New Technologies Offer the Possibility of Identifying Cancer from a Single Blood Draw

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ASCO Perspective

“Blood tests that can identify cancer in asymptomatic individuals — particularly those at higher-risk — could change cancer diagnostics by making it easier to accurately screen for cancer and identify it at an earlier stage. While more research is needed, these results bring us one step closer to clinical use,” said ASCO Expert Merry-Jennifer Markham, MD, FACP.

This release contains updated information not included in the abstracts in the online Meeting Library (release last updated October 10, 5:30 AM ET, 4:30 PM ICT).

ALEXANDRIA, Va. - Two blood tests show promise as screening tools to identify patients with cancer of different types and across different stages. Results from the two approaches will be presented at the ASCO Breakthrough meeting October 11-13, 2019 in Bangkok.

While the technology and science behind the two tests to be presented are complex, the concept is simple. Collect a blood sample. Screen it for cancer. Detect and diagnose cancer at an earlier stage.

While both approaches use cell-free DNA to identify molecular signals of cancer, one of the approaches also uses protein marker results. Cell-free DNA are degraded DNA fragments circulating through the bloodstream, which can come from a number of sources, including tumor cells that have died and released DNA fragments.

Blood Test Identifies Location and Stage of Cancer

The first test works to detect multiple types of cancers across stages. It is based on DNA
methylation — a chemical process that can change how a gene’s function is carried out by the body without changing the order of the DNA. Methylation plays a role in many processes in the body, including the development of cancer. The researchers use a technique called bisulfite sequencing, which allows them to identify a pattern of methylation, or signature.

For the study, the researchers included more than 20 tumor types and all disease stages. Plasma DNA underwent targeted methylation analysis to develop an algorithm which could identify the cancer status and tissue of origin — the presence or absence of cancer and its location (this data was previously presented). In this independent validation analysis, the technology had a 76% overall detection rate across stages for a pre-specified set of 12 key cancer types. In addition, when the test detected cancer, the technology identified where the cancer originated in the body in 96% of the cases. Of those, 93% of the results were correct. The data presented at ASCO Breakthrough included 1,264 individuals, 654 of whom had cancer. It confirms the accuracy of the technology and represents an improved performance, including a 30% lower false-positive rate (a decrease from a 1% chance of a false-positive result to 0.7% chance in the validation data).

“The low false-positive rate is critical because we need to minimize the potential for unnecessary diagnostic tests and anxiety that will occur from false-positive results,” said Minetta Liu, MD, who is a Medical Oncologist and Chair of Oncology Research at the Mayo Clinic in Rochester, Minnesota. “The findings support the potential clinical applicability of this targeted methylation technology, reinforcing our ongoing efforts to bring a multi-cancer, blood based, early detection test into the clinic to help physicians and patients in the effort to improve cancer specific outcomes.”

The data presented at the ASCO Breakthrough meeting include the validation analysis from a pre-planned sub-study of the Circulating Cell-free Genome Atlas (CCGA) study.

The study was funded by GRAIL, Inc.

**Whole Genome-Based Blood Test Identifies Cancer Accurately**

The second test integrates shallow whole-genome sequencing data from cfDNA and protein marker results to identify cancer from a blood sample. Shallow sequencing means performing sequencing at lower depths on a single sample but running many samples at the same time, which makes the approach more cost-effective than traditional sequencing.

The multivariate cancer risk score (MCRS) was developed from a set of 76 patients with stages I-IV cancer and 152 healthy individuals. The score was validated with data from 466 pregnant women; 39 of the women were diagnosed with cancer using imaging and histology methods. The MRCS model effectively detected multiple cancer types with 71.8% sensitivity at 97.7% specificity.
The study was funded by SeekIn, Inc.

Doctor-approved information for your readers from Cancer.Net:

- The Genetics of Cancer
- Cancer Screening

View the 2019 ASCO Breakthrough Summit News Planning Team and their disclosures.

ATTRIBUTION TO 2019 ASCO BREAKTHROUGH: A GLOBAL SUMMIT FOR ONCOLOGY INNOVATORS IS REQUESTED IN ALL NEWS COVERAGE.

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Abstract 44: Simultaneous multi-cancer detection and tissue of origin (TOO) localization using targeted bisulfite sequencing of plasma cell-free DNA (cfDNA).

**Authors:** Geoffrey R. Oxnard, Eric A. Klein, Michael Seiden, Earl Hubbell, Oliver Venn, Arash Jamshidi, Nan Zhang, John F. Beausang, Samuel Gross, Kathryn N. Kurtzman, Eric T. Fung, Jessica Yecies, Rita Shaknovich, Alexander P. Fields, Mikkael A. Sekeres, Donald A. Richards, Peter Paul Yu, Alex Aravanis, Anne-Renee Hartman, Minetta C. Liu; Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic Foundation, Cleveland, OH; McKesson Specialty Health, The Woodlands, TX; GRAIL, Inc., Menlo Park, CA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; US Oncology Research, Tyler, TX; Hartford HealthCare Cancer Institute, Hartford, CT; Mayo Clinic, Rochester, MN

**Background:** A noninvasive cfDNA blood test detecting multiple cancers at earlier stages could decrease cancer mortality. In earlier discovery work, whole-genome bisulfite sequencing outperformed whole-genome and targeted sequencing approaches for multi-cancer detection across stages at high specificity. Here, multi-cancer detection and TOO localization using bisulfite sequencing of plasma cfDNA to identify methylomic signatures was evaluated in preparation for clinical validation, utility, and implementation studies. **Methods:** 2301 analyzable participants (1422 cancer [ > 20 tumor types, all stages], 879 non-cancer) were included in this prespecified
substudy from the Circulating Cell-free Genome Atlas (CCGA) (NCT02889978) study - a prospective, multi-center, observational, case-control study with longitudinal follow-up. Plasma cfDNA was subjected to a targeted methylation sequencing assay using high-efficiency methylation chemistry to enrich for methylation targets, and a machine learning classifier determined cancer status and tissue of origin (TOO). Observed methylation fragments characteristic of cancer and TOO were combined across targeted regions and assigned a relative probability of cancer and of a specific TOO. **Results:** Performance is reported at 99% specificity (ie, a combined false positive rate across all cancer types of 1%), a level required for population-level screening. Across cancer types, sensitivity ranged from 59 to 86%. Combined cancer detection (sensitivity [95% CI]) was 34% (27-43%) in stage I (n = 151), 77% (70-83%) in stage II (n = 171), 84% (79-89%) in stage III (n = 204), and 92% (88-95%) in stage IV (n = 281). TOO was provided for 94% of all cancers detected; of these, TOO was correct in > 90% of cases. **Conclusions:** Detection of multiple deadly cancers across stages using methylation signatures in plasma cfDNA was achieved with a single, fixed, low false positive rate, and simultaneously provided accurate TOO localization. This targeted methylation assay is undergoing validation in preparation for prospective clinical investigation as a cancer detection diagnostic. **Disclosures:** Geoffrey R. Oxnard, MD, Consulting or Advisory Role with AstraZeneca, Invitae, Takeda, LOXO, Ignyta, DropWorks, GRAIL, Janssen, Sysmex, Patents, Royalties, Other Intellectual Property with DFCI, Honoraria from Sysmex, Guardant Health, Foundation Medicine; Eric A. Klein, MD, Consulting or Advisory Role with GenomeDx, Genomic Health, Speakers’ Bureau for Genomic Health; Michael Seiden, MD, PhD, Employment with McKesson, Employment (Immediate Family Member) with Texas Oncology, Consulting or Advisory Role with Grail, Leadership with US Oncology, Nemucore Medical Innovations, Next Oncology, Travel, Accommodations, Expenses from McKesson, Bristol-Myers Squibb, Grail, Stock and Other Ownership Interests with McKesson, Nemucore Medical Innovations, Merck, Bristol-Myers Squibb, Honoraria from Bristol-Myers Squibb; Earl Hubbell, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.; Oliver Venn, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.; Arash Jamshidi, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.; Nan Zhang, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.; John F. Beausang, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.; Samuel Gross, PhD, Employment with GRAIL, Stock and Other Ownership Interests with GRAIL, Patents, Royalties, Other Intellectual Property (Institutional) with GRAIL, Inc.;
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Research Funding Source: GRAIL, Inc.

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<td>Mao Mao, PhD, MD</td>
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Abstract 45: Development of a blood-based cancer screening assay with a novel multivariate cancer risk score (MCRS) model by integrating shallow WGS data and plasma protein markers.

Authors: Mao Mao, Shiyong Li, Qingqi Ren, Guolin Zhong, Ruizhen Li, Yan Chen, Xin Jin, Jia Li, Jia Ju, Guanghui Long; SeekIn, Shenzhen, China; Peking University Shenzhen Hospital, Shenzhen, China; BGI Genomics, BGI-Shenzhen, Shenzhen, China

Background: Despite the increase of our knowledge about carcinogenesis and recent successful development of innovative cancer drugs, cancer mortality has only slightly decreased in the past decades. Cancer early detection is probably the most cost-effective means to reduce cancer mortality as prognosis is much better when cancer is detected and treated at the early stage. Recently studies have demonstrated that blood-based mutation detection approaches may be effective to identify asymptomatic cancer patients from general population. Methods: Here we reported a novel multivariate cancer risk score (MCRS) model that interrogates shallow whole
genome sequencing (WGS) data from cell-free DNA (cfDNA) and protein markers results in a single blood draw. **Results:** In a prospective clinical study consisting of 76 stage I-IV cancer patients and 152 normal individuals, the MCRS model demonstrated 60% sensitivity at 98.5% specificity. In order to validate clinical utility of the MCRS model in detection of cancer patients, we collated the data from a previous study of occult maternal malignancies from 1.93 million pregnant women undergoing NIPT test between 2016 and 2017. 466 out of the 639 pregnant women who tested positive for multiple chromosomal aneuploidies (MCAs) in the initial NIPTs (i.e. 0.06 - 0.1x WGS), have also underwent the protein markers test. Out of the 466 subjects, 39 maternal malignant cancer cases were diagnosed with a median follow-up of 399 days (IR, 303 - 487 days) by imaging and histology. The cancer patients presented a wide spectrum of cancer types, the most frequent being breast cancer (10 cases), liver cancer (8) and lymphoma (8), at stage II to IV. This subgroup of 466 subjects was selected as an independent validation cohort for our study. Through our new method, we analyzed shallow WGS and proteins data. The MCRS model allowed 28 of the 39 (71.8%) cancer cases to be identified with a positive predictive value of 73.7% and specificity of 97.7%. **Conclusions:** Taken together, these data demonstrate the MCRS model holds promise for detecting cancer in asymptomatic individuals, particularly in the populations at high risk of cancer.

**Disclosures:** Mao Mao, MD, PhD, Employment with SeekIn, Consulting or Advisory Role with Yuce Biotechnology, Leadership with SeekIn, Patents, Royalties, Other Intellectual Property with SeekIn, Stock and Other Ownership Interests with SeekIn, WuXi Biologics, Research Funding with SeekIn.

**Research Funding Source:** SeekIn Inc

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