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Early Real-World Experience With Positive Multi-Cancer Early Detection (MCED) Test Cases and Negative Initial Diagnostic Work-Up

Presented at the Annual Meeting of the
European Society For Medical Oncology (ESMO)
13–17 September 2024
Barcelona, Spain

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INTRODUCTION

- The Galleri® multi-cancer early detection (MCED) test uses machine learning and targeted methylation analysis of cell-free DNA to detect a cancer signal in blood
- This MCED test has been available by prescription since April 2021 and is intended for use in adults over the age of 50 or who have another cancer risk factor
- The MCED test detects a signal shared by many cancers and can also predict a cancer signal origin (CSO)[1–3]
- Patients with a cancer signal detected (CSD) test result have a health care provider (HCP)-led clinical diagnostic work-up, typically directed by the MCED test CSO prediction
- If cancer is not found after an initial set of diagnostic workups, HCPs can choose to repeat the MCED test within ~3-6 months from the original test result to help guide patient management
- In a recent modeling study, when initial confirmatory testing (informed by CSO) did not provide diagnostic resolution, the residual risk of cancer was more than three times higher than the 3% NICE-recommended cancer risk threshold that warrants investigation in symptomatic individuals[4,5]
- Management of this risk is therefore critical for HCP decision making

OBJECTIVES

- To report the real-world outcomes of patients with a CSD MCED result, followed by a diagnostic evaluation that did not result in cancer diagnosis, followed by a second MCED test (Retest)

METHODS

Retest Data Collection

- Data are collected as part of a quality assurance/quality improvement (QA/QI) program and performance monitoring in order to characterize the use of the MCED test in real-world clinical practice and evaluate MCED test execution and delivery
- QA/QI data captured from outreach to HCPs include demographics, medical history, current medical conditions, test results, cancer status, and cancer type and stage (if diagnosed)
- Data reported here are for Retest results through 20 March 2024

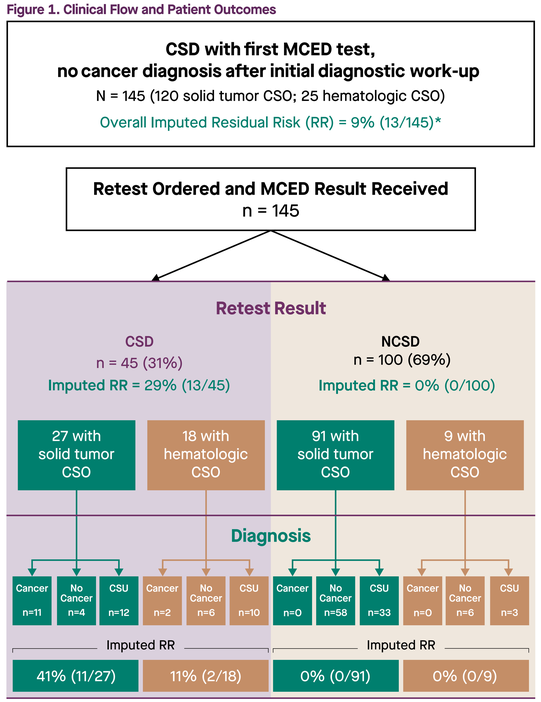
Residual Risk

- Residual risk is defined as the risk that cancer is present in the individual at the time of assessment given that a CSD result was observed with the first test and cancer was not found during the initial diagnostic evaluation
  - **Observed residual risk** is calculated using data only from those with known clinical status at the last follow-up contact
  - **Imputed residual risk** is a conservative risk estimate that assumes all patients with an unknown clinical status do not have cancer at the last follow-up, reflecting that cancer is rare in the general population
- Due to the limited nature of available real-world evidence (RWE), residual risk is not categorized by cancer type or the extent of diagnostic evaluation

KEY RESULTS: A NEGATIVE MCED RETEST RESULT INDICATES LOW LIKELIHOOD OF CURRENT CANCER, WHEREAS A PERSISTENT POSITIVE RESULT INDICATES HIGHER LIKELIHOOD OF CANCER

Clinical Decision Points and Diagnostic Outcomes

Figure 1. Clinical Flow and Patient Outcomes

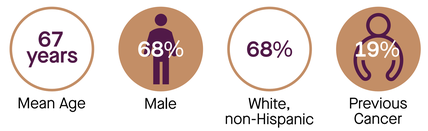


*Residual risk based on 13 cancers diagnosed after retest-initiated diagnostic work-up out of 145 patients with a retest. CSD, cancer signal detected; CSO, cancer signal origin; CSU, clinical status unavailable at time of analysis; MCED, multi-cancer early detection; NCSD, no cancer signal detected; RR, residual risk; SD, standard deviation.

- As of 20 March 2024, 145 patients had an MCED Retest (**Figure 1**)
- Mean time between the first MCED test and Retest was similar in the CSD and NCSD groups
  - Retest CSD (n = 45): 5.0 months (SD 1.9)
  - Retest NCSD (n = 100): 5.4 months (SD 2.2)
- Of these 145 patients, 118 (81%) had clinical follow-up reported through the QA/QI program (see Methods for additional details)
  - Mean time from first test to last follow-up contact was 13.3 (SD 8.4) months
  - Patients with no cancer diagnosis had longer mean follow-up time than those with a cancer diagnosis
    - 16.7 (SD 8.0) months for patients without cancer diagnosed (n = 72)
    - 10.3 (SD 3.7) months for patients with cancer diagnosed (n = 13)
  - At the time of this analysis, 13 of 45 (29%) patients with a CSD Retest result were diagnosed with cancer (**Figure 3**, **Table 2**), compared to none (0/100) with an NCSD Retest result

Demographics

Figure 2. Demographics of Patients With Retest (n = 145*)



*20% of patient records were missing race/ethnicity and 11% were missing previous cancer history information; age and sex were available for all 145 patients.

- The age range of patients with a Retest was 29 to 89 years and most were male (**Figure 2**)

Residual Risk

Table 1. Imputed (Conservative) and Observed Residual Risk by Test and CSO Type (n = 145)

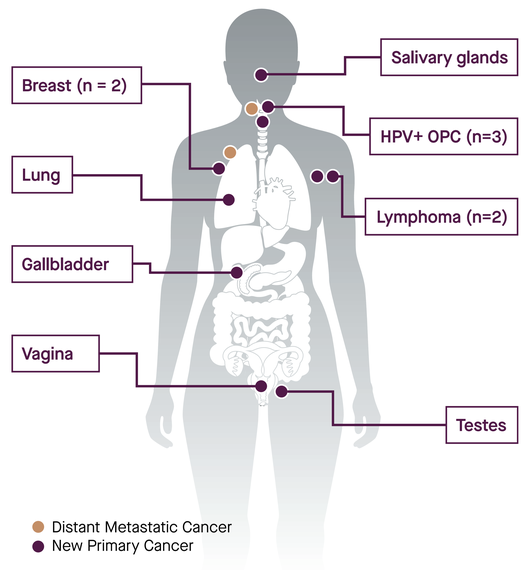
	Total	Clinical Status Available, N	Cancer Diagnosis Confirmed, n	Observed Residual Risk, n/N (%)	Imputed Residual Risk, n/Total (%)
Residual Risk Before Retest by CSO Type					
First test, All CSOs	145	93	13	**13/93 (14)**	**13/145 (9)**
Solid Tumor CSO	120	73	11	11/73 (15)	11/120 (9)
Hematologic CSO	25	14	2	2/14 (14)	2/25 (8)
Residual Risk After No Cancer Confirmation With Initial Work-Up by Retest Result and CSO Type					
CSD on Retest	45	23	13	**13/23 (57)**	**13/45 (29)**
Solid Tumor CSO	27	15	11	11/15 (73)	11/27 (41)
Hematologic CSO	18	8	2	2/8 (25)	2/18 (11)
NCSD on Retest	100	64	0	**0/64 (0)**	**0/100 (0)**

See Methods for details of imputed versus observed residual risk calculations. CSD, cancer signal detected; CSO, cancer signal origin; NCSD, no cancer signal detected.

- Preliminary observed residual risk calculations were between 0% (NCSD on Retest) and 73% (CSD on Retest and solid tumor CSO), based on the limited clinical outcomes available at this time (**Table 1**)
- Preliminary imputed residual risk calculations were between 0% (NCSD on Retest) and 41% (CSD on Retest and solid tumor CSO) (**Figure 1**, **Table 1**)

Details of Diagnosed Cancers

Figure 3. Cancers Diagnosed After Retest (n = 12*)



*One patient was confirmed to have cancer, but did not have cancer type available at time of analysis. n = 1 for cancer type unless otherwise noted. HPV, human papillomavirus; OPC, oropharyngeal cancer.

- Of the 12 diagnosed cancers with confirmed AJCC cancer type information, only breast and lung have a current USPSTF-recommended screening test[6]

Table 2. CSOs and Clinical Details of Cancers Diagnosed After Retest (n = 13)

Retest CSO*	Test 1 CSO*	Diagnosed Cancer Type (AJCC)	Cancer Stage	Histologic Type	Prior Cancer History
Breast	Breast	Breast	IV	Adenocarcinoma, NOS	No
Breast	Prostate	Major Salivary Glands	IV	Infiltrating duct carcinoma, NOS	No
Head and Neck	Breast	Vagina	IV	Squamous cell carcinoma, NOS	Yes
Head and Neck	Head and Neck	HPV+ OPC	I	Squamous cell carcinoma, HPV+	No
Head and Neck	Head and Neck	HPV+ OPC	Distant Recurrent	Squamous cell carcinoma, HPV+	Yes
Head and Neck	Head and Neck	HPV+ OPC	IV	Squamous cell carcinoma, HPV+	No
Lung	Lung	Lung	III	Adenocarcinoma, NOS	No
Lymphoid Lineage	Lymphoid Lineage	Hodgkin and NHL	III	Follicular lymphoma, NOS	Yes
Lymphoid Lineage	Lymphoid Lineage	Hodgkin and NHL	NA	Malignant lymphoma, non-Hodgkin, NOS	Yes
Neuroendocrine	Neuroendocrine	Testis	NA	Germinoma	No
Pancreas, Gallbladder	Pancreas, Gallbladder	Breast	Distant Recurrent	Infiltrating duct carcinoma, NOS	Yes, Breast
Pancreas, Gallbladder	Pancreas, Gallbladder	Missing	IV	Adenocarcinoma, NOS	Yes
Stomach, Esophagus	Stomach, Esophagus	Gallbladder	NA	Adenocarcinoma, NOS	No

*First CSO only is listed; the Retest CSO most recently precedes cancer diagnosis. AJCC, American Joint Committee on Cancer staging manual, version 8; HPV, human papillomavirus; CSO, cancer signal origin; NHL, non-Hodgkin lymphoma; NA, not available; NOS, not otherwise specified; OPC, oropharyngeal cancer.

CONCLUSIONS

- The high specificity (99.5%) of Galleri suggests that <1% of tested individuals would have a false positive MCED result[1]
  - However, the positive predictive value of 44% indicates false positives must be taken into account when working up CSD cases[1]
- Out of >150,000 patients with Galleri results at time of analysis, 1399 (0.9%) had a CSD result, and ~145 (10%) of these did not achieve diagnostic resolution after initial work-up and had an MCED Retest
- Early RWE shows that persistent CSD on Retest is associated with a higher risk of cancer diagnosis, suggesting the need for close monitoring and/or additional diagnostic evaluation in these patients
- No cancers have been diagnosed in patients with NCSD on Retest, within a mean of 17 months of follow-up from their first test result
- Further evaluation of diagnostic approaches in ongoing prospective clinical trials (PATHFINDER2 [NCT05155605], NHS-Galleri trial [ISRCTN 91431511]) and additional RWE may lead to formulation of the most effective diagnostic approaches
- Galleri retesting appears useful in those with a CSD and no cancer found on initial diagnostic evaluation

LIMITATIONS

- RWE is not collected in a systematic protocol-driven manner typically found in a clinical study
- Common biases in oncology RWE studies include incomplete data collection of key variables and outcomes and heterogeneous timelines for the measurement of different variables[7]
  - These are reflected in this data set as missing demographic data, variability in time to follow-up, and lack of uniform data collection for clinical outcomes
- There may be diagnostic confirmation biases based on a CSD or NCSD Retest result, influencing further work-up procedures done by HCPs
- This is a preliminary data set, with a small sample size, and the ongoing clinical studies and RWE evidence gathering mentioned above will be critical to confirm any trends seen here

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Disclosures

Study funded by GRAIL, Inc. CW is a speaker/consultant for Myriad Genetics, GRAIL, and AstraZeneca. OG reports institutional support by GRAIL, Inc. and is a Scientific Advisor for GRAIL, Inc. and Genetic Technologies Corp. MM, RJ, EH, EF, EK, JV, and RS are current or former employees of GRAIL, Inc., with equity in the company. WJ and JF are clinical consultants for GRAIL, Inc. All other authors declare no competing interests.

Acknowledgements

Funded by GRAIL, Inc. Substantial data analysis provided by Victoria Le of GRAIL, Inc. Recognition extended to Yoobin Oh and Suzan Leake, formerly of GRAIL, Inc., for their contributions.
Writing, editorial, and graphic assistance provided by Prescott Medical Communications Group, a Citrus Health Group, Inc. company (Chicago, IL).

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