Blood Test Shows Potential as a Detection Tool for Early-Stage Lung Cancer

Summary includes updated data not in the abstract

ASCO Perspective

“We’re one step closer to being able to detect early lung cancer from a simple blood test. While there’s still a way to go before cell-free DNA from blood can be used for cancer detection on a broad scale, this research serves as a building block for the development of future tests,” said ASCO Expert David Graham, MD, FASCO.

CHICAGO – An initial report from the large, ongoing Circulating Cell-Free Genome Atlas (CCGA) study provides preliminary evidence that a blood test may be able to detect early-stage lung cancer. This is one of the first studies to explore blood tests analyzing free-floating or cell-free DNA as a tool for early detection of cancer.

The findings will be featured in a press briefing today and presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

“We’re excited that initial results from the CCGA study show it is possible to detect early-stage lung cancer from blood samples using genome sequencing,” said lead study author Geoffrey R. Oxnard, MD, Associate Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, MA. “There is an unmet need globally for early detection tests for lung cancer that can be easily implemented by health care systems.”

Survival rates are significantly higher when lung cancer is diagnosed early. In the United States, annual lung cancer screening with low-dose computed tomography (LDCT) is recommended by the U.S. Preventive Services Task Force (USPSTF) for people with significant smoking history, but screening is vastly underutilized (see Annual Meeting abstract #6504). Globally, LDCT is not widely adopted due to cost and lack of health infrastructure.
Having a blood test that can be done through a simple blood draw at the doctor’s office may improve lung cancer screening rates, but before such a test could be widely used, additional validation in larger data sets and in studies with people who have not been diagnosed with cancer would be needed.

Analysis of cell-free DNA from blood is already used to help choose targeted therapies (e.g., the cobas EGFR mutation test), but such “liquid biopsies” are used only for people with advanced lung cancer. Until recently there has been limited evidence to show cell-free DNA analysis may be feasible for early detection of lung cancer.

**About the study**
The CCGA study has enrolled more than 12,000 of the planned 15,000 participants (70% with cancer, 30% without cancer), across 141 sites in the United States and Canada. This report is from the first pre-planned sub-study from the CCGA, in which three prototype sequencing assays were performed on blood samples from approximately 1,700 participants. Twenty different cancer types across all stages were included in the sub-study (additional early results from the sub-study, including breast, gastrointestinal, gynecologic, blood and other cancers will be presented separately at the 2018 ASCO Annual Meeting, see abstracts #536 and #12021, and #12003).

In this initial sub-analysis, researchers explored the ability of three different assays to detect cancer in 127 people with stage I-IV lung cancer.

The three assays that were designed to detect cancer-defining signals (mutations and other genomic changes) that could be used in the development of an early cancer detection test are:

- **Targeted sequencing** to detect non-inherited (somatic) mutations, such as single nucleotide variants and small insertions and/or deletions
- **Whole-genome sequencing (WGS)** to detect somatic gene copy number changes
- **Whole-genome bisulfite sequencing (WGBS)** of cfDNA to detect abnormal cfDNA methylation patterns (epigenetic changes)

**Key findings**
Among the 127 participants with lung cancer, the biologic signal for lung cancer was comparable across the assays, and the signal increased with cancer stage. At 98% specificity, the WGBS assay detected 41% of early stage (stage I-IIIA) lung cancers and 89% of late-stage (stage IIIB-IV) cancers. The WGS assay was similarly effective, detecting 38% of early-stage cancers and 87% of late-stage cancers, whereas the targeted assay detected 51% of early-stage cancers and 89% of late-stage cancers.

Initial results showed that all three prototype assays could detect lung cancer with a low rate of false positive findings (a false positive occurs when the test suggests a person has cancer when there is no cancer). Of the 580 control samples (from people without cancer at study enrollment) in the sub-study, five (<1%) had a cancer-like signal across all three assays. Of those five participants, two were subsequently diagnosed with cancer (one with stage III ovarian cancer, and one with stage II endometrial cancer), highlighting the potential for such a test to identify early stage cancers.

The study also found that in the participants with lung cancer, more than 54% of somatic (non-inherited) mutations detected in the blood samples were derived from white blood cells and not from tumors. These mutations are likely due
to natural aging processes (so-called clonal hematopoiesis of indeterminate potential, or CHIP) and will be important to consider when developing blood tests for early detection of cancer, noted Dr. Oxnard.

Next steps
The researchers are verifying these results in an independent group of approximately 1,000 participants from CCGA as part of the same sub-study.

“These are promising early results, and next steps are to further optimize the assays and validate results in a larger group of people,” said Dr. Oxnard. With increased sample sizes, machine learning approaches are expected to improve assay performance, he noted.

This study was funded by GRAIL, Inc.

Study at a Glance

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lung Cancer</th>
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<tr>
<td><strong>Trial Phase, Type</strong></td>
<td>Genomic Study, Liquid Biopsy for Cancer Screening</td>
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<tr>
<td><strong>Patients on Trial</strong></td>
<td>1,627 clinically evaluable participants in the sub-study, of which 127 lung cancer participants were included in this sub-analysis of lung cancer</td>
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<td><strong>Primary Finding</strong></td>
<td>Three prototype assays can detect early-stage lung cancer from blood samples.</td>
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ATTRIBUTION TO THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING IS REQUESTED IN ALL COVERAGE.

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2018 ASCO Annual Meeting: Presentation Information

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other | Geoffrey R. Oxnard, MD
Thoracic Cancers Oral Abstract Session | Dana-Farber Cancer Institute
Monday, June 4, 2018: 8:12-8:24 a.m. CT | Boston, Massachusetts
McCormick Place, Hall B1
Abstract LBA8501: Genome-wide sequencing for early stage lung cancer detection from plasma cell-free DNA (cfDNA): The Circulating Cancer Genome Atlas (CCGA) study.

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Background: Plasma cfDNA genomic analysis is used widely for the care of advanced lung cancer, but its suitability for early stage lung cancer detection is not well established. CCGA (NCT02889978) is a prospective, multi-center, observational study launched for the development of a noninvasive assay for cancer detection. Methods: Blood was prospectively collected (N = 1627) from 749 controls (no cancer diagnosis) and 878 participants (pts) with newly-diagnosed untreated cancer in this preplanned substudy, including 127 pts with lung cancer. Three prototype sequencing assays were performed: paired cfDNA and white blood cell (WBC) targeted sequencing (507 genes, 60,000X) for single nucleotide variants/indels; paired cfDNA and WBC whole genome sequencing (WGS) for copy number variation (30X); and cfDNA whole genome bisulfite sequencing (WGBS) for methylation (30X). For each assay, a classification model using 10-fold cross-validation was developed for all pts with cancer, then evaluated in the pts with lung cancer; sensitivity was estimated at 95% specificity. Results: We evaluated pts with lung cancer (127) and a subset of controls (580) with similar ages (mean±SD yrs: 67±9, 60±13), 85% and 43% were ever-smokers, and 46% and 22% were men, respectively. Of 3055 nonsynonymous mutations detected across 122 evaluable pts with lung cancer, > 50% were detected in WBC consistent with clonal hematopoiesis (CH). Accounting for CH, sensitivity in 63 stage I-IIIA pts evaluable across all 3 assays was 48% (35-61, targeted), 54% (41-67, WGS), and 56% (43-68, WGBS); in 54 stage IIIB-IV pts it was 85% (73-93, targeted), 91% (80-97, WGS), and 93% (82-98, WGBS). Similar sensitivities were observed across histological subtypes (adenocarcinoma, squamous cell, small cell). Comparison to tumor WGS and multi-assay classification will be reported. Conclusions: Early stage lung cancers are detectable in cfDNA using a genome-wide sequencing approach. For lung cancer detection using targeted assays, CH must be accounted for to minimize false positives. Assay optimization is ongoing to allow further clinical development in the intended use population.

Disclosures: Geoffrey R. Oxnard, MD, Consulting or Advisory Role with AstraZeneca, Inivata, Boehringer Ingelheim, Takeda, Genentech/Roche, Novartis, LOXO, Ignyta, DropWorks, GRAIL, Patents, Royalties, Other Intellectual Property with Chugai Pharma, Bio-Rad, Sysmex, Guardant Health; Tara Maddala, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Earl Hubbell, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Thermo Fisher Scientific; Alex Aravanis, MD, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Nan Zhang, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Oliver Venn, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Anton Valouev, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Ling Shen, MPH, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Shilpen Patel, MD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Arash Jamshidi, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Samuel Gross, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Karthik Jagadeesh, MS, Employment with GRAIL; Samuel Gross, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Darya Filippova, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; John F. Beausang, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Minetta C. Liu, MD, Travel, Accommodations, Expenses from GRAIL, Merck, Celgene, Agena Biosciences, Menarini Silicon Biosystems, Cyvennio Biosystems, Research Funding (Institutional) from Eisai, Seattle Genetics, Novartis, Roche/Gentech, GRAIL, Merck, Janssen Diagnostics; Donald A. Richards, MD, PhD, Consulting or Advisory Role with IntegraGen, Lilly, Boehringer Ingelheim, Insys Therapeutics, Pharmacyclics, Merrimack, Speakers’ Bureau for Celgene; Sylvia Plevritis, PhD, Research Funding (Institutional) from Eisai, Celgene, GRAIL, Janssen/Veridx, Novartis, Gentech/Roche, Seattle Genetics, Merck and Co Inc, Richard Thomas Williams, PhD, MBBS, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL; Anne-Renee Hartman, MD, Employment with Myriad Genetics, GRAIL, Stock and Other Ownership Interests with Myriad Genetics, GRAIL; Charles Swanton, MD, FCRP, PhD, Consulting or Advisory Role with Gentech/Roche, Patents, Royalties, Other Intellectual Property with Achilles Therapeutics and others, Stock and Other Ownership Interests with Epic Sciences, Apogen Biotechnologies, GRAIL, Achilles Therapeutics, Honoraria from Roche, Boehringer Ingelheim, GlaxoSmithKline, Lilly, Celgene, Ono Pharmaceutical, SERVIER, Pfizer, Research Funding from Boehringer Ingelheim.

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