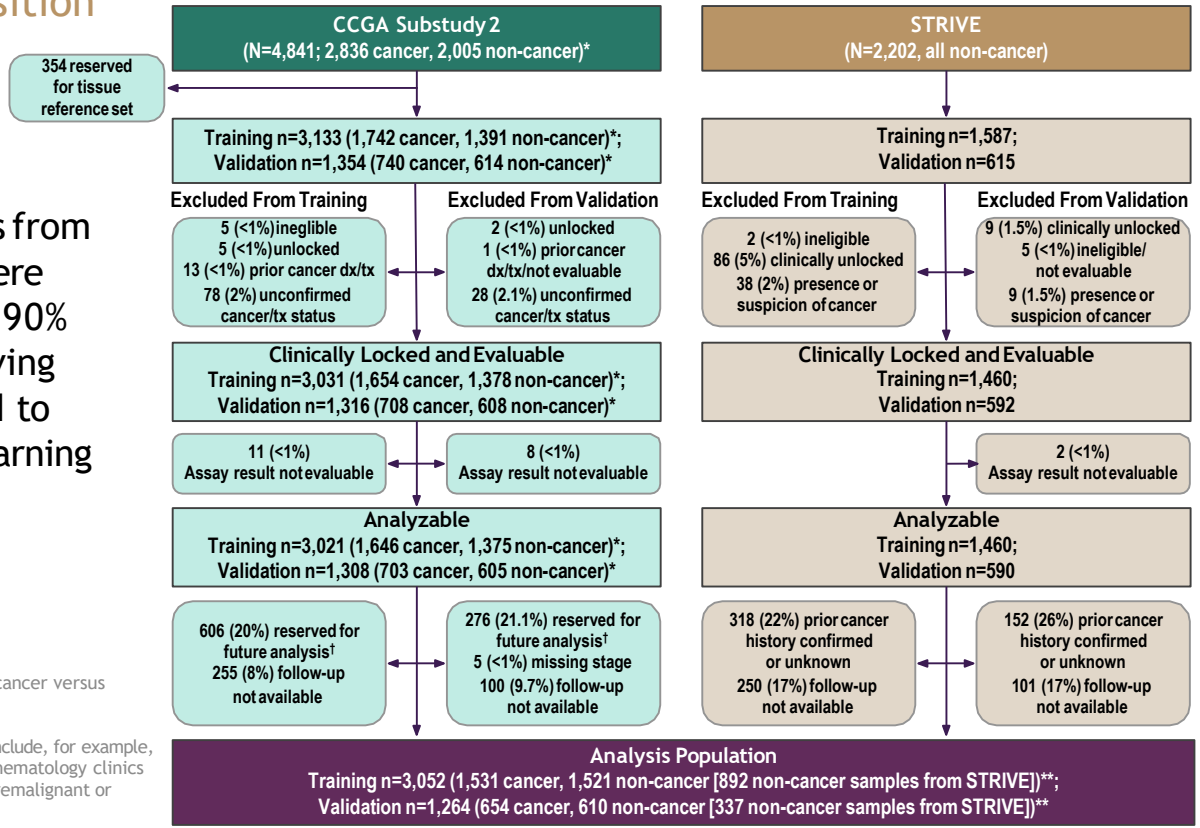
cfDNA, cell-free DNA; MCED, multi-cancer early detection test; TOO, tissue of origin.
Sources: ASCO 2019; based on an initial analysis of 2,301 participants from training phase. Liu MC, et al. *J Clin Oncol*. 2019;37(suppl; abstr 3049). ASCO 2018; Klein EA, et al. *J Clin Oncol*. 2018;36(15_suppl):12021. Liu MC, et al. *J Clin Oncol*. 2018;36(15 suppl):536.

Circulating Cell-free Genome Atlas (CCGA) Study

Participant Disposition

CCGA

Non-cancer samples from the STRIVE study were included to ensure >90% confidence of achieving >99% specificity and to train the machine-learning classifier



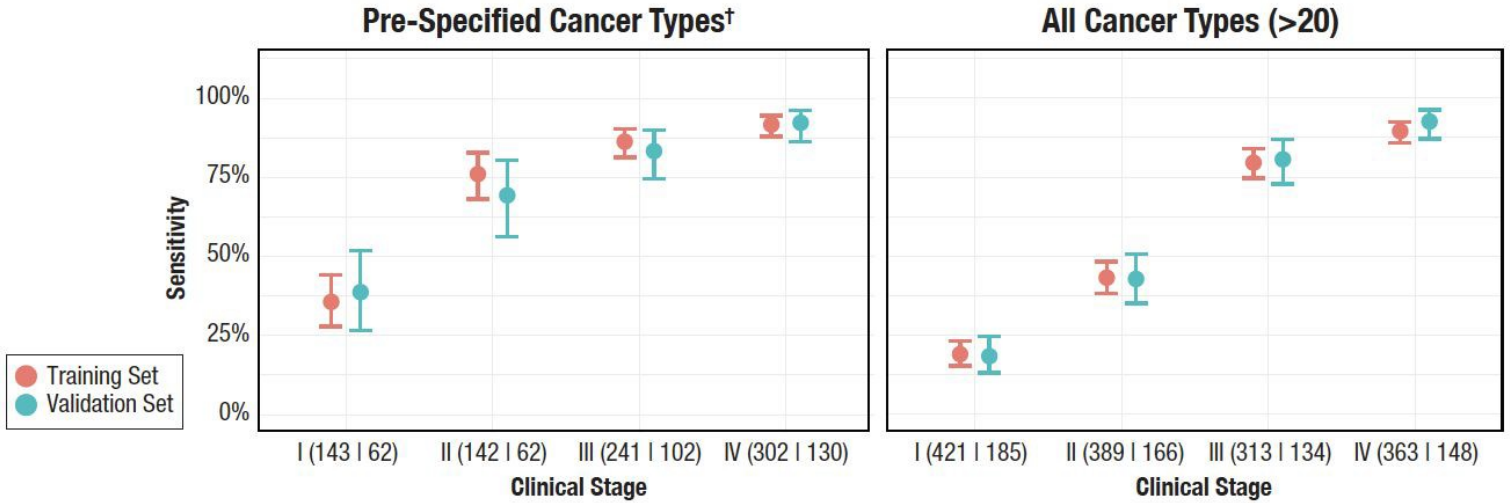
*At enrollment, prior to confirmation of cancer versus non-cancer status.
**Confirmed cancer/non-cancer.
†Samples reserved for future analysis include, for example, a cohort of participants recruited from hematology clinics meant to understand ctDNA signal in premalignant or other hematologic conditions.

Circulating Cell-free Genome Atlas (CCGA) Study

Test sensitivity and specificity

CCGA

- 76.4% (71.6-80.7%) sensitivity in pre-specified† cancer types (validationset)
- 54.9% (51.0-58.8%) overall sensitivity in >20 cancer types (validation set)
- Single fixed false positive rate (0.7%) across all cancer types

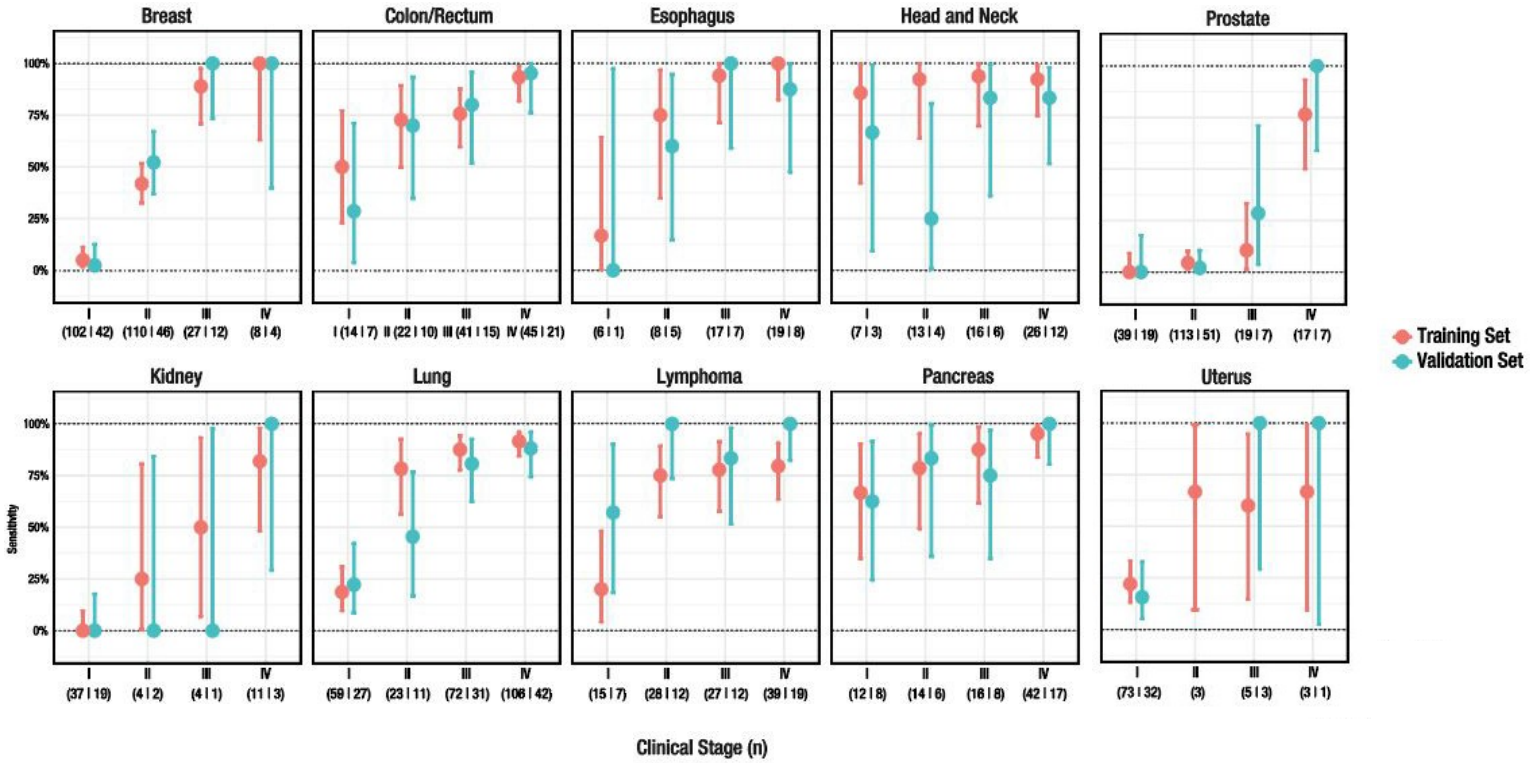


†Anus, bladder, colon/rectum, esophagus, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach. Plot excludes unstaged cancers.

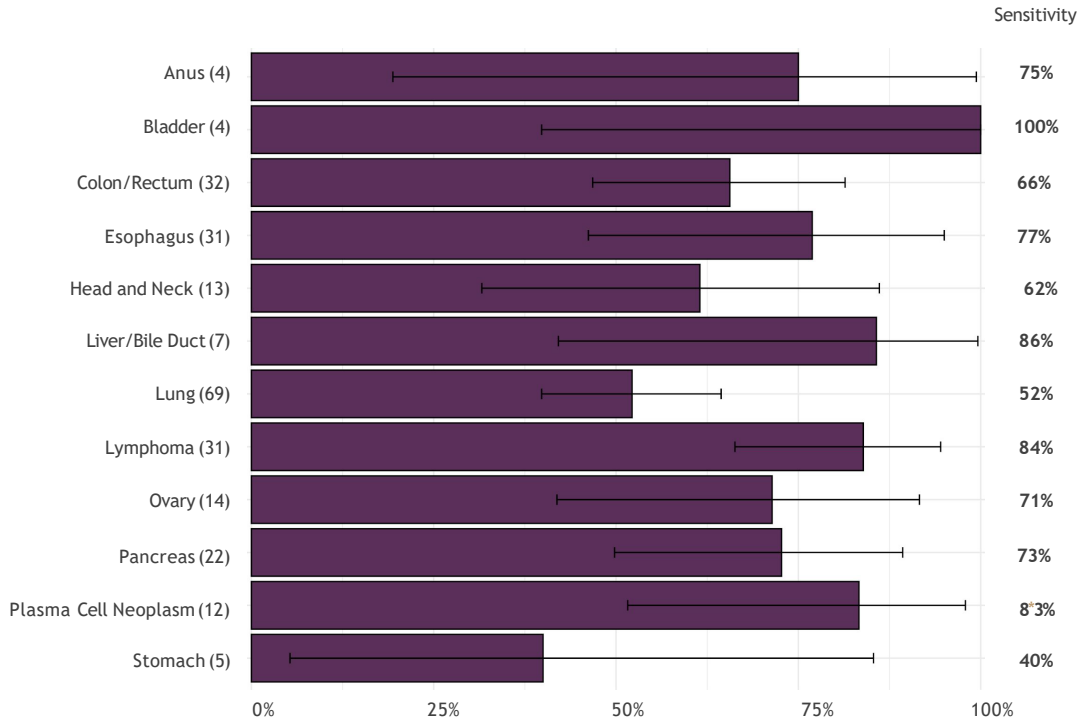
Circulating Cell-free Genome Atlas (CCGA) Study

Sensitivity by stage at 99.3% specificity

CCGA



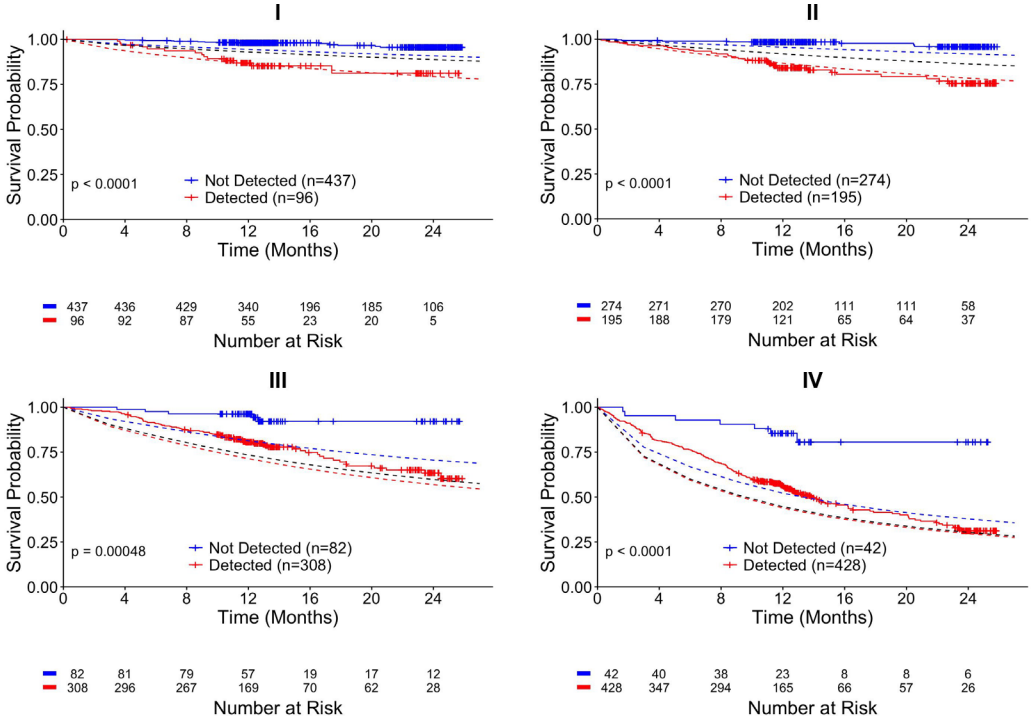
Strong detection at early stages (I-III) of pre-specified cancer types



[1] Leukemia includes chronic lymphocytic leukemia and hairy cell leukemia (unstaged)
Source: Liu MC (for Oxnard GR et al). Poster and oral presentation at: American Society of Clinical Oncology Breakthrough Meeting October 11, 2019: Bangkok, Thailand. Abstract 44.

Undetected Cancers Had Better Prognosis Than Expected* When Adjusted for Age, Cancer Type, and Tumor Stage

Impact is greater for stages III/IV



SEER adjusted for total CCGA2 population

SEER adjusted for CCGA2 not detected population

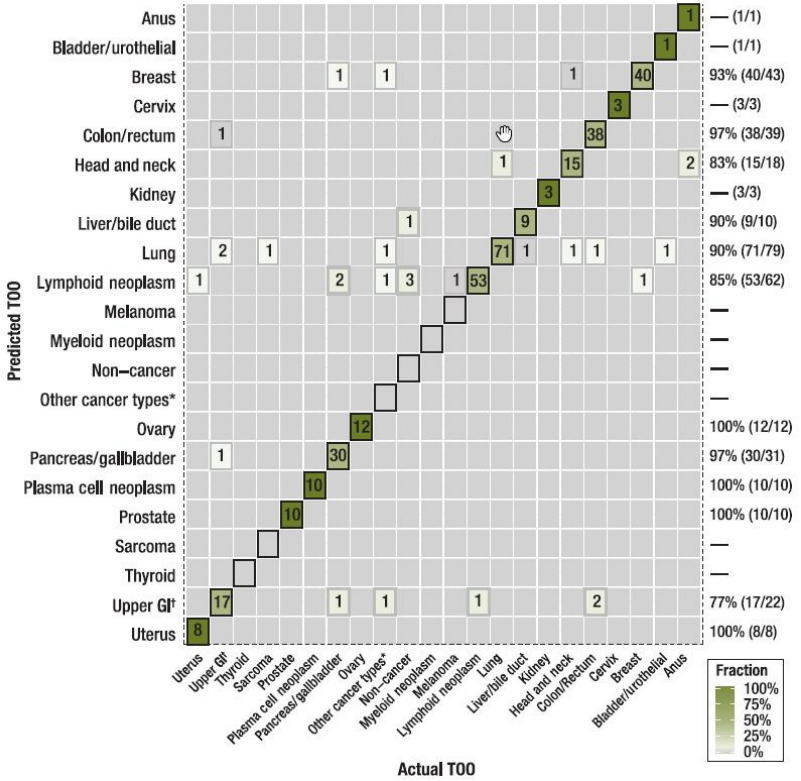
SEER adjusted for CCGA2 detected population

*SEER population adjusted for: age, clinical stage, and cancer type. Data on file.

Highly Accurate Tissue of Origin Localization

CCGA

- 96% of samples with assigned TOO (validation set)
- 93% of those calls were correct
- Highly precise localization to a single tissue site across >20 distinct tumor sites
- Consistent performance in the training set



TOO, tissue of origin.
*Other cancer types, training: mesothelioma, penis, pleura, small intestine, testis, and vulva, as well as one sample missing primary cancer type information. Other cancer types, validation: orbit, merkel cell carcinoma of the scalp, penis, testis, vagina, vulva.
†Upper GI: Esophagus and stomach.

Key Performance Features of Multi-Cancer Early Detection Test

Demonstrated in CCGA Sub-study 2 validation

> 50	Cancers detected
42%	Positive predictive value (modeled)
0.7%	False-positive rate
44%	Sensitivity stages I-III for all cancer
67%	Sensitivity stages I-III for prespecified cancers representing ⅔ of cancer mortality in US
93%	Rate tissue of origin predicted correctly[1]

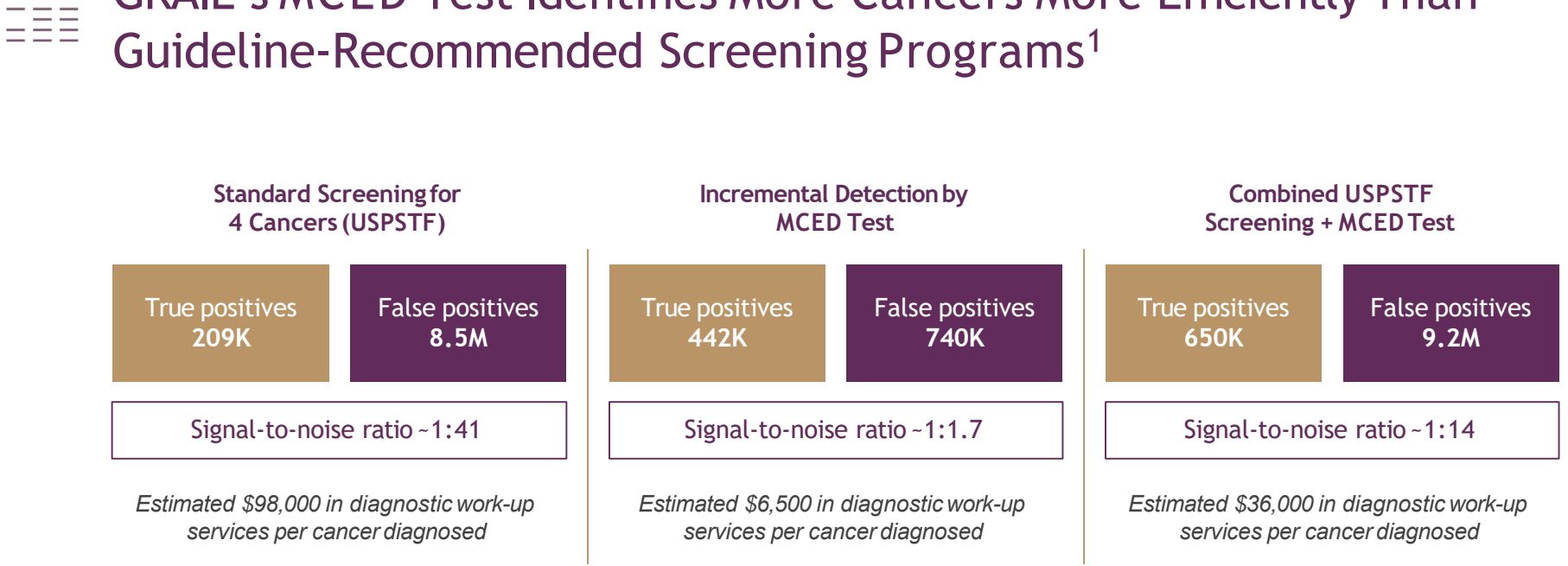
Anorectal
Bladder/urothelial
Esophageal
Gastric
Head and neck
Liver/bile-duct
Lymphoid neoplasm[2]
Melanoma
Myeloid neoplasm
Ovarian
Pancreas/gallbladder
Plasma cell neoplasm
Renal
Sarcoma
Seminoma
Skin
Testicular
Thyroid
Uterine
Vaginal
Vulva

Currently screened

Breast
Cervical
Colorectal
Lung
Prostate

CCGA, Circulating Cell-free Genome Atlas.
Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.
[1]Based on tissue of origin class assigned in 96% of cases where cancer was detected.
[2]Lymphoid neoplasm includes lymphoma and leukemia. Leukemia includes chronic lymphocytic leukemia and hairy cell leukemia.

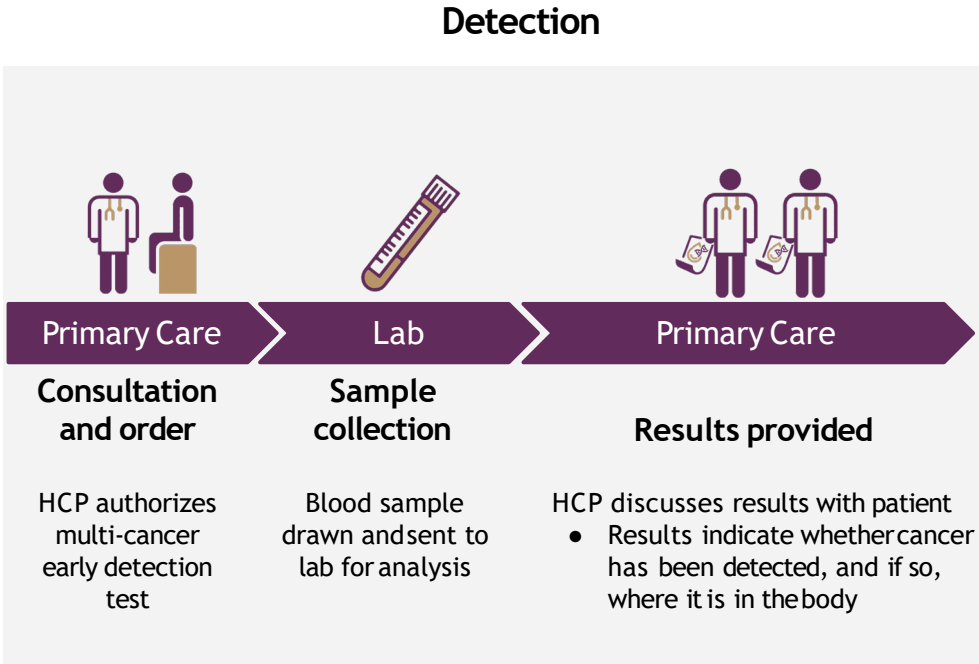
GRAIL's MCED Test Identifies More Cancers More Efficiently Than Guideline-Recommended Screening Programs[1]

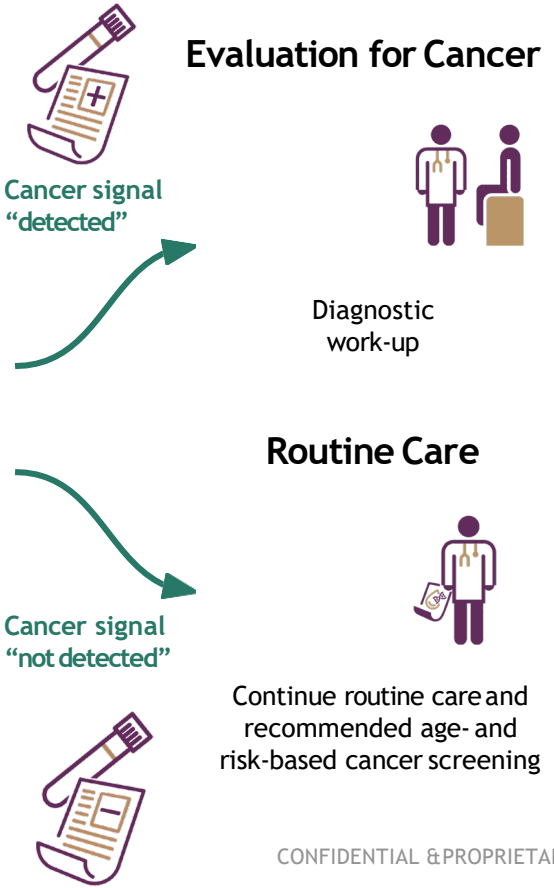


K, thousand; M, million; MCED, multi-cancer early detection test; USPSTF, United States Preventive Services Task Force.

[1]Based on Surveillance, Epidemiology, and End Results (SEER) incidence in individuals 50-79 years old who are screening eligible and have average risk of cancer. Data on file. Diagnostic work up based on National Comprehensive Cancer Network (NCCN) guidelines, with unit costs applied based on Medicare pricing and a commercial multiplier (2.3×). Assumes nationally-representative adherence to USPSTF A or B recommended screening (breast, colorectal, lung, and cervical cancer) and 100% screening with MCED test in the USPSTF-screened group.

A Multi-Cancer Early Detection Test Can Easily Be Integrated Into Existing Clinical Workflows





HCP, healthcare practitioner.

GRAIL

PATHFINDER

A return-of-results study to assess implementation in existing clinical workflows

PATH FINDER

Study Objectives

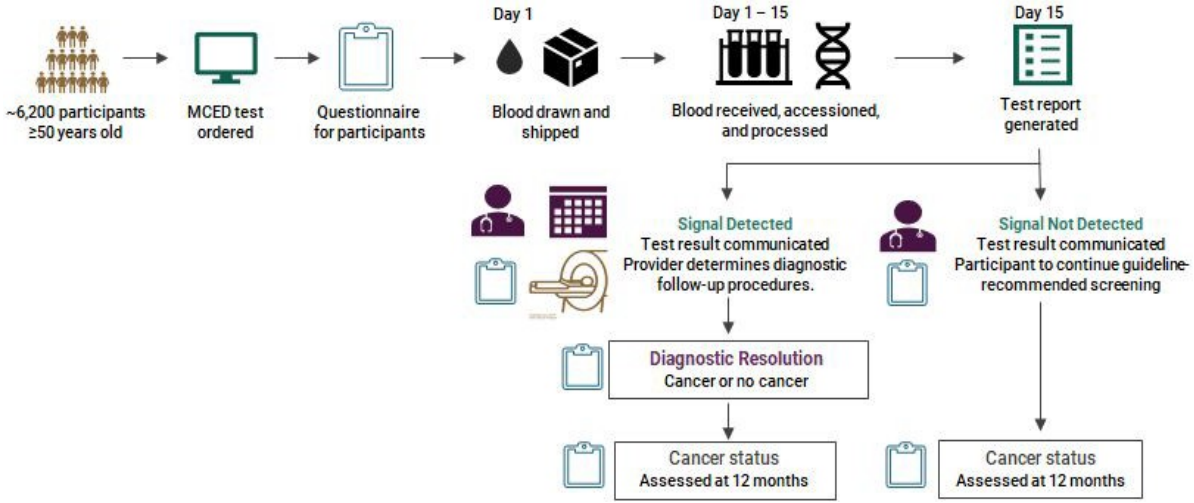
Primary

- Determine the extent of diagnostic testing needed to achieve diagnostic resolution[1] following a "signal detected" test result

Secondary

- To evaluate test performance
- To assess participants' perceptions about the MCED test

Study Design



MCED, multi-cancer early detection.

[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..

The GRAIL Approach: Cell-Free DNA-Based Multi-Cancer Early Detection

Circulating Cell-free Genome Atlas (CCGA) Sub-Study 2

- Targeted methylation analysis of cfDNA simultaneously detected >50 cancers, and accurately predicted their tissue of origin, including high-mortality cancers that lack screening paradigms
- Cancers were detected across all stages (stage I-III sensitivity: 43.9%; stage I-IV sensitivity: 54.9%) at a specificity of >99% and a single false positive rate of <1%, approaching that needed for population-scale multi-cancer early detection
- Tissue of origin can be predicted with >90% accuracy, which will be critical to help direct follow-up diagnostic evaluations
- These findings support continued development of this test for clinical use

cfDNA, cell-free DNA.

Liu MC *et al, Ann Oncol.* 2020;31(6):745-759. DOI:10.1016/j.annonc.2020.02.011.

5 minute Q&A

SC Chair/Co-Chair

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