GRAIL

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NCCN Guidelines Panel: Head and Neck Cancers

Re: Circulating cell-free DNA (cfDNA) methylation-based multi-cancer early detection test

On behalf of GRAIL, Inc., I respectfully request the NCCN Head and Neck Panel to consider the enclosed clinical evidence[1-5] in support of Galleri™ as a methylation-based blood test for detecting cancer and predicting cancer origin for occult primary head and neck cancers.

Suggested Changes:

- **OCC-1, Occult Primary Workup** – please add bullet "Consider circulating cell-free DNA (cfDNA) methylation-based multi-cancer detection blood test (Galleri)" with new footnote: "Consider as a non-invasive complementary test for select patients, not as a replacement of existing diagnostic tests."
- **Discussion Manuscript** – A methylation-based multi-cancer early detection test (Galleri) has been developed that can detect cancer signals from cell-free DNA in peripheral blood. This test meets key criteria for a safe and effective multi-cancer detection test, including maximal cancer detection (simultaneous detection of cancer signals across more than 50 different cancers in an elevated risk population, for example, >50 years of age); preferential detection of deadly cancers to avoid overdiagnosis of cancers that are not fatal if left untreated; an extremely low false positive rate; ease of use; and prediction of the cancer signal origin (CSO), or the location in the body where the cancer started, which can help guide diagnostic evaluation and treatment.[1-5]

Regulatory Clearance: Galleri is performed in the GRAIL laboratory that is certified under the Clinical Laboratory Improvement Amendments (CLIA) and accredited by the College of American Pathologists (CAP).

Rationale Summary: Occult primary head and neck cancer, although uncommon, presents a medical conundrum. There is a lack of non-invasive and efficient complementary tests that can efficiently identify the tissue of origin for these cancers. The Circulating Cell-Free Genome Atlas (CCGA) study is the largest prospective clinical genomics program with over 15,000 participants to evaluate a methylation-based cfDNA blood test for multi-cancer detection (Galleri).[1-3] Galleri is also being studied in another large prospective trial PATHFINDER (N=6,662) in individuals without an existing cancer diagnosis (≥50 years).[4,5] Results of both studies showed significant specificity (>99%), sensitivity (67% for Stage I-III), and accuracy (>88%) in detecting cancer signal origin.[2-4] The non-invasiveness and high accuracy in predicting cancer signal origin for multiple cancers renders this test an efficient and viable option for complementing existing diagnostic workup in patients with occult primary head and neck cancer.

Supporting Literature:

CCGA[1-3] (NCT02889978) is a prospective, multicenter, case-controlled, observational study with longitudinal follow-up to determine whether targeted methylation analysis of the cfDNA multi-cancer detection blood test (Galleri) can detect and localize over 50 AJCC cancer types. In this trial, 15,254 participants with newly diagnosed cancer (n=8,584) or without cancer (n=6,670) were enrolled from 142

sites. The trial is divided into three pre-specified sub-studies for discovery (CCGA1),[1] training / validation (CCGA2),[2] and further validation (CCGA3).[3] Follow-up for all participants is planned to be at least 5 years. Results are summarized in the table below.

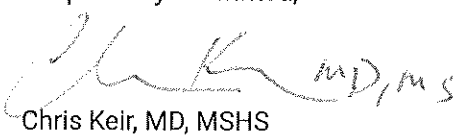
PATHFINDER[4,5] (NCT04241796) is a prospective, multi-center study that assesses the implementation of the Galleri test in 6,662 participants in the general population aged 50 years or older. Test results will be returned to providers for communication to participants to help guide the diagnostic workup of more than 50 cancer types. The number and types of diagnostic procedures required to achieve diagnostic resolution will be assessed. Performance of multi-cancer early detection test will be evaluated. Additionally, participant-reported outcomes will be collected at several time points to assess participants' perceptions about the multi-cancer early detection test. Participants are followed for 12 months. Results of the interim analysis are summarized in the table below.

Summary of CCGA and PATHFINDER results on cfDNA methylation-based blood test (Galleri).

Study	Design	N	Key findings
CCGA	Prospective, longitudinal	15,254	See below
CCGA2[2]		6,689*	Stage I-III sensitivity 67.3% (pre-specified 12 cancer types) Specificity 99.3% Cancer signal origin accuracy 93%
CCGA3[3]		5,309	Sensitivity 51.5% (Stage I: 16.8%, II: 40.4%, III: 77.0%, IV: 90.1%) Specificity 99.5% Cancer signal origin accuracy 88.7%
PATHFINDER[4,5]	Prospective, interventional	6,662	Cancer detection in 38/4011 (0.95%) Minimal positive predictive value (PPV) 43% Cancer signal origin accuracy 92%

*2202 non-cancer participants from STRIVE study.

Respectfully submitted,



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References:

1. **CCGA1**: Liu MC, Klein E, Hubbell E, et al. Plasma cell-free DNA (cfDNA) assays for early multi-cancer detection: the circulating cell-free genome atlas (CCGA) study. Ann Oncol. 2018;29(suppl 8):500.
2. **CCGA2**: Liu MC, Oxnard GR, Klein EA, et al. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Annals Oncol 2020; 31:745-759.
3. **CCGA3**: Klein EA, Richards D, Cohn A, et al. Clinical Validation of a Targeted Methylation-Based Multi-Cancer Early Detection Test. AACR Annual Meeting (Virtual). 2021. Abstract LB013.
4. **PATHFINDER**: Beer TM, McDonnell CH, Nadauld L, et al. A Prespecified Interim Analysis of the PATHFINDER Study: Performance of a Multi-Cancer Early Detection Test in Support of Clinical Implementation. J Clin Oncol. 2021;39(suppl 15;abstr 3070). Presented at ASCO Annual Meeting (Virtual). 2021.
5. **PATHFINDER**: Beer TM, McDonnell CH, Nadauld L, et al. Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. J Clin Oncol. 2021;39(suppl 15;abstr 3010). Presented at ASCO Annual Meeting (Virtual). 2021.