Freenome Shares New cfDNA Data, Building Evidence for Colorectal Cancer Blood Test

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NEW YORK (GenomeWeb) – Non-invasive cancer detection firm Freenome has presented a new set of data from its early efforts using machine learning to investigate signatures in cell-free DNA that can detect cancer in otherwise healthy individuals.

The study used a large cohort of colorectal cancer patients, enriched for the early-stage tumors such a test will need to be able to detect if successfully commercialized. Although sensitivity varied some based on cancer stage, the approach could detect tumors overall, with up to 82 percent sensitivity at 85 percent specificity.

Shared in a poster at the American College of Gastroenterology Annual Meeting in Philadelphia this week, the study joins what remains a very limited peek at the early study results that companies like Freenome are generating as they develop methods to can glean the presence of nascent tumors from molecules in the blood or other body fluids.

When it announced its intentions in the space in 2016, Freenome outlined plans to create tests that could detect a wide range of cancers, but quickly narrowed its initial focus to four tumor types: colorectal, lung, breast, and prostate — for which there already exist some sort of screening paradigm.

In the case of colorectal cancer, existing colonoscopy protocols — and more recently, stool tests — provide a benchmark for new assays to prove themselves, as well as an established clinical infrastructure to demonstrate clinical utility and convince payors to provide insurance coverage.

According to Freenome CEO and Co-founder Gabriel Otte, cancer screening companies are realizing that "the bar for getting a test out to market and accessible to patients requires many hurdles, only one of which is science and technology."

Focusing on indications with prior established paradigms is less about the ability to show superiority over existing tests, he added, and more about the fact that it makes it much easier to make utility arguments without having to conduct years-long outcome studies.

In the study presented at ACG, Freenome investigators evaluated 1,253 samples, including 797 samples from cancer patients, 82 percent of whom had early-stage disease (up to stage II).

The company performed whole-genome sequencing on cell-free DNA extracted from these plasma samples and calculated an estimated cfDNA tumor fraction using a recently described method called IchorCNA, develop by investigators at the Broad Institute and other Boston-area institutions.
Researchers then applied Freenome’s machine learning methodology to the sequencing data to develop a classifier that could distinguish the cancer cases from controls with up to 82 percent sensitivity at 85 percent specificity.

Graphs splitting the cohort by stage illustrate that sensitivity was lower for the earliest-stage cancers — dropping below 80 percent — but stayed close to the 82 percent level for stage II and III patients, and jumped to close to 100 percent for late-stage cancers.

The numbers are strong in relation to the performance of what is the only clinically available blood-based test that has been launched so far: Epigenomics’ PCR-based Epi proColon test, which is approved by the US Food and Drug Administration, but has struggled to gain a foothold in clinical practice.

They also compare well to results shared by other firms that are working to develop blood-based screening tests.

At the annual meeting of the American Society for Clinical Oncology earlier this year, for example, Freenome competitor Grail reported on an analysis of a subset of samples from its ongoing Circulating Cell-free Genome Atlas study.

With specificity adjusted to 95 percent, the company reported it could glean a signature from bisulfite sequencing data that picked up 65 percent of stage I-III cancers, and a full 95 percent of the stage IV cancers.

Whole genome analysis of cell-free DNA yielded 61 percent sensitivity in earlier stages and 89 percent detection of stage IV cancers.

Finally, in a breakout of only CRC patients, the company could detect 69 percent of stage I and II CRC cases and 85 percent detection of stage III and IV tumors.

Researchers at Johns Hopkins also reported in January on a method they have developed, called CancerSEEK, that sifts through a combination of circulating tumor mutations, proteins, and other analytes to detect a signal of cancer.

At 99 percent specificity, the median sensitivity in detecting Stage II cancers was 73 percent, authors reported, with a rise to 78 percent sensitivity for Stage III patients. For Stage I, median sensitivity dropped down to 43 percent.

CellMax Life has presented data showing that its approach, based on circulating tumor cell analysis, could reach 77 percent sensitivity in detecting precancerous colorectal lesions.

A challenge in directly comparing results like these is that companies and research groups are reporting their data in different ways. Test sensitivity at 85 percent specificity does not mean the same thing at a higher specificity figure such as 95 percent.

Freenome Chief Medical Officer Ghirish Putcha said that the choice to report sensitivity at a locked-in 85 percent specificity at the ACG meeting was based on input from clinicians.

But Johns Hopkins’ Bert Vogelstein, one of the researchers behind the CancerSEEK study earlier this year, has argued that cancer early detection tests will ultimately require much higher specificity, to insure a minimum of false positives when applied to a general population.

Otte said that Freenome is preparing a more detailed paper on the study for peer review that describes sensitivity across the different stages at 95 percent specificity, as well. This lowered the sensitivity, as expected, he said, but the results are still very promising.

Importantly for Freenome, the cfDNA data being shared this week reflect only one analyte that the company is investigating through its larger, prospective AI-EMERGE trial.
According to Otte, the data so far seem to indicate that the different signals are at least somewhat orthogonal, or statistically independent. Based on that, he said, the firm would expect that it would see better performance with a combined approach.

"It doesn’t prove that it’s going to improve the signal, but it’s a good indication," he said.

Otte and Putcha also highlighted another aspect of the study, which used the company’s machine learning strategy to analyze how different types of variability — samples from different institutions or with different tumor fractions, for example — affected the ultimate sensitivity results.

Otte said that companies often see a drop in performance when their research progresses from a case-control setting to clinical validation, because it’s impossible to quantify and control for all of the variables that will play into performance in a cohort that better reflects the intended testing population.

Being able to understand these factors from the beginning, and potentially control for them, could mean that Freenome will be in a better position to maintain the numbers it is seeing in early experiments as it moves to later validation, he suggested.