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Multi-Cancer Early Detection Test is Sensitive and Accurate in Detecting Shared DNA Methylation Signal in a Variety of Lymphoid and Plasma Cell Neoplasms

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INTRODUCTION

- In 2023, hematological cancers are expected to be 9.4% of new cancer cases diagnosed in the US;[1] however, there are currently no effective screening regimens to detect these cancers in asymptomatic individuals
- Recent technological advances in molecular diagnostics have facilitated development of blood-based multi-cancer early detection (MCED) tests, intended to complement standard-of-care single-cancer screening methods
- The Galleri® test, launched in 2021, is the first validated, commercially available liquid biopsy MCED test in the US[2,3]
- Implementation of MCED screening at population scale has the potential to improve survival for patients with hematological cancers by detecting cancers at earlier stages, when treatments are more effective

OBJECTIVE

- Report the performance of the Galleri MCED test in detecting a shared cancer signal from lymphoid neoplasms (LyN) and plasma cell neoplasms (PCN) in two large clinical studies and real-world implementation (RWE) among 100,000 individuals

METHODS

- Galleri is a genome-wide targeted methylation sequencing test that detects cancer-related DNA methylation patterns in circulating tumor DNA (ctDNA) that are shared by many cancers
  - Galleri targets 100K fragments in the genome and ~1 million CpGs in cell-free DNA (cfDNA) from peripheral blood, processed by a machine learning classification algorithm, to detect the presence of a cancer signal, and then reports the most likely cancer signal origin (CSO) in a tissue or organ
- Reported here is the performance of Galleri for lymphoid or plasma cell CSO predictions across two clinical studies and RWE collected as part of a controlled quality assurance (QA) program
  - The prospective interventional PATHFINDER study (NCT04241796) included 6,578 asymptomatic individuals, aged ≥50 years, who received an earlier version of the MCED test to assess the feasibility of implementing MCED testing in an outpatient setting
  - The case-control Circulating Cell-free Genome Atlas study (CCGA; NCT02889978) included 2,823 cancer participants (cases, pre-treatment) and 1,254 non-cancer participants (controls)
  - With more than 100,000 Galleri test results returned to providers across the US, we report data from systematic collection of outcomes for cases with a cancer signal detected result and follow up information collected via a controlled QA program to monitor MCED testing in a real-world population
- Sensitivity was calculated based on detection of a cancer signal in cases where cancer was confirmed to be present; accuracy of CSO prediction was calculated for true positives

KEY RESULTS: GALLERI DETECTED A SHARED CANCER SIGNAL ACROSS MANY HEMATOLOGICAL CANCERS CURRENTLY WITHOUT STANDARD SCREENING REGIMENS

PATHFINDER Interventional Study[4]

- The Galleri test is a refined version of the PATHFINDER MCED test calibrated to detect fewer preneoplastic hematologic conditions
- In an analysis of PATHFINDER samples using the Galleri test, a cancer signal with a cancer signal origin (CSO) prediction consistent with a hematologic malignancy was detected in 11 subjects, aged 55 to 83 years (7 LyN and 4 PCN; **Table 1**)
  - Upon follow-up, a total of 7/11 (63.6%) participants were diagnosed with hematologic malignancies: 6 lymphomas and 1 PCN
  - Thus, the positive predictive value (PPV) of Galleri was 63.6% for cases with either a LyN or PCN CSO prediction and 71.4% (5/7) for cases with predicted LyN CSO
  - 4/11 (36%) participants had no cancer diagnosis:
    - 3 had monoclonal gammopathy of undetermined significance (MGUS) or monoclonal B-cell lymphocytosis (MBL) diagnosed during the study; 1 had history of MGUS prior to enrollment
    - Detected cases of MGUS and MBL represent a fraction of those present in the PATHFINDER subjects, based on an overall prevalence of ~1-3% in those aged ≥50 years[5]

Circulating Cell-free Genome Atlas (CCGA) Observational Study[2,3]

- In the third substudy of CCGA, the overall sensitivity of Galleri for LyN, based on detection of a cancer signal in cases where LyN was present, was 52.9% (119/225; [95% confidence interval, CI: 46.4%, 59.3%]); the overall sensitivity for PCN was 72.3% (34/47; [CI: 58.2%, 83.1%]; **Table 2**)
- Galleri detected a shared cancer signal from a variety of lymphoid and plasmacytic neoplasms, including B- and T-cell neoplasms, Hodgkin lymphomas, and non-Hodgkin lymphomas (**Table 2**)
  - Sensitivity was higher in more aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL; 70.5% [CI: 55.8%, 81.8%]), compared to more indolent subtypes, such as follicular lymphoma (47.8% [CI: 34.1%, 61.9%])
  - Sensitivity for difficult to diagnose Hodgkin lymphoma was 71.0% (CI: 53.4%, 83.9%)
- Galleri predicted CSO with 99% accuracy for LyN and 100% accuracy for PCN in true cancer cases (**Table 2**)
- For LyN, the sensitivity increased from stage I to stage IV (**Table 3**) (an observation that may reflect greater tumor burden and higher levels of ctDNA)[6]
  - The sensitivity for combined early stage I and II cancers was 45.7% (CI: 35.3%, 56.5%) and combined stages I-III cancers was 55.1% (CI: 46.4%, 63.5%)

Early Outcomes From Real World Data (RWD)

- Early clinical outcomes data showed results similar to the clinical trial data
  - Galleri detected a shared cancer signal from a variety of lymphomas, including chronic lymphocytic leukemia, DLBCL, follicular lymphoma, Hodgkin lymphoma, and peripheral T-cell lymphoma
  - Some cancers, including Hodgkin lymphoma, were detected as early as stage I

Table 1. Cases of asymptotic individuals with CSO prediction for hematological malignancy in the prospective interventional PATHFINDER study

Sex	Prior Cancer History	Galleri Top CSO[a]	Diagnostic Resolution	Cancer Type at Resolution	Stage at Resolution
M	None	PCN	Cancer	Lymphoma	Missing
M	None	LyN	Cancer	Lymphoma	III
M	Yes (Head & Neck)	LyN	Cancer	Lymphoma	IV
M	None	LyN	Cancer	Lymphoma	I
F	None	PCN	Cancer	Plasma Cell Neoplasm	Missing
F	None	LyN	Cancer	Lymphoid Leukemia	O
M	None	LyN	Cancer	Lymphoma	II
M	None	PCN	No Cancer		
M	None	LyN	No Cancer		
F	None	PCN	No Cancer		
M	None	LyN	No Cancer		

[a]After detection of a cancer signal, Galleri reports up to two CSO predictions.
CSO, cancer signal origin; F, female; LyN, lymphoid neoplasm; M, male; PCN, plasma cell neoplasm.

Table 2. Sensitivity and CSO accuracy of Galleri in detecting a shared cancer signal in histopathologic subtypes of lymphoma in the CCGA case-control observational third substudy

	Total cases	Sensitivity (95% CI)	Accuracy of CSO (95% CI)
LyN (overall)	225	52.9% (46.4%, 59.3%)	99.2% (95.4%, 100.0%)
Mediastinal Large B-Cell Lymphoma	2	100.0% (34.2%, 100.0%)	100.0% (34.2%, 100.0%)
Hodgkin Lymphoma	31	71.0% (53.4%, 83.9%)	100.0% (85.1%, 100.0%)
Diffuse Large B-cell Lymphoma	44	70.5% (55.8%, 81.8%)	100.0% (89.0%, 100.0%)
Mantle Cell Lymphoma	11	63.6% (35.4%, 84.8%)	100.0% (64.6%, 100.0%)
Follicular Lymphoma	46	47.8% (34.1%, 61.9%)	100.0% (85.1%, 100.0%)
Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma	40	45.0% (30.7%, 60.2%)	94.4% (74.2%, 99.7%)
B-cell Lymphoma, NOS	30	40.0% (24.6%, 57.7%)	100.0% (75.8%, 100.0%)
Peripheral T Cell Lymphoma	5	40.0% (11.8%, 76.9%)	100.0% (34.2%, 100.0%)
Lymphoplasmacytic Lymphoma	4	25.0% (1.3%, 69.9%)	100.0% (5.1%, 100.0%)
Mucosa Associated Lymphoid Tissue/Nodal Marginal Zone Lymphoma	8	0.0% (0.0%, 32.4%)	0.0% (0.0%, 0.0%)
Hairy Cell Leukemia	2	0.0% (0.0%, 65.8%)	0.0% (0.0%, 0.0%)
PCN (overall)	47	72.3% (58.2%, 83.1%)	100% (89.9%, 100.0%)

CI, confidence interval; CSO, cancer signal origin; LyN, lymphoid neoplasm; NOS, not otherwise specified; PCN, plasma cell neoplasm.

Table 3. Sensitivity and CSO accuracy of Galleri in detecting LyN and PCN by clinical stage[a]

Cancer type	Stage	Total number	Sensitivity (95% CI)	Accuracy of CSO (95% CI)
LyN[b]	Not expected to be staged	51	41.2% (28.8%, 54.8%)	95.2% (77.3%, 99.8%)
	I	33	27.3% (15.1%, 44.2%)	100.0% (70.1%, 100.0%)
	II	48	58.3% (44.3%, 71.2%)	100.0% (87.9%, 100.0%)
	III	46	71.7% (57.5%, 82.7%)	100.0% (89.6%, 100.0%)
	IV	46	60.9% (46.5%, 73.6%)	100.0% (87.9%, 100.0%)
	Missing	1	0.0% (0.0%, 94.9%)	NA
	I-II	81	45.7% (35.3%, 56.5%)	100.0% (90.6%, 100.0%)
	I-III	127	55.1% (46.4%, 63.5%)	100.0% (94.8%, 100.0%)
PCN	I	17	64.7% (41.3%, 82.7%)	100.0% (74.1%, 100.0%)
	II	16	87.5% (64.0%, 96.5%)	100.0% (78.5%, 100.0%)
	III	14	64.3% (38.8%, 83.7%)	100.0% (70.1%, 100.0%)
	I-II	33	75.8% (59.0%, 87.2%)	100.0% (86.7%, 100.0%)
	I-III	47	72.3% (58.2%, 83.1%)	100.0% (89.9%, 100.0%)

[a]Ann Arbor staging system used for LyN; Durie-Salmon staging system used for PCN.
[b]All histo-pathologic subtypes overall.
CI, confidence interval; CSO, cancer signal origin; LyN, lymphoid neoplasm; PCN, plasma cell neoplasm.

CONCLUSIONS

- Findings from two large studies and RWE demonstrate that Galleri detects a shared cancer signal and is able to identify cancer across a wide spectrum of histopathologic entities of lymphoid and plasmacytic origin, which currently have no other standard-of care-screening regimens
- This promising state of the art molecular tool may lead to better treatment outcomes and decreased mortality, saving lives through earlier detection of these previously unscreened cancers

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