

THE PROMISE OF
MULTI-CANCER
EARLY
DETECTION

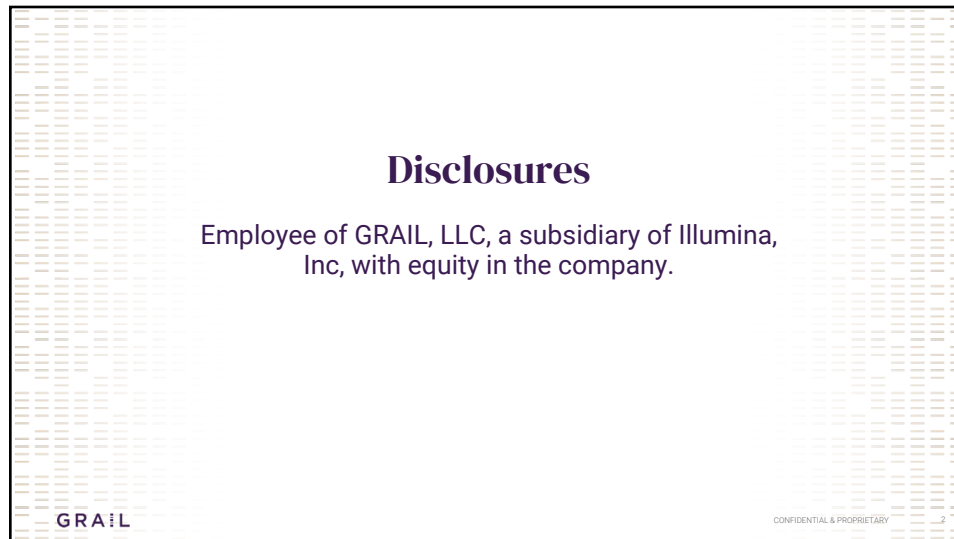
CLINICAL OVERVIEW

JORDAN J KARLITZ MD, SENIOR MEDICAL DIRECTOR,
MEDICAL AFFAIRS

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Disclosures

Employee of GRAIL, LLC, a subsidiary of Illumina,
Inc, with equity in the company.

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GRAIL, LLC.

Founded in January 2016 to take on one of the world's biggest challenges

<p>Headquartered in Silicon Valley – the hub of life sciences and tech industries</p>	<p>World-class team of leaders, scientists, clinicians, engineers, and other experts</p>	<p>Acquired by Illumina in August 2021 for ~\$10B in consideration</p>	<p>Rapidly growing to >1200 employees by end of 2022</p>
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Cancers Without USPSTF-Recommended Screening Represent ~70% of Cancer Deaths

~70%

Of cancer deaths are due to cancers **without USPSTF A, B, or C recommended screening tests**

~30%

Of deaths due to cancers with available screening*

USPSTF, United States Preventive Services Task Force
 Assumes screening is available for all prostate, 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).
 Estimated deaths per year in 2021 from American Cancer Society Cancer Facts and Figures 2021. Available at: <http://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf>. Data on file GA-2021-0065.
 * USPSTF A, B or C rating

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GRAIL Has Developed Galleri®, 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 cancer signal origin** to direct diagnostic work-up

Test is **targeted for use as a complement to guideline-recommended screening** (eg, mammography)

Designed to detect **detect a cancer signal common to >50 cancers, including unscreened types**, from a single blood draw

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

Colorectal
Esophageal Head & Neck
Liver Lung Lymphoma
Plasma Cell Neoplasm
Pancreatic Ovarian
Stomach Anus Bladder

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Tumors shed nucleic acids into blood and other body fluids, carrying cancer-specific information^{1,2}

Normal cell
Tumor cell
Normal cfDNA
Tumor cfDNA

cfDNA shedding

Necrosis

Apoptosis

Tumor tissue

Plasma cfDNA

Cancer-associated aberrations in cfDNA

- Mutations
- Chromosome alterations
- DNA methylation patterns

cfDNA, cell-free DNA.
1. Corcoran R et al. *N Engl J Med.* 2018;379:1754-1765; 2. Thierry A et al. *Cancer Metastasis Rev.* 2016;35:347-376.

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GRAIL's technology is powered by our methylation assay, which preferentially targets informative regions of the genome

Our discovery study showed methylation is a highly informative biological signal for cancer detection and tissue of origin localization

- High cancer detection due to multitude of informative sites compared to other approaches
- Tissue differentiation is driven by methylation, hence patterns are informative for tissue of origin
- Largest known methylation sequence data set for cancer and non-cancer

Source: Presented at AACR 2018: Aravanis et al., Abstract LB-343; Data on file

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Process Overview of Multi-Cancer Early Detection With Galleri® Test

Cancer can be anywhere: using a targeted methylation, next-generation sequencing (NGS)-based assay analyzing cfDNA and machine learning to detect cancer and predict cancer signal origin

Tumor sheds cfDNA fragments into bloodstream

Blood plasma isolated (contains cfDNA fragments)

Targeted methylation analysis of cfDNA^a (sequencing, mapping, alignment)

Machine learning classifier

Cancer signal detected

cancer signal origin prediction

No cancer signal detected

cfDNA, cell-free DNA. ^aBisulfite treatment; targeted probes pull out fragments matching regions of interest. The Galleri® test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider. Adapted from Liu MC, et al. Ann Oncol. 2020;31(6):745-759. DOI:10.1016/j.annonc.2020.02.011. Galleri is a registered trademark of GRAIL, LLC.

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Clinical Development Program

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

1	CCGA (n=15,254) NCT02889978	Develop and validate a cell-free DNA-based MCED test Enrollment: complete; FU complete Mar 2024. Analysis: EOS complete; 5-yr FU TBD
2	STRIVE (n=99,481) NCT03085888	Evaluate MCED test performance in women to detect invasive cancers^a Enrollment: complete; 3-yr FU complete May 2025. Analysis: EOS TBD; FU TBD
3	SUMMIT (n=13,035) NCT03934866	Clinical validation in individuals at high risk of lung cancer Enrollment: complete; FU complete: Apr 2023. Analysis: EOS TBD; FU Q3 2023
4	PATHFINDER (n=6,662) NCT04241796	Evaluate clinical implementation and perceptions of MCED test Enrollment: complete; Analysis: EOS ongoing (Q3 2022)
5	SYMPHONY (n=6,242) ISRCTN 10226380	Assess MCED test in individuals with signs/symptoms of cancer Enrollment: complete; FU complete Nov 2022. Analysis: EOS Aug 2022; FU Q1 2023
6	NHS-Galleri (n~140,000) ISRCTN 91431511	Assess clinical utility of MCED for population screening in the UK Enrollment: complete. Analysis: IA Mar 2024 (not publishing) EOS Jun 2026
7	REFLECTION (n~35,000) NCT05205967	Assess experience/clinical outcomes in real-world setting Enrollment: ongoing (complete Aug 2024); FU complete Jul 2027. Analysis: IA-1 Q4 2023; IA-2 Q4 2026; EOS Mar 2028; FU Jul 2030
8	PATHFINDER 2 (n~20,000) NCT05155605	Evaluate MCED test performance in eligible screening population Enrollment: ongoing (complete Jul 2023); Analysis: IA-1 Jun 2024; IA-2 Dec 2024; EOS Mar 2027

~335,000 participants

^aIn women undergoing mammography screening.
n~ indicates approximate enrollment. Follow-up indicates end of study data post follow-up.
CCGA, Circulating Cell-free Genome Atlas; EOS, end of study; FU, follow-up; MCED, multi-cancer early detection; TBD, to be determined; UK, United Kingdom.

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Circulating Cell-Free Genome Atlas (CCGA) Study

Prospective, observational, longitudinal, case-control study divided into 3 substudies for discovery, training, and validation of multi-cancer detection test

NCT02889978

Substudy 1	Substudy 2	Substudy 3
Discovery	Training / Validation - V1	Validation - V2
Methylation Patterns	Methylation Patterns	Methylation Patterns
Mutations	Machine-learning classifiers to differentiate cancer vs non-cancer and predict CSO	Clinical Validation supporting Galleri[®] launch
Chromosome Alterations		

15,254 participants

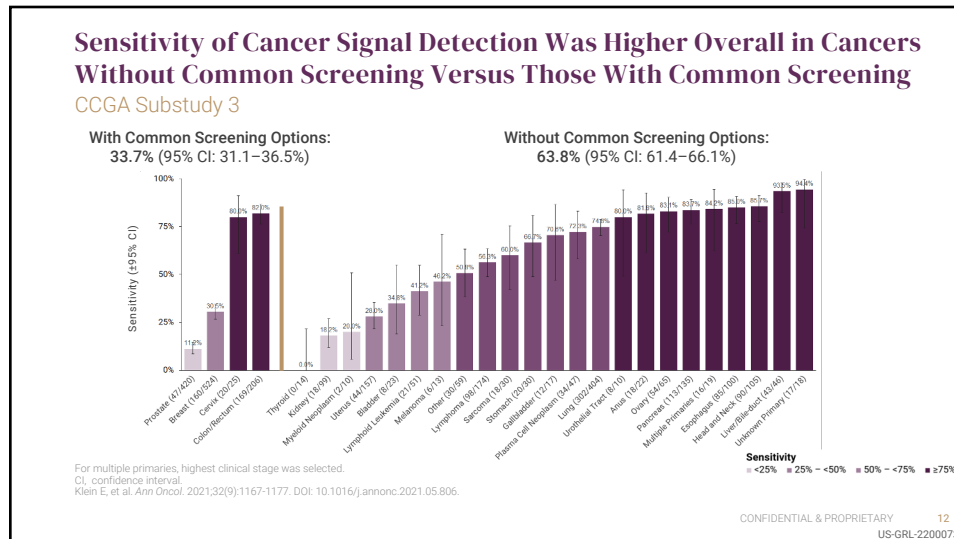
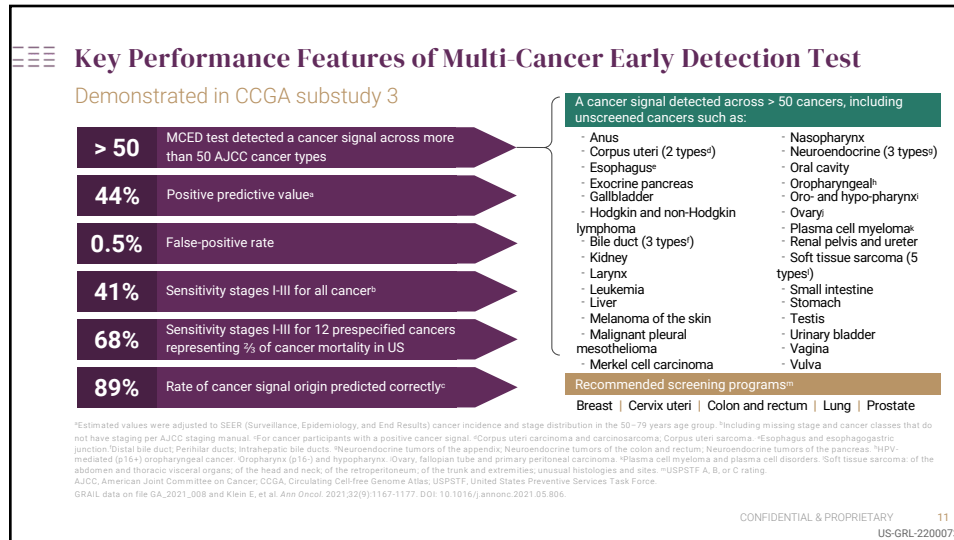
Blood samples
all participants

Tissue samples
cancer only

Follow up for 5 years
vital & cancer status

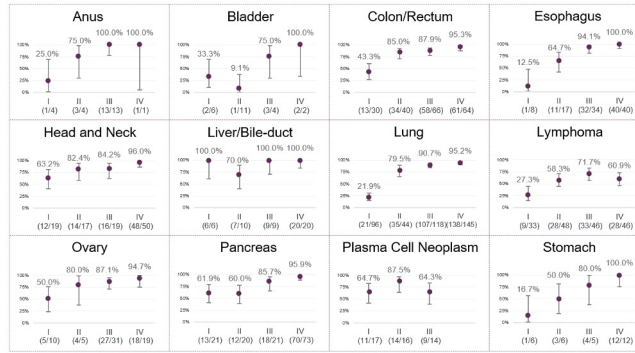
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Sensitivity of Cancer Signal Detection by Stage in 12 Pre-Specified Cancers Responsible for Two-Thirds of Cancer Deaths

CCGA Substudy 3



List of 12 cancers that account for 62% of US cancer deaths from American Cancer Society, Cancer Facts & Figures 2021. Atlanta: American Cancer Society, 2021. <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>. Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

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Significant Challenges Exist for Single-Cancer Screening

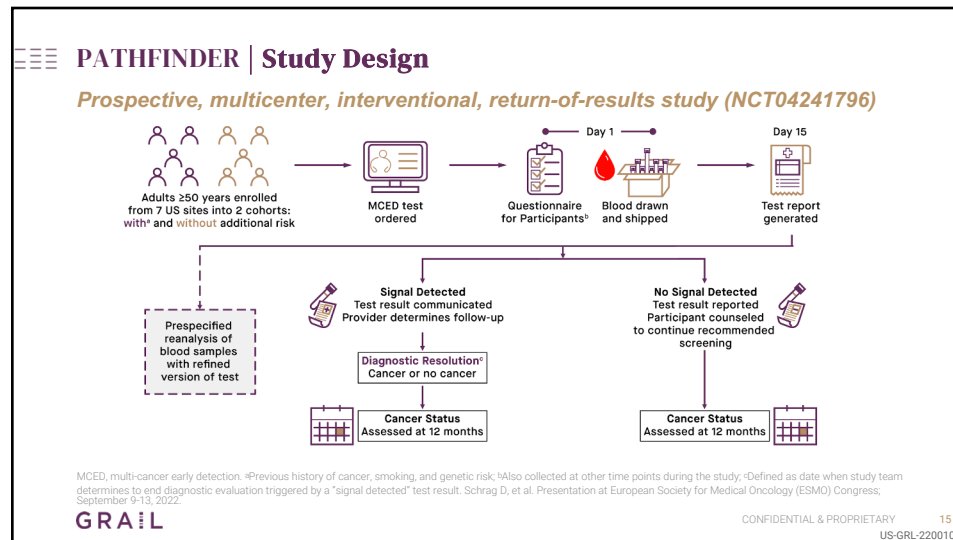
Cancer	Prevalence (%)	USPSTF Recommended Screening	Compliance With Recommended Screening (%) ⁶	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	False Positives Per 1,000 People [#]
Breast ¹	0.6	Biennial mammography, women ages 50–74	78.3	87	89	4.4	110
Cervical ²	<0.1	Triennial cytology or quinquennial cytology/HPV test, women ages 21–65	77.7	95	85.5	<1*	145
		Decennial colonoscopy		Reference	Reference	Reference	
Colorectal ³	0.65	Triennial stool-based screening (Cologuard)		92.3	86.6	3.7*	134
		Annual stool-based screening (FIT)	74.2	73.8	94.9	8.7	51
Lung ⁴	1.1 (high risk) ⁵	Annual low-dose CT for high-risk persons ages 50–80 ⁵	5*	85*	87*	6.9*	130

CT, computed tomography; FIT, fecal immunochemical test; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.
¹Non-cancerous lesions were excluded. ²Based on previous USPSTF recommendations of adults 50–80 years with a 30 pack-year smoking history. ³Calculated by using inverse of specificity value and multiplying by 10.
⁴USPSTF. 2016. *Lehman, et al. Radiology* 2017;283(1):49-58. Kim, et al. *JAMA*. 2018;320(7):706-714. ⁵USPSTF. 2017. United States Food and Drug Administration Premarket Approval P130017. Accessed March 26, 2019. Cologuard Test. Available from www.cologuardtest.com/faq/faq-screening-recommended. Accessed March 26, 2019. ⁶Pinsky, et al. *Ann Intern Med*. 2015; Apr 7:192(7):485-491. ⁷Mesa, B, et al. *JAMA*. 2021;325(18):988-997. Recommendation for lung screening limited to high-risk smoking population, which accounts for less than 33% of all lung cancers. ⁸Compliance from BRFSS Prevalence & Trends Data. 2020. [accessed Dec. 8, 2021]. URL: <https://www.cdc.gov/brfss/brfssprevalence/> except LDCT from Fedewa et al. *J Natl Cancer Inst*. 2021;113(8):1044-1052. doi: 10.1093/jnci/djab170. Data on file GA-2021-0065. ⁹<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening#bootstrap-panel-6>. Accessed October 13, 2021. Data on file GA-2021-0065.

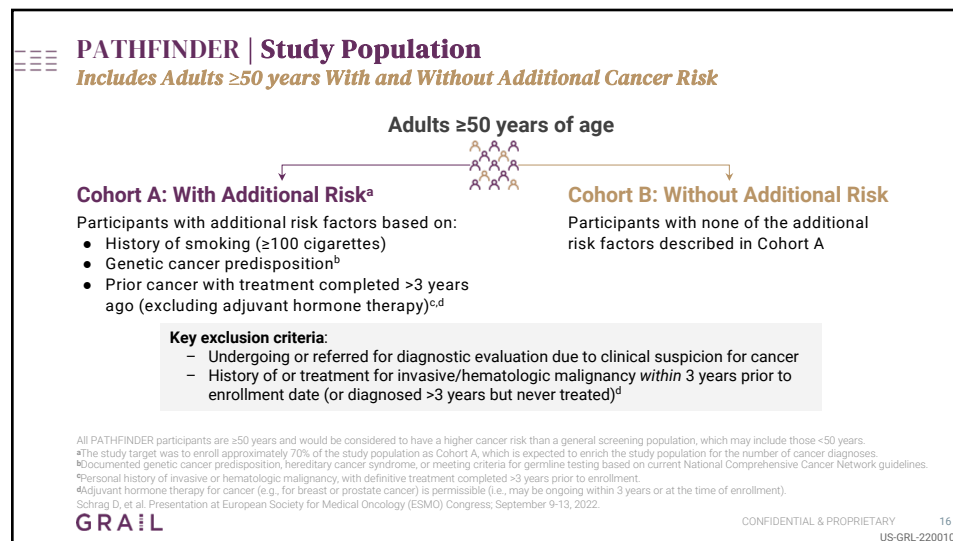
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Relatively low PPV and specificity for many single cancer screening tests

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PATHFINDER | Study Objectives

Primary

Assess extent of diagnostic testing required to achieve diagnostic resolution following a "signal detected" test result

Per Participant:

- Number of imaging tests and invasive test/procedures
- Number of clinical lab visits (Including blood and urine collection) and lab tests
- Number of clinic visits
- Time required to achieve diagnostic resolution defined as the number of days from when the test result is returned through the reporting portal to the date of diagnostic resolution

Secondary

Evaluate Test Performance:

Cancer Detection

- Resolution per MCED test
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Specificity

Signal Origin Prediction

- Return rate
- Overall accuracy

Assess participant-reported outcomes and perceptions about the MCED test

→ **Satisfaction, Perceptions of MCED results, Health-related quality of life and Anxiety** following MCED

GRAIL Schrag D, et al. Presentation at European Society for Medical Oncology (ESMO) Congress, September 9-13, 2022.

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PATHFINDER | Cancers Diagnosed After a True Positive MCED Signal

36 Cancers in 35 Participants, including 27 cancers not routinely screened for

18 Participants had 19 Solid Tumors

- Oropharyngeal (n=2)
- Breast ♀ (n=5)
- Liver (n=1)
- Intrahepatic Bile Ducts (n=1)
- Colon/Rectum (n=2)
- Prostate ♂ (n=2)
- Lung (n=1)
- Pancreas (n=1)
- Small Intestine (n=1)
- Uterus (n=1)
- Ovary ♀ (n=1)
- Bone (n=1)

17 Participants had 17 Hematologic Malignancies

- Plasma Cell Myeloma/Disorders (n=1)
- Lymphoid Leukemia (n=2)
- Waldenstrom Macroglobulinemia (n=2)
- Lymphoma (n=12)

MCED-Detected Cancers

- n=24 in elevated risk cohort
- n=11 in non-elevated risk cohort
- n=14/29 (48%) of those with non-recurrent cancers had early stage (I/II) diagnoses
- n=25/35 (71%) for which there is no standard screening

▲ Stage I ■ Stage II ● Stage III/IV/No Stage ● USPSTF cancer screenings* ● No standard screening^b

* Tumor types shown in orange include those for which the US Preventive Services Task Force (USPSTF) advises screening and includes breast, cervical, colorectal, prostate and lung cancer. However, the lung cancer diagnosed was identified in an individual who did not meet USPSTF guidelines and therefore is unlikely to have been screened. ^bMalignancies shown in blue are those for which there is no standard screening per the USPSTF. Schrag D, et al. Presentation at European Society for Medical Oncology (ESMO) Congress, September 9-13, 2022. graill is a registered trademark of GRAIL, Inc.

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PATHFINDER | 67% of new cancers were diagnosed in Stage I-III

Refined MCED TEST

Cancer Type Diagnosed	Clinical AJCC Stage (New Cancers)					Recurrent Cancers	First Predicted Cancer Signal Origin
	I	II	III	IV	NA ^a	Distant	
Breast						5	Breast
Colon or rectum				2			Colon/Rectum
Endometrium (Uterus)	1						Breast
Head and Neck		1		1			Head and Neck
Liver or intrahepatic bile duct	1		1				Liver, bile-duct
Lung			1				Lung
Lymphoid leukemia					1		Lymphoid Neoplasm
Lymphoma	1	1	1	1			Lymphoid Neoplasm
Ovary, peritoneum, or FT			2				Ovary; Uterus
Pancreas		1					Pancreas/Gallbladder
Plasma cell neoplasm					1		Plasma Cell Neoplasm
Prostate			1				Breast
Sarcoma		1					Sarcoma
Small intestine	1						Colon/Rectum ^b
Waldenstrom macroglobulinemia					1		Plasma Cell Neoplasm
Total	4	4	6	4	3	5	

No current screening available

Incorrect CSO

21/26 (81%) of cancers diagnosed were de novo and 5/26 (19%) were recurrent

AJCC, the American Joint Committee on Cancer 8th edition Cancer Staging Manual; FT, fallopian tube; GI, gastrointestinal; MCED, multi-cancer early detection test refined for screening; NA, not applicable
^aNo AJCC stage expected; ^bSmall intestine is an untrained cancer not included in a CSO label. GRAIL data on file GR-2222-008, EDS analysis

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PATHFINDER | Cancer Diagnosis Was Expedient (Even During COVID-19)

Early MCED Test

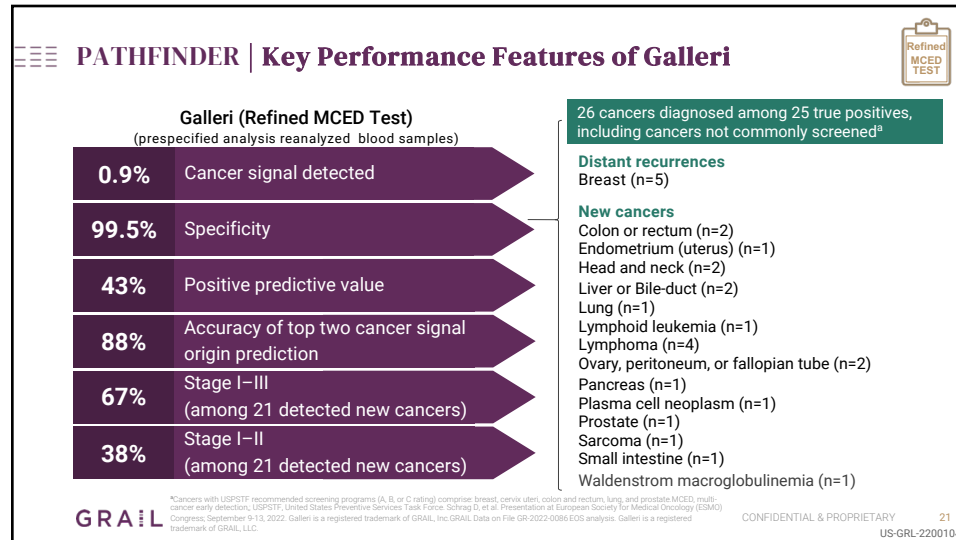
Diagnostic resolution was faster for true positives

	True Positives 33 ^a	False Positives 57 ^b	Total 90 ^c
Diagnostic Resolution, Median Days (Q1, Q3)	57 (33, 143)	162 (44, 248)	79 (37, 219)
Number of Participants With Planned Reevaluation at >=3 Month Interval	6	25	31

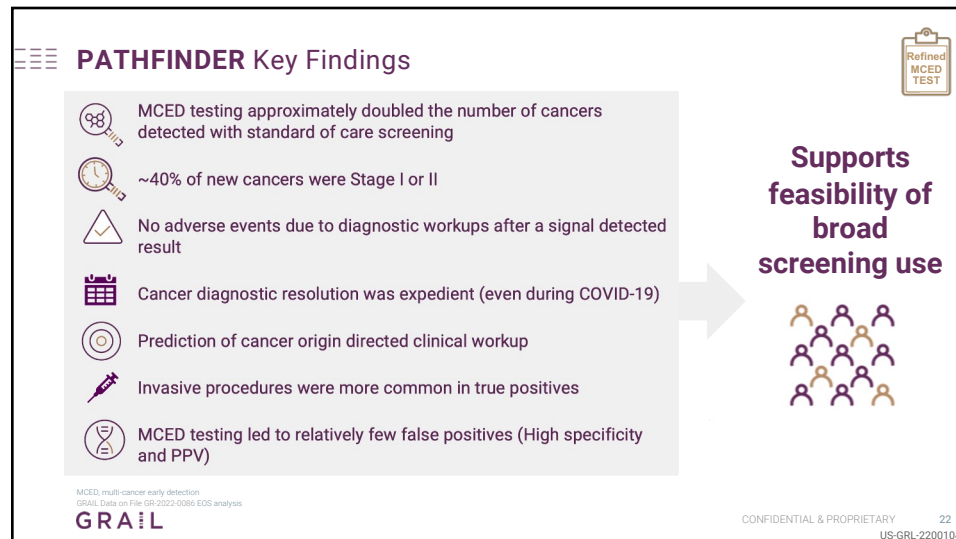
- Median time to diagnostic resolution was longer for false positives than true positives
- 73% of true positives reached resolution in less than 3 months
- 50% of those true positives cancers were diagnosed in 2 months or less
- Planned reevaluation intervals of 3 months or longer were more common in false positives, likely reflecting repeat or scheduled follow-up testing

^aTwo participants with 'signal detected' MCED test result (TPs) were excluded from the diagnostic workup analysis because diagnostic testing was initiated before MCED results were returned.
^bIncludes 1 participant without diagnostic resolution who was conservatively assumed to be FP.
^cMCED, multi-cancer early detection; Schreyer D, et al. Presentation at European Society for Medical Oncology (ESMO) Congress, September 9-13, 2022. Galleri is a registered trademark of GRAIL, Inc.

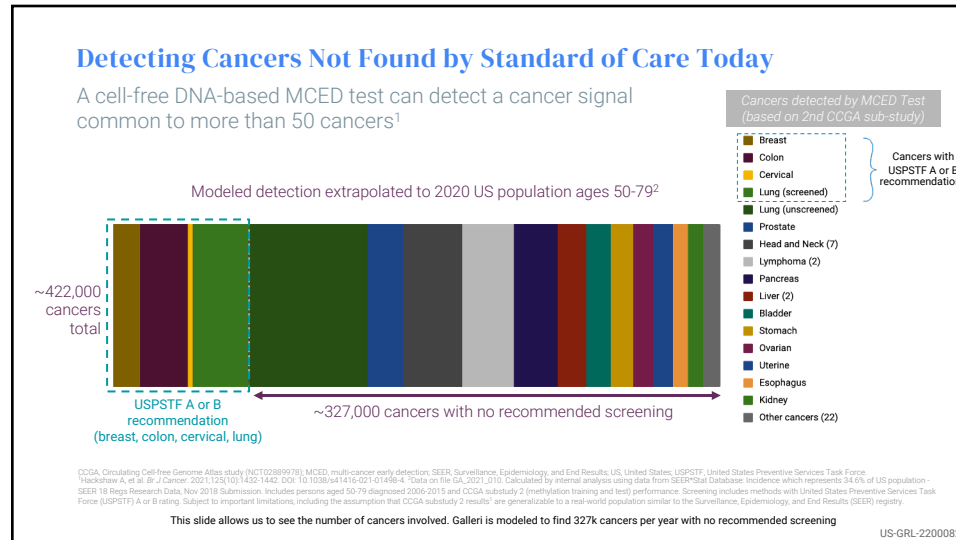
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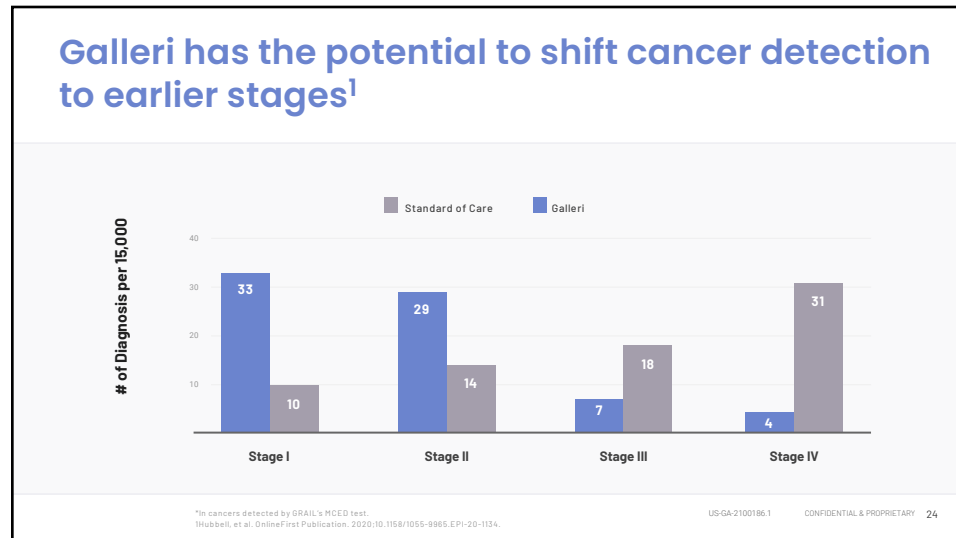
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Galleri Test Experience in Clinical Practice

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100,000 tests completed, 7,100+ prescribing physicians across the U.S.

Galleri test experience in clinical practice:

Cancer signal detection rate as expected for an intended use population¹

<p style="font-size: 2em; color: #e91e63;">+</p> <p style="font-size: 1.5em; color: #e91e63;">0.9%</p> <p>of test results were Cancer Signal Detected</p>	<p style="font-size: 2em; color: #0070c0;">-</p> <p style="font-size: 1.5em; color: #0070c0;">99.1%</p> <p>of test results were No Cancer Signal Detected</p>
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True cancer status for these results is unknown. 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. The Galleri test does not detect a signal for all cancers and not all cancers can be detected in the blood. False positive and false negative results do occur.

GRAIL ¹. National Cancer Institute. Age and Cancer Risk: Incidence rates by age at diagnosis, all cancer types. SEER 21 2013-2017, all races, both sexes. Adults with increased risk for cancer. Data on file. GA-2022-0076. First 100,000 tests included Galleri prescribed outside of intended use. US-GA-2300244-2 CONFIDENTIAL & PROPRIETARY 2/6

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Cancer Signal Detected: Pages 1 & 2

Multi-cancer early detection test report

Results
Cancer Signal Detected

Head & Neck

Considerations from Clinical Studies

Multi-cancer early detection test report

Cancer Categories Detected

Intended use

Do you have more questions?

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Thank you

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