3071

Performance of a Targeted Methylation-Based Multi-Cancer Early Detection Test by Race/Ethnicity

American Society of Clinical Oncology (ASCO)
June 4-8, 2021

Wai Hong Wilson Tang,[1] Habte Yimer,[2] Mohan Tummala,[3] Spencer Shao,[4] Gina Chung,[5] Jessica Clement,[6] Jingjing Gao,[7] Earl Hubbell,[7] Kathryn N Kurtzman,[7] Charles Swanton,[8,9] and Lewis Roberts[10]
[1]Cleveland Clinic, Cleveland, OH, USA; [2]The U.S. Oncology Network, Tyler, TX, USA; [3]Mercy Clinic Cancer Center, Springfield, OH, USA; [4]Compass Oncology, Portland, OR, USA; [5]The Christ Hospital Health Network, Cincinnati, OH, USA
[6]Hartford HealthCare Cancer Institute, Hartford, CT, USA; [7]GRAIL, Inc., Menlo Park, CA, USA; [8,9]The Francis Crick Institute, London, UK and University College London Cancer Institute, London, UK; [10]Mayo Clinic, Rochester, MN, USA.

INTRODUCTION

- Disparities in cancer screening and outcomes among different demographic groups in the US are well documented.[1]
  - Racial/ethnic group disparities exist in the incidence, survival time, and ultimate mortality rates of a number of different cancers, with genetic, cultural, and socioeconomic differences between groups thought to be contributing factors.[2,3,4]
  - A particularly important factor in racial/ethnic cancer survival disparities is disease stage at diagnosis, suggesting advancements in early diagnosis that are widely accessible may reduce these disparities.[5]
- The Circulating Cell-free Genome Atlas study (CCGA; NCT02889978) demonstrated that a blood-based multi-cancer early detection (MCED) test analyzing plasma cell-free DNA (cfDNA) with machine learning could detect cancer signals across multiple cancer types and predict cancer signal origin.[6]
- Reported here are results of the final pre-specified CCGA validation substudy with a refined version of this MCED test planned for clinical implementation as a general multi-cancer screening tool.[7]

OBJECTIVE

- To explore performance among racial/ethnic groups in MCED cancer signal detection by evaluating findings stratified by race/ethnicity from the third and final CCGA validation substudy.

A MULTI-CANCER EARLY DETECTION TEST PERFORMED SIMILARLY ACROSS RACIAL/ETHNIC SUBGROUPS, SUPPORTING BROAD APPLICABILITY IN CLINICAL PRACTICE

Cancer Signal Detection

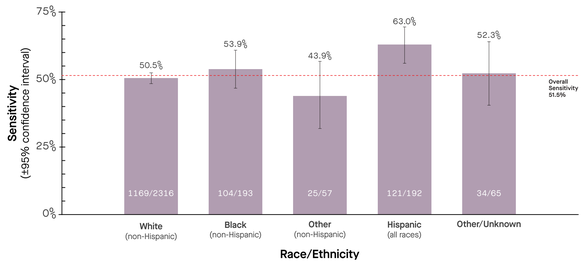
Specificity

- Overall specificity for cancer signal detection was 99.5% [1248/1254; 95% confidence interval: 99.0-99.8%].
- Specificity for cancer signal detection was similar across racial/ethnic groups with overlapping 95% confidence intervals:
  - White (non-Hispanic): 99.6% [992/996; 99.0-99.8%].
  - Black (non-Hispanic): 100.0% [85/85; 95.7-100.0%].
  - Other (non-Hispanic): 100.0% [33/33; 89.6-100.0%].
  - Hispanic (all races): 98.1% [101/103; 93.2-99.5%].
  - Other/Unknown: 100% [37/37; 90.6-100.0%].

Sensitivity

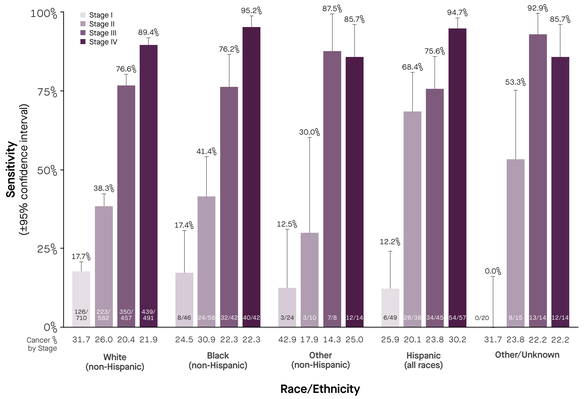
- Overall sensitivity for cancer signal detection was 51.5% [1453/2823; 49.6-53.3%].[7]
- Despite differences in cancer class and staging across racial/ethnic groups, sensitivity was generally comparable among racial/ethnic groups, ranging from 43.9% to 63.0% (**Figure 1**).

Figure 1. Overall Sensitivity of Cancer Signal Detection by Race/Ethnicity



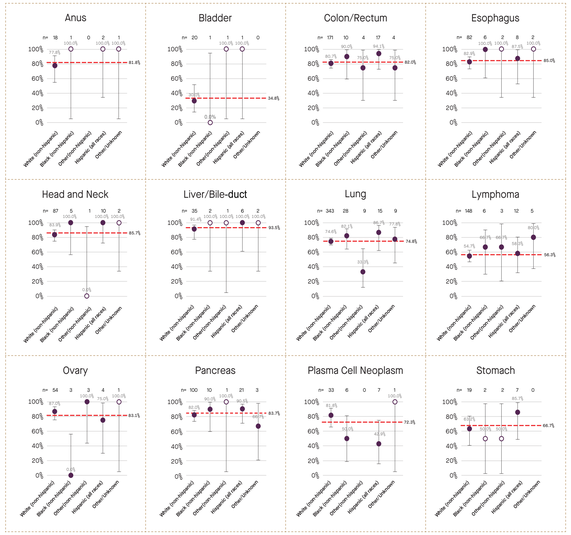
- For all racial/ethnic groups, sensitivity increased with clinical stage (with minor exceptions at Stage IV in two groups with small sample sizes; **Figure 2**).

Figure 2. Sensitivity of Cancer Signal Detection by Race/Ethnicity and Clinical Stage



- Apart from some groups with extremely small sample sizes, overall sensitivity was generally comparable among racial/ethnic groups in most of 12 pre-specified cancers that account for approximately two-thirds of annual U.S. cancer deaths[1] (**Figure 3**).
  - Sensitivity for lung cancer was lower in the Other (non-Hispanic) group than in other racial/ethnic groups, and sensitivity for plasma cell neoplasm was lower in the Black (non-Hispanic) and Hispanic (all races) groups than for the White (non-Hispanic) group, though descriptive comparisons are limited by small sample sizes for these groups; no statistical comparisons were made.

Figure 3. Sensitivity of Cancer Signal Detection by Cancer Class in 12 Pre-Specified Cancers by Race/Ethnicity



n, participants in each racial/ethnic group with specified cancer; open symbols indicate extremely small group size (n ≤2)
Dotted red lines indicate overall sensitivity for each cancer.
Two-sided 95% Wilson confidence intervals were calculated.

CONCLUSIONS

- In this large-scale, clinical validation substudy with pre-specified analyses, the MCED test demonstrated consistently high specificity regardless of race/ethnicity, and sensitivity of cancer signal detection was similar across racial/ethnic groups; minor differences may be explained by different stage and cancer distributions in groups.
- Sensitivity was generally comparable among racial/ethnic groups in most of 12 pre-specified cancers that account for nearly two-thirds of annual U.S. cancer deaths, though comparisons are limited due to small sample sizes for some groups.
- Taken together, these results demonstrate that this targeted methylation-based MCED test detected cancer signals across a broad range of cancers with high specificity that was generalizable across racial/ethnic populations, supporting the potential use of this blood-based MCED test on a population-wide scale as a complement to existing single-cancer screening tests.

References

1. Cancer Facts & Figures (2021) [Internet]. American Cancer Society; Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf.
2. Ellis L et al. Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. *J Clin Oncol.* 2018;36:25-33.
3. Zavala VA et al. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer.* 2021;124:315-332.
4. Cancer Disparities. National Cancer Institute. URL: https://www.cancer.gov/about-cancer/understanding/disparities#ui-id-2. Accessed: 4/1/2021.
5. Esnaola NF and Ford ME. Racial differences and disparities in cancer care and outcomes: where's the rub? *Surg Oncol Clin N Am.* 2012;21:417-37.
6. Liu MC et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol.* 2020;31(6):745-759.
7. Klein E et al. Clinical Validation of a Targeted Methylation-Based Multi-Cancer Early Detection Test. Presented at the annual meeting of the American Association for Cancer Research. April 10-15, 2021. www.aacr.org/aacr2021. Abstract #LB103 (2021).

Disclosures

Study funded by GRAIL, Inc. **JG**, **EH**, and **KNK** are current or former employees of GRAIL, Inc., with equity in the company. All financial relationships disclosed at abstract submission. In addition to consulting relationships with GRAIL, Inc. (**CS**, **LR**), financial disclosures related to stock ownership are: **CS** (Epic Biosciences, Apogen Biotech, GRAIL, Inc., Achilles Therapeutics).

Acknowledgements

Writing and editorial assistance provided by Prescott Medical Communications Group (Chicago, IL).

METHODS

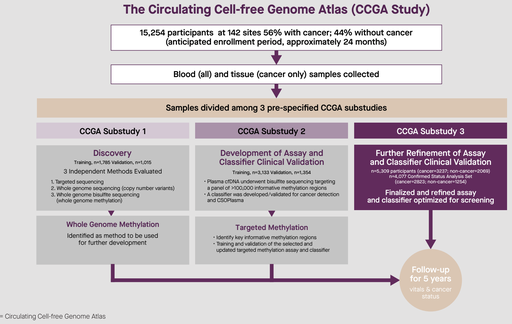
Study Design

- CCGA is a prospective, multicenter, case-control, observational study with longitudinal follow-up that enrolled 15254 participants (8584 with cancer; 6670 without cancer) from 142 sites in North America between August 2016-February 2019 (**Figure 4**).
  - Participants eligible for the cancer arm included adults (≥20 years of age) diagnosed with cancer and/or who were scheduled to undergo biopsy and/or surgical resection for known or highly suspected malignancy.
- CCGA was divided into three pre-specified substudies (**Figure 4**); in this pre-specified exploratory analysis from the third substudy, test performance for cancer signal detection (specificity, overall sensitivity, sensitivity by cancer class, and sensitivity by clinical stage) was evaluated among racial/ethnic groups.
- The groups stratified by race/ethnicity were White non-Hispanic, Black non-Hispanic, Other non-Hispanic (including but not limited to Asian, Native Hawaiian, Pacific Islander, American Indian, Alaska Native), Hispanic (all races), and Other/Unknown.
- Importantly, this pre-specified, exploratory analysis was not powered to detect statistical differences between racial/ethnic groups.

Targeted Methylation Assay

- Plasma cfDNA (up to 75 ng) was subjected to customized bisulfite conversion reaction prepared as a dual indexed sequencing library, and enriched using standard hybridization capture conditions, for 150-bp paired-end sequencing on the Illumina NovaSeq.

Figure 4. Study Design



CCGA = Circulating Cell-free Genome Atlas

SUPPORTING DATA

Participant Disposition

- A total of 5309 participants were included in the third and final CCGA validation substudy (enrolled as cancer, n=3237; enrolled as non-cancer, n=2069; missing enrollment status, n=3).
- Of these, 4077 (cancer, n=2823; non-cancer with non-cancer status confirmed at year one, n=1254) were included in the Confirmed Status Analysis Set.
- The most common reasons for exclusion were incomplete year-one follow-up for non-cancer participants (n=324), presence of non-malignant conditions at enrollment (n=283), and unconfirmed cancer or treatment status at blood draw (n=171).

Participant Demographics and Baseline Characteristics

- Demographics and baseline characteristics were generally comparable between cancer and non-cancer groups (**Table 1**).
- Mean (SD) age was 60.6 (12.4) years and 55.4% of participants were female (with a higher percentage in the non-cancer versus cancer group).
- In the cancer group, most participants (54.9%) had stage I/II cancer.
- Both cancer and non-cancer groups were predominantly non-Hispanic White (82.0% and 79.4%, respectively).

Table 1. Participant Demographics and Baseline Characteristics

		Cancer (N = 2823)	Non-cancer (N = 1254)	Total (N = 4077)
Age (years)	Mean (SD)	62.6 (11.8)	56.2 (12.6)	60.6 (12.4)
Gender	Female	1394 (49.4%)	864 (68.9%)	2258 (55.4%)
Race/Ethnicity	White, non-Hispanic	2316 (82.0%)	996 (79.4%)	3312 (81.2%)
	Black, non-Hispanic	193 (6.8%)	85 (6.8%)	278 (6.8%)
	Hispanic	192 (6.8%)	103 (8.2%)	295 (7.2%)
	Asian, Native Hawaiian or Pacific Islander	49 (1.7%)	26 (2.1%)	75 (1.8%)
	American Indian or Alaska Native	8 (0.3%)	7 (0.6%)	15 (0.4%)
	Other	65 (2.3%)	37 (3.0%)	102 (2.5%)
Family History of Cancer	Yes	2254 (79.8%)	1014 (80.9%)	3268 (80.2%)
	No	493 (17.5%)	210 (16.7%)	703 (17.2%)
	Not sure	76 (2.7%)	30 (2.4%)	106 (2.6%)
Clinical Cancer Stage	I	849 (30.1%)		849 (20.8%)
	II	703 (24.9%)		703 (17.2%)
	III	566 (20.0%)		566 (13.9%)
	IV	618 (21.9%)		618 (15.2%)
	Not expected to be staged[a]	67 (2.4%)		67 (1.6%)
	Missing	20 (0.7%)		20 (0.5%)

[a]Includes cancers that do not have a staging classification per AJCC criteria such as myeloid neoplasm and lymphoid leukemia