The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

803.EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

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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Background: 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. Implementing MCED at population scale has the potential to improve survival for patients with lymphoid neoplasms (LyN) and plasma cell neoplasms (PCN). The Galleri test, launched in 2021, is the first commercially available liquid biopsy MCED test in the United States that has been validated.Galleri is a genome-wide targeted methylation sequencing test that detects cancer-related DNA methylation changes in cfDNA that are shared by many cancers. By targeting 100K fragments in the genome and ~1 million CpGs, processed by a machine learning classification algorithm, Galleri is able to not only detect the presence of a cancer signal, but also to identify the most likely origin of the cancer signal (CSO) in a tissue or organ. Here we report specific performance of Galleri in LyN and PCN, reported as either lymphoid or plasma cell CSO from two large clinical studies and real-world implementation (RWE) among 100,000 individuals.

Methods: The case-control (CCGA3) Circulating Cell-free Genome Atlas study (NCT02889978) included 2,823 cancer participants (cases, pre-treatment) and 1,254 non-cancer participants (controls), the prospective interventional PATHFINDER study (NCT04241796), included 6,578 asymptomatic individuals aged ≥50 and received an earlier version of MCED to assess the feasibility of implementing MCED testing. With more than 100,000 results returned to providers across the US to date, we also report early data from systematic collection of outcomes for cases with a Cancer Signal Detected (CSD) result via a controlled quality assurance (QA) program to monitor MCED testing in a real-world population.

Results: In CCGA3, the overall sensitivity of Galleri in LyN was 52.9% (119/225; 95% CI 46.4%, 59.3%); the overall sensitivity in PCN was 72.3% (34/47; 95% CI 58.2%, 83.1%) (**Table 1**). Galleri can detect a shared cancer signal from a variety of lymphoid and plasmacytic neoplasms, including Hodgkin lymphomas (HL) and non-Hodgkin lymphomas; B- and T-cell neoplasms; from mostly indolent follicular lymphoma (FL) to aggressive Diffuse Large B-Cell Lymphomas (DLBCL) and Multiple Myeloma (**Table 1**). Sensitivity was higher in more aggressive lymphomas, like DLBCL (70.5%).

Galleri demonstrated excellent performance in hematologic cancers predicting lymphoid CSO with 99% accuracy and plasma cell CSO with 100% accuracy in true cancer cases.

Galleri is intended to detect bona fide cancers and not preneoplastic conditions (ex. MGUS, MBL, CHIP). The sensitivity increased from stage I to stage IV, likely reflecting higher tumor burden and tumor fraction in cfDNA (**Table 2**). The sensitivity for early combined stage I and II cancers, which are more responsive to treatments, was 45.7%.

In PATHFINDER, using an updated commercial version of the test, there were 11 cases with CSD result and a top CSO prediction consistent with a hematologic malignancy: 7 lymphoid and 4 plasma cell neoplasia. A total of 7/11 (63.6%) participants had hematologic malignancies diagnosed: 6 lymphomas (stages I-IV) and 1 PCN. Galleri demonstrated a high PPV of 54.5% for cases with predicted CSO either LyN or PCN, and 71.4% for cases with predicted CSO Lymphoma.

Early clinical outcomes data from a controlled QA quality assurance (QA) program collected from an initial limited subset of CSD cases with follow up information showed that, similar to our clinical trial data, this test is able to detect a shared cancer signal in a variety of lymphomas (chronic lymphocytic leukemia [CLL], DLBCL, FL, PTCL, HL), some in early stages, such as HL stage I. More detail on the MCED real-world experience will be presented at the meeting.

Conclusions: Findings from two large validation studies and RWE demonstrate that Galleri promises to be a state of the art molecular tool that detects a shared cancer signal and is able to identify a large variety of histopathologic entities of lymphoid and plasmacytic origin, which currently have no other standard of care screening regimen. This tool may lead to better treatment outcomes and decreased mortality saving lives through the early detection of these previously unscreened cancers.

Disclosures Westgate: *Myriad Genetics labs:* Consultancy, Speakers Bureau; *Grail, LLC:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Salles:** *Nurix:* Consultancy; *Molecular Partners:* Consultancy; *BMS/Celgene:* Consultancy; *Loxo/Lilly:* Consultancy; *Orna:* Consultancy; *Owkin:* Current holder of *stock options* in a privately-held company; *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Novartis:* Consultancy; *Nordic Nanovector:* Consultancy; *Merck:* Consultancy, Honoraria; *Kite/Gilead:* Consultancy; *Janssen:* Consultancy, Research Funding; *Incyte:* Consultancy; *Genmab:* Consultancy; *Debiopharm:* Consultancy; *Ipsen:* Consultancy, Research Funding; *ATB Therapeutics:* Consultancy; *AbbVie:* Consultancy, Honoraria; *BeiGene:* Consultancy; *EPIZYME:* Consultancy. **Shih:** *Grail, LLC:* Current Employment; *Illumina, Inc:* Current holder of *stock options* in a privately-held company. **Lopatin:** *Grail, LLC:* Current Employment; *Illumina, Inc:* Current holder of *stock options* in a privately-held company. **Kurtzman:** *Grail, LLC:* Current Employment; *Illumina, Inc:* Current holder of *stock options* in a privately-held company. **Venn:** *Grail, LLC:* Current Employment, Research Funding; *Illumina, Inc:* Current holder of *stock options* in a privately-held company. **Parekh:** *Celgene/BMS Corporation:* Research Funding; *Karyopharm Therapeutics:* Research Funding; *Caribou Biosciences:* Research Funding; *Amgen:* Research Funding; *Grail, LLC:* Membership on an entity's Board of Directors or advisory committees. **Venstrom:** *Grail, LLC:* Current Employment; *Illumina, Inc:* Current holder of *stock options* in a privately-held company. **Younes:** *AstraZeneca:* Current Employment. **Shaknovich:** *Grail, LLC:* Current Employment.

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Table 1. High sensitivity and CSO accuracy of Galleri in detecting shared cancer-specific DNA methylation signals in diverse histopathologic subtypes of lymphoma.

	Total cases	Sensitivity	Accuracy of CSO
Lymphoid Neoplasms (overall)	225	52.9% (46.4%, 59.3%)	99.2% (95.4%, 100.0%)
Mediastinal Large B-Cell Lymphomas	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%)
DLBCL	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 (CLL)/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 (PTCL)	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 (MALT/NMZL)	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%)

Table 2. Sensitivity and CSO accuracy of Galleri in detecting lymphoid and plasma cell neoplasms by clinical stage (Ann Arbor for LyN; Durie-Salmon for PCN).

Cancer type	Stage	Total number	Sensitivity (95% CI)	Accuracy of CSO (95% CI)
Lymphoid Neoplasm (all histo-pathologic subtypes overall)	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
Plasma Cell Neoplasm	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%)

Figure 1