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Detection of Cancer Signal for over 50 AJCC Cancer Types with a Multi-Cancer Early Detection Test

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

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INTRODUCTION

- 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 cancers and predict cancer signal origin.[1]
- Within the CCGA study, individuals with cancer had primary site of origin and histologic type recorded; cancers were grouped into cancer classes for the purpose of sensitivity reporting.
- Separately, cancer types as defined by American Joint Committee on Cancer (AJCC) criteria were assigned to each cancer from these data.
- A relevant clinical question for the implementation of this MCED test is how are cancer classes that are defined within the study reflected in the distribution of standardized AJCC cancer types.
- Here, we report CCGA 'cancer class' designation and AJCC 'cancer type' assignment within the third and final CCGA validation substudy.[2]

OBJECTIVE

- To better characterize the diversity of cancers across which a signal could be detected with this MCED test planned for clinical implementation as a general multi-cancer screening tool.

THIS MCED TEST DETECTED CANCER SIGNALS ACROSS >50 AJCC CANCER TYPES REPRESENTING A WIDE RANGE OF CANCER BIOLOGICAL CHARACTERISTICS

Sensitivity Cancer Classes and AJCC Cancer Types

- According to AJCC classification, the MCED test detected cancer signals across >50 AJCC cancers, including some not present in the training set; some cancers had limited representation (Tables 1 and 2).
- Sensitivity was reported for 24 cancer classes (sample sizes ranged from 10 to 524 participants; **Table 1**), as well as an "other" cancer class (59 participants; **Table 2**).

Table 1. Test Positive Rate by CCGA-Defined Cancer Class (Except "Other") and AJCC Cancer Type (Confirmed Status Analysis Set)

	Sensitivity			Test Positive Rate	
CCGA Cancer Class*	% (n/N)	(95% CI)	AJCC Cancer Type	% (n/N)	(95% CI)
Anus	81.8% (18/22)	(61.5-92.7%)	Anus	81.8% (18/22)	(61.5-92.7%)
Bladder	34.8% (8/23)	(18.8-55.1%)	Urinary bladder	34.8% (8/23)	(18.8-55.1%)
Breast	30.5% (160/524)	(26.7-34.6%)	Breast	30.5% (160/524)	(26.7-34.6%)
Cervix	80.0% (20/25)	(60.9-91.1%)	Cervix uteri	80.0% (20/25)	(60.9-91.1%)
Colon/Rectum	82.0% (169/206)	(76.2-86.7%)	Appendix carcinoma	25.0% (1/4)	(1.3-69.9%)
			Colon and rectum	83.6% (163/195)	(77.8-88.1%)
			Colon and rectum; Neuroendocrine tumors of the appendix†	100.0% (1/1)	(5.1-100.0%)
			Neuroendocrine tumors of the appendix	100.0% (1/1)	(5.1-100.0%)
			Neuroendocrine tumors of the colon and rectum	60.0% (3/5)	(23.1-88.2%)
Esophagus	85.0% (85/100)	(76.7-90.7%)	Esophagus and esophagogastric junction	85.0% (85/100)	(76.7-90.7%)
Gallbladder	70.6% (12/17)	(46.9-86.7%)	Ampulla of vater‡§	0.0% (0/1)	(0.0-94.9%)
			Distal bile duct	50.0% (3/6)	(18.8-81.2%)
			Gallbladder	100.0% (8/8)	(67.6-100.0%)
			Perihilar ducts	50.0% (1/2)	(2.6-97.4%)
Head and Neck	85.7% (90/105)	(77.8-91.1%)	HPV-mediated (p16+) oropharyngeal cancer	96.0% (48/50)	(86.5-98.9%)
			Larynx	57.1% (12/21)	(36.5-75.5%)
			Nasal cavity and paranasal sinuses	50.0% (1/2)	(2.6-97.4%)
			Nasopharynx	100.0% (3/3)	(43.9-100.0%)
			Oral cavity	50.0% (3/6)	(18.8-81.2%)
			Oropharynx (p16-) and hypopharynx	100.0% (23/23)	(85.7-100.0%)
Kidney	18.2% (18/99)	(11.8-26.9%)	Kidney	18.2% (18/99)	(11.8-26.9%)
Liver/Bile-duct	93.5% (43/46)	(82.5-97.8%)	Intrahepatic bile ducts	95.0% (19/20)	(76.4-99.7%)
			Liver	92.3% (24/26)	(75.9-97.9%)

Table 1. (cont). Test Positive Rate by CCGA-Defined Cancer Class (Except "Other") and AJCC Cancer Type (Confirmed Status Analysis Set)

	Sensitivity			Test Positive Rate	
CCGA Cancer Class*	% (n/N)	(95% CI)	AJCC Cancer Type	% (n/N)	(95% CI)
Lung	74.8% (302/404)	(70.3-78.7%)	Lung	74.8% (302/404)	(70.3-78.7%)
Lymphoid Leukemia	41.2% (21/51)	(28.8-54.8%)	Hodgkin and non-Hodgkin lymphoma	42.0% (21/50)	(29.4-55.8%)
			Leukemia‡	0.0% (0/1)	(0.0-94.9%)
Lymphoma	56.3% (98/174)	(48.9-63.5%)	Hodgkin and non-Hodgkin lymphoma	56.3% (98/174)	(48.9-63.5%)
Melanoma	46.2% (6/13)	(23.2-70.9%)	Melanoma of the skin	46.2% (6/13)	(23.2-70.9%)
Myeloid Neoplasm	20.0% (2/10)	(5.7-51.0%)	Leukemia	20.0% (2/10)	(5.7-51.0%)
Ovary	83.1% (54/65)	(72.2-90.3%)	Ovary, fallopian tube and primary peritoneal carcinoma	83.1% (54/65)	(72.2-90.3%)
Pancreas	83.7% (113/135)	(76.6-89.0%)	Exocrine pancreas	86.6% (110/127)	(79.6-91.5%)
			Neuroendocrine tumors of the pancreas	37.5% (3/8)	(13.7-69.4%)
Plasma Cell Neoplasm	72.3% (34/47)	(58.2-83.1%)	Plasma cell myeloma and plasma cell disorders	72.3% (34/47)	(58.2-83.1%)
Prostate	11.2% (47/420)	(8.5-14.6%)	Prostate	11.2% (47/420)	(8.5-14.6%)
Sarcoma	60.0% (18/30)	(42.3-75.4%)	Bone	100.0% (1/1)	(5.1-100.0%)
			Corpus uteri sarcoma	100.0% (3/3)	(43.9-100.0%)
			Gastrointestinal stromal tumor	100.0% (1/1)	(5.1-100.0%)
			Soft tissue sarcoma of the abdomen and thoracic visceral organs	50.0% (2/4)	(15.0-85.0%)
			Soft tissue sarcoma of the head and neck	33.3% (1/3)	(1.7-79.2%)
			Soft tissue sarcoma of the retroperitoneum	40.0% (2/5)	(11.8-76.9%)
			Soft tissue sarcoma of the trunk and extremities	54.5% (6/11)	(28.0-78.7%)
			Soft tissue sarcoma unusual histologies and sites	100.0% (2/2)	(34.2-100.0%)
Stomach	66.7% (20/30)	(48.8-80.8%)	Neuroendocrine tumors of the stomach†	0.0% (0/3)	(0.0-56.1%)
			Stomach	74.1% (20/27)	(55.3-86.8%)
Thyroid	0.0% (0/14)	(0.0-21.5%)	Thyroid differentiated and anaplastic carcinoma‡	0.0% (0/13)	(0.0-22.8%)
			Thyroid medullary‡	0.0% (0/1)	(0.0-94.9%)
Urothelial Tract	80.0% (8/10)	(49.0-94.3%)	Renal pelvis and ureter	80.0% (8/10)	(49.0-94.3%)
Uterus	28.0% (44/157)	(21.6-35.5%)	Corpus uteri carcinoma and carcinosarcoma	28.0% (44/157)	(21.6-35.5%)

When tallying the total number of AJCC cancer types detected by the MCED test, only one AJCC cancer type is counted for repeated entries.
**The AJCC cancer types within the CCGA3-defined cancer classes of "multiple primaries" (n=19) and "unknown primary" (n=18) are not included in the count of AJCC cancer types detected by this MCED test or the overall reported AJCC test positive rate.*
†The participant had a cancer class assignment of "colon/rectum" but was independently assigned per AJCC criteria as having two cancer types ("Colon and rectum" and "Neuroendocrine tumors of the appendix"); these were each already individually accounted for in the count of AJCC cancer types detected by this MCED test.
‡AJCC cancer types with Test Positive = 0 (Test Positive Rate = 0%) were not included in the count of AJCC cancer types detected by this MCED test.
§Another ampulla of vater case was assigned to the "Other" CCGA3-defined cancer class due to incomplete information at the time of assignment.
AJCC = American Joint Committee on Cancer; CCGA = Circulating Cell-free Genome Atlas; MCED = multi-cancer early detection.

Table 2. Test Positive Rate by CCGA-Defined Cancer Class "Other" and AJCC Cancer Type (Confirmed Status Analysis Set)

	Sensitivity			Test Positive Rate	
CCGA Cancer Class	% (n/N)	(95% CI)	AJCC Cancer Type	% (n/N)	(95% CI)
Other	50.8% (30/59)	(38.4-63.2%)	Adrenal cortical carcinoma	100.0% (1/1)	(5.1-100.0%)
			Ampulla of vater§	100.0% (1/1)	(5.1-100.0%)
			Brain and spinal cord‡	0.0% (0/6)	(0.0-39.0%)
			Gestational trophoblastic neoplasms	100.0% (1/1)	(5.1-100.0%)
			Malignant pleural mesothelioma	42.9% (3/7)	(15.8-75.0%)
			Merkel cell carcinoma	100.0% (2/2)	(34.2-100.0%)
			Neuroendocrine tumors of the duodenum and ampulla of vater‡	0.0% (0/2)	(0.0-65.8%)
			Neuroendocrine tumors of the jejunum and ileum‡	0.0% (0/8)	(0.0-32.4%)
			Other/unknown **	70.0% (7/10)	(39.7-89.2%)
			Penis	100.0% (1/1)	(5.1-100.0%)
			Small intestine	100.0% (3/3)	(43.9-100.0%)
			Testis	83.3% (5/6)	(43.6-99.1%)
			Thymus‡	0.0% (0/2)	(0.0-65.8%)
			Vagina	100.0% (2/2)	(34.2-100.0%)
			Vulva	57.1% (4/7)	(25.0-84.2%)

When tallying the total number of AJCC cancer types detected by the MCED test, only one AJCC cancer type is counted for repeated entries.
‡AJCC cancer types with Test Positive = 0 (Test Positive Rate = 0%) were not included in the count of AJCC cancer types detected by this MCED test.
§This ampulla of vater case was assigned to the "Other" CCGA3-defined cancer class due to incomplete information at the time of assignment.
Other ampulla of vater cases were assigned to the gallbladder CCGA3-defined cancer class.
***"Other/unknown" AJCC cancer type was not included in the count of AJCC cancer types detected by this MCED test.*
AJCC = American Joint Committee on Cancer; CCGA = Circulating Cell-free Genome Atlas; MCED = multi-cancer early detection.

CONCLUSIONS

- This MCED test that was evaluated in the third CCGA substudy detected cancer signals across >50 AJCC cancer types.
- Reporting CCGA cancer classes and AJCC cancer types demonstrates the ability of the MCED test to detect cancer signals across a set of diverse cancers representing a wide range of biologic characteristics, including cancers on which the classifier has not been trained.
- These results support the potential use of this blood-based MCED test on a population-wide scale as a complement to existing single-cancer screening tests.

References

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Disclosures

Study funded by GRAIL, Inc. **JG, OV, 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**), 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

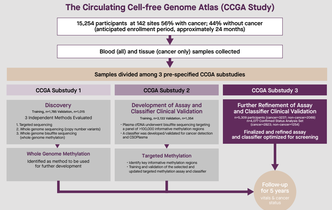
Study Design

- 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 1**).
- 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 1**); in this pre-specified exploratory analysis from the third substudy, the test positive rate based on the AJCC cancer classification and histologic subtypes was evaluated.
- For sensitivity reporting, CCGA cancer classes were assigned to cancer cases consistent with methylation biology and based on the type of primary cancer reported by the site and tumor characteristics abstracted from the site pathology reports by GRAIL pathologists.
- Each cancer participant also was separately assigned an AJCC cancer type based on the same source data using AJCC staging manual (7th or 8th edition) classifications.[3]

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 1. Study Design



CCGA = Circulating Cell-free Genome Atlas

SUPPORTING DATA

Participant Disposition

- A total of 5309 participants were included (enrolled as cancer, n=3237; enrolled as non-cancer, n=2069; missing enrollment status, n=3).
- Of these, 4077 (cancer, n=2823; non-cancer, n=1254 with non-cancer status confirmed at year-one follow-up) 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 3**).
- Mean (SD) age was 60.6 (12.4) years, 55.4% of participants were female, and 81.2% of participants were non-Hispanic White.
- In the cancer group, most participants (54.9%) had stage I/II cancer.

Table 3. 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§	67 (2.4%)		67 (1.6%)
	Missing	20 (0.7%)		20 (0.5%)

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