GRAIL

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

Early Detection Research Network
Breast and Gynecologic Cancers

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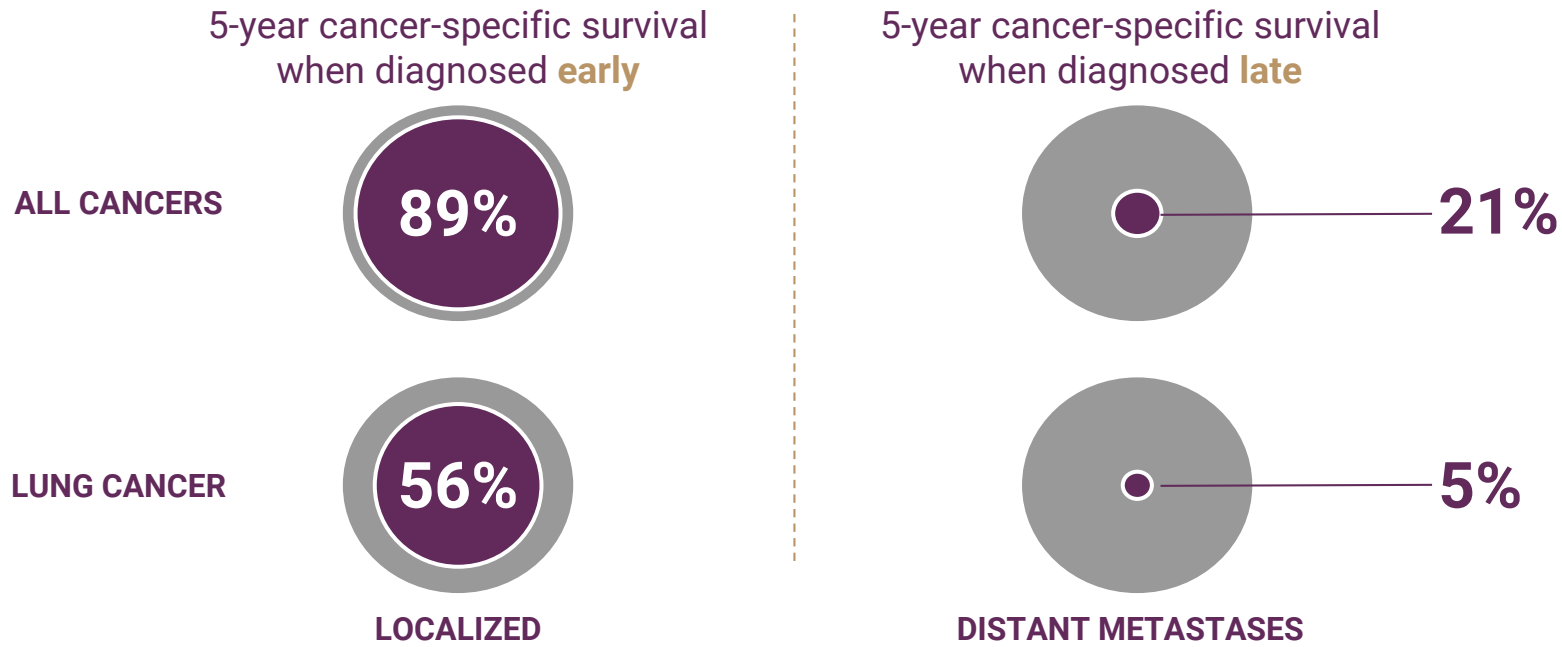
BRIAN ALLEN IS AN EMPLOYEE AND SHAREHOLDER OF GRAIL, INC.

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.

Requirements for multi-cancer tests for use at population-scale

Achieve benefits of early detection while minimizing harms:

- **Low false positives:** achieved through high specificity
- **Localizing ability:** identification of anatomic location to direct appropriate diagnostic work-up
- **Limited over-diagnosis:** preferential detection of clinically significant cancers

Demonstrate test performance, reproducibility, and generalizability to population:

Pre-specified statistical analyses to reduce bias

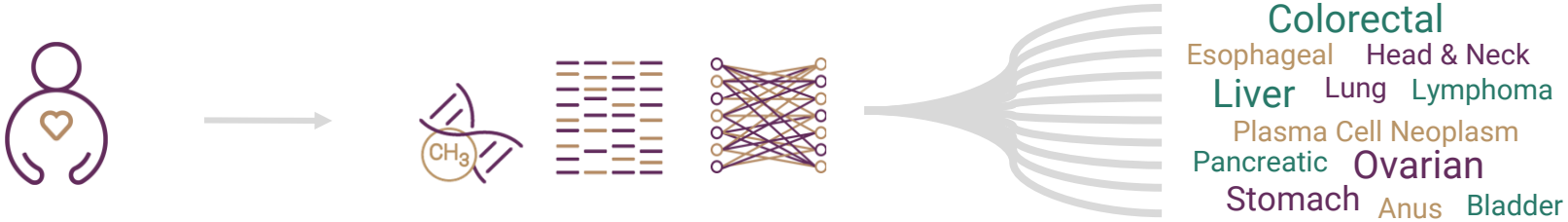
Inclusion of potentially confounding conditions to ensure specificity

Assessment of performance in an independent test set

Evaluation of performance in population scale studies with people with no known diagnosis

Multiple study sites for demographic diversity

GRAIL Is Developing a Multi-Cancer Early Detection Test



Single blood draw

Detect cancer signal with **targeted methylation sequencing** and **machine-learning** classifiers

If cancer signal is detected, **predict tissue of origin** to direct diagnostic work-up

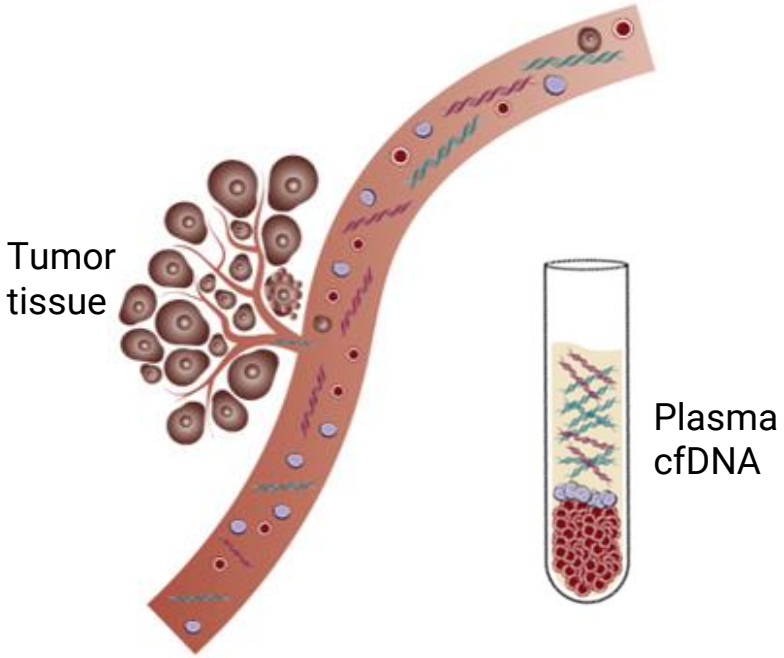
Test is **intended to complement guideline-recommended screening** (eg, mammography)

Designed to detect **many lethal cancers, including unscreened types** from a single blood draw

High specificity (~99%) minimizes false positives and unnecessary work-ups

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.

Clinical Development Program

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

1 **CCGA** (n=15,284)
NCT02889978

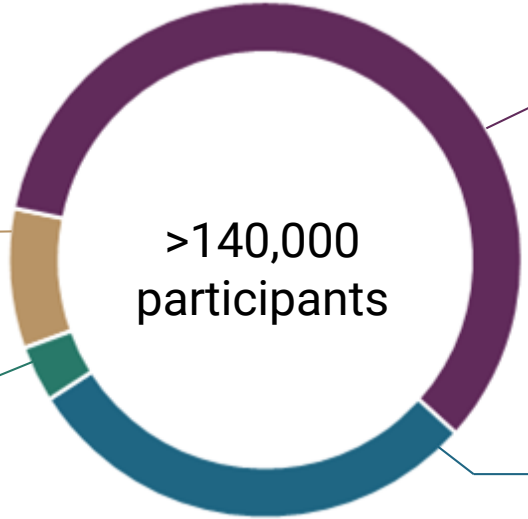
Develop and validate a cell-free DNA-based MCED test

Expected completion: March 2024

2 **STRIVE** (n≈100,000)
NCT03085888

Clinical validation in women undergoing mammography screening

Expected completion: May 2025



3 **SUMMIT** (n≈25,000)
NCT03934866

Clinical validation in individuals with different risk levels for lung cancer

Expected completion: August 2030

4 **PATHFINDER** (n≈6,200)
NCT04241796

Assess clinical implementation and perceptions of MCED test

Expected completion: June 2021

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

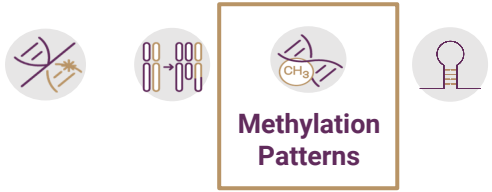
Circulating Cell-free Genome Atlas (CCGA) Study

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)

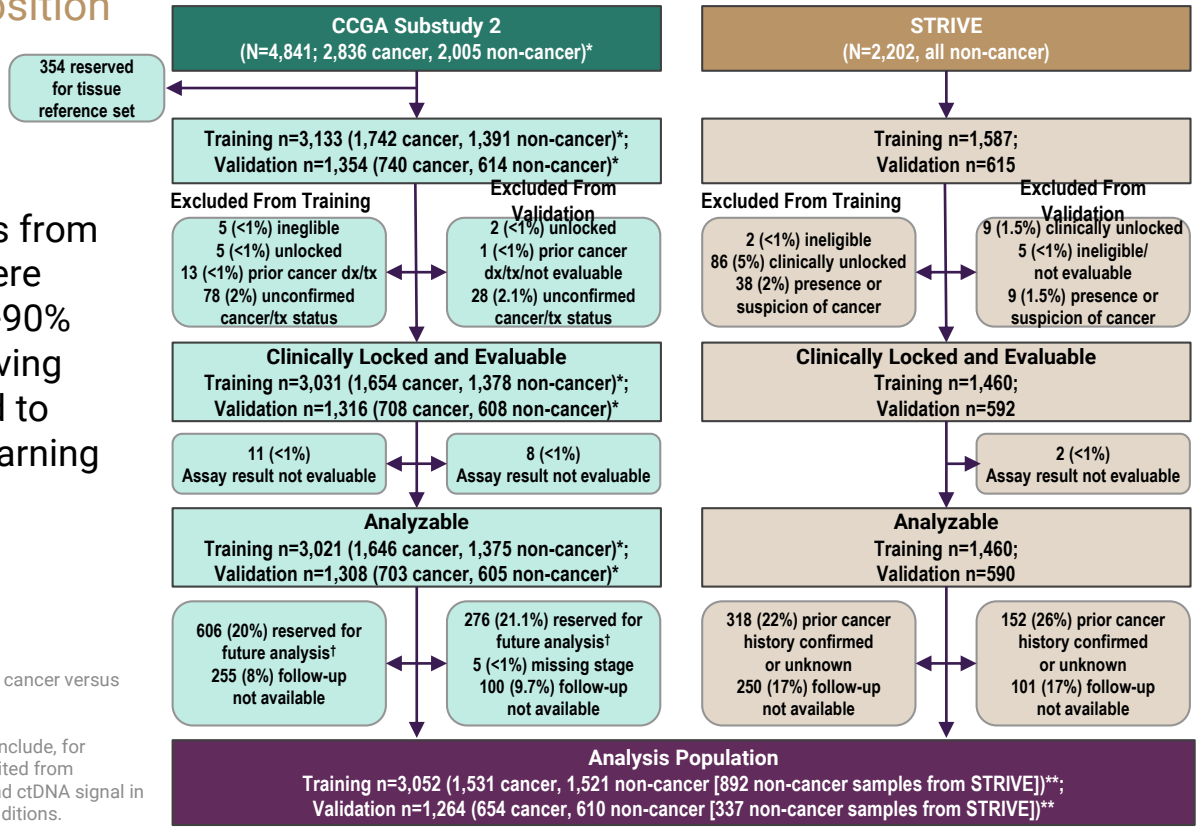
cfDNA, cell-free DNA; MCED, multi-cancer early detection test; TOO, tissue of origin.
Sources: ASCO 2019; based on an initial analysis of 2,301 participants from training phase. Liu MC, et al. *J Clin Oncol*. 2019;37(suppl; abstr 3049). ASCO 2018; Klein EA, et al. *J Clin Oncol*. 2018;36(15_suppl):12021.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



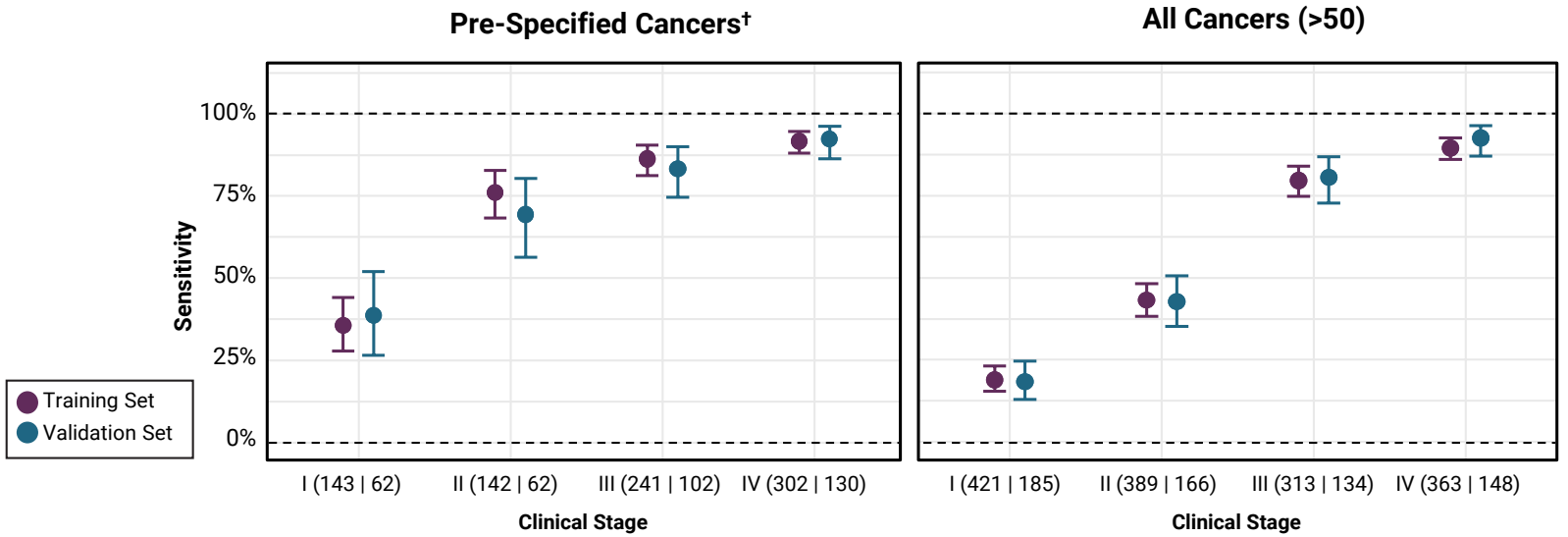
*At enrollment, prior to confirmation of cancer versus non-cancer status.
**Confirmed cancer/non-cancer.
†Samples reserved for future analysis include, for example, a cohort of participants recruited from hematology clinics meant to understand ctDNA signal in premalignant or other hematologic conditions.

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

Test sensitivity and specificity

CCGA

- 76.4% (71.6-80.7%) sensitivity in pre-specified† cancers (validation set)
- 54.9% (51.0-58.8%) overall sensitivity in >50 cancers (validation set)
- Single fixed false positive rate (0.7%) across all cancers

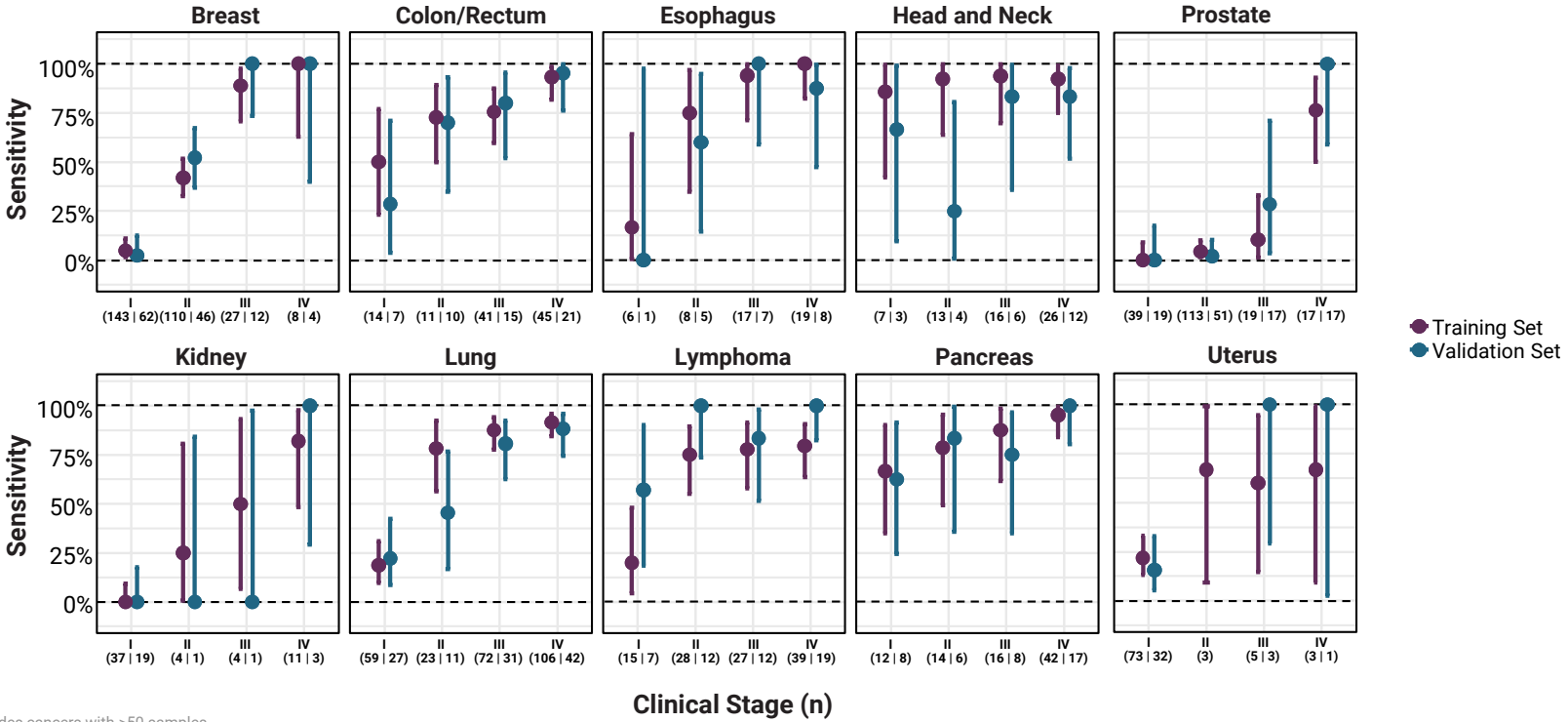


†Anus, bladder, colon/rectum, esophagus, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach.
Plot excludes unstaged cancers.

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

Sensitivity by stage at 99.3% specificity

CCGA

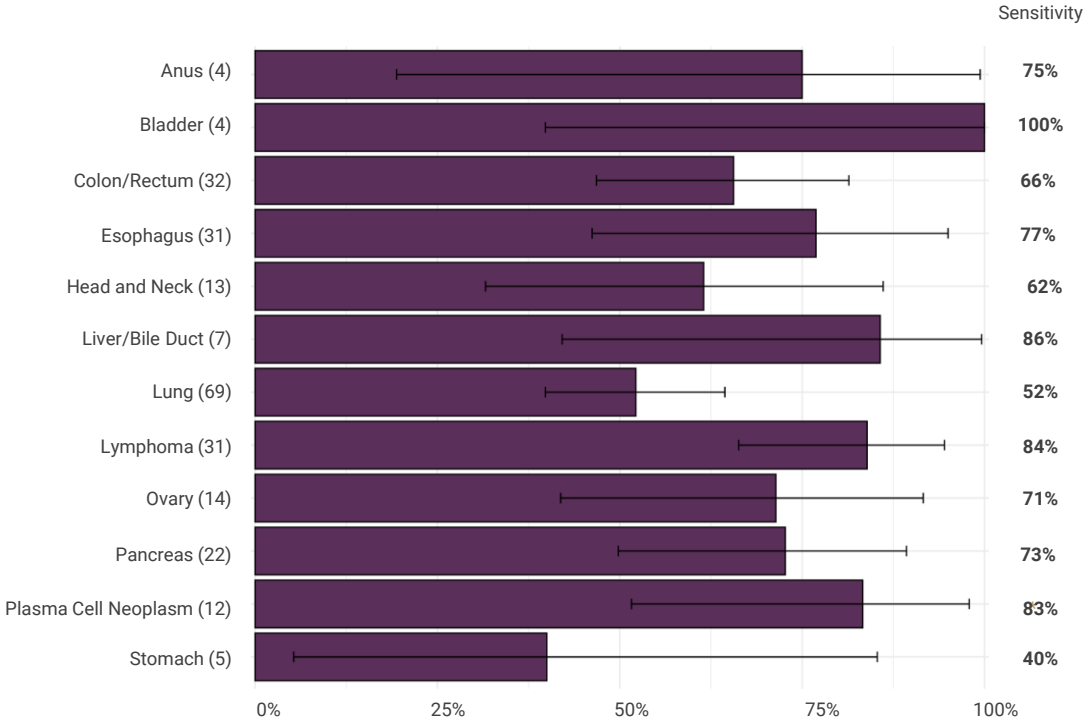


[a]Includes cancers with >50 samples.

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

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

CCGA



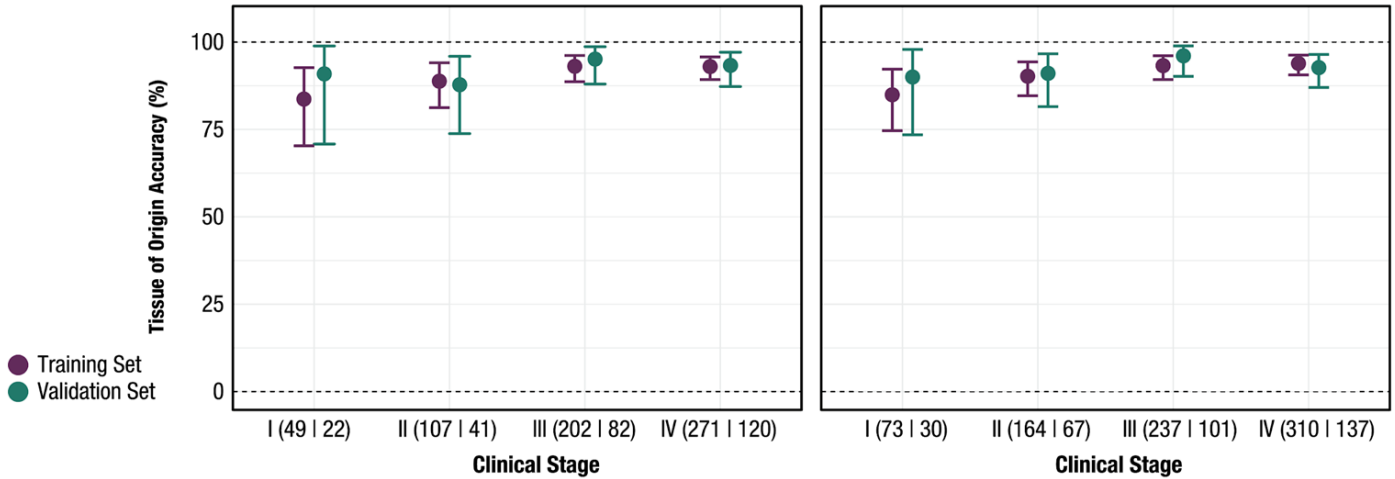
[1] Leukemia includes chronic lymphocytic leukemia and hairy cell leukemia (unstaged)
Source: Liu MC (for Oxnard GR et al). Poster and oral presentation at: American Society of Clinical Oncology Breakthrough Meeting October 11, 2019: Bangkok, Thailand. Abstract 44.

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

Tissue of Origin Accuracy

CCGA

- 96% of samples with assigned tissue of origin (validation set)
- 93% of those calls were correct
- Highly precise localization to a single tissue site across >50 distinct tumor sites
- Consistent performance in the training and validation sets



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

STRIVE: Fully enrolled longitudinal cohort study of women

CCGA | **STRIVE** | PATHFINDER | SUMMIT

~100,000 Women seeking mammography screening

Blood draw, mammogram

All participants - follow-up for 30 mo
Data collection including:
Cancer diagnosis, treatment, cancer specific mortality, overall survival through EMR and linkage to SEER registries for long term follow-up

Testing and analysis conducted according to the Statistical Analysis Plan using a case-cohort design

FPI: 02/28/2017 **Total Enrollment: 99,308 participants** **LPI: 11/5/2018**

Primary Objective: To evaluate the performance of the GRAIL multi-cancer test to detect invasive cancers (including hematologic malignancies)

Summary and conclusions

Cell-free DNA-based multi-cancer early detection is feasible

- Targeted methylation analysis of cfDNA simultaneously detected and localized >50 cancers, 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 localized 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
- GRAIL has established a population scale research plan to demonstrate clinical validity

cfDNA, cell-free DNA.

Liu MC *et al, Ann Oncol.* 2020. DOI:10.1016/j.annonc.2020.02.011