Researchers Describe Improved Epigenetic Cancer Detection Method

Jun 14, 2018 | Molika Ashford

Premium

NEW YORK (GenomeWeb) – A UCLA team working on epigenetic analyses that can detect early cancers in a person's blood published a new study this week in *Nucleic Acids Research*, describing a method they call CancerDetector, which proved highly sensitive in detecting early-stage liver cancers in a small proof-of-principle.

The approach, which authors said they hope to commercialize as a clinical test through a company called Early Diagnostics, uses what the group believes is a novel probabilistic methodology, which projects methylation states of multiple adjacent CpG sites for each individual sequencing read.

The method comprises three main steps. First, the identification of a DNA methylation signature that is specific to cancer — in the case of this study, liver cancer. This is done through analysis of methylation data from tumors, matched normal tissues, and normal plasma cfDNA samples from public databases like The Cancer Genome Atlas.

The second step is to perform methylation sequencing on the plasma cell-free DNA of an individual — analyzing each read from those areas of the genome identified in step 1 and calculating the likelihood that that read is tumor-derived. These calculations can then be used to derive a measure of tumor fraction in a sample, which provides a prediction of whether a particular individual has cancer.

A main advantage in the approach is that it can help amplify an aberrant methylation signature that is present only in a tiny fraction of cell-free DNA without the need to increase sequencing depth.

Jasmine Zhou, the study's senior author said that the analogy she uses to describe the probabilistic approach is that it addresses the task of finding "needles in a haystack," i.e. small fragments of aberrantly methylated tumor DNA in the blood, by aggregating needles into sticks and sticks into larger, more easily detected blocks.

The same team is responsible for a prior method — also based on analysis of DNA methylation — which

they reported last year in *Genome Biology*.

That method, called CancerLocator, was more akin to others that have been proposed, which use an overall calculation of the rate of CpG methylation at specific sites to differentiate cancer and non-cancer patterns.

In the new study this week, Zhou and colleagues compared their earlier approach with the newer CancerDetector methodology using a set of simulated datasets that they created by combining actual methylation sequencing reads from normal plasma cell-free DNA and from solid tumor samples — melding the two to create data that represent a variety of tumor fractions and sequencing coverages.

According to the authors, CancerDetector showed itself able to mark the presence of tumor cfDNA in contrived data with a lower tumor fraction and at lower sequencing coverage than the earlier CancerLocator method.

After the experiments with simulated samples, the investigators then applied CancerDetector to real plasma cfDNA samples — from 32 healthy individuals, 8 HBV carriers, and 33 liver cancer patients.

The investigators randomly split the 32 healthy plasma samples, putting three-quarters into a training set and using the rest for testing the method. Using sequencing data from the training set, along with TCGA microarray data of solid liver tumors and matched normal tissues, the team used their probabilistic approach to identify liver cancer-specific markers that would then be applied to predict tumor fraction in the test set samples.

Encouragingly, even looking just at detection levels if specificity were locked at 100 percent, CancerDetector showed strong sensitivity — 94.9 percent on average across 10 runs with standard deviation of just 2.7 percent. CancerLocator, in contrast, only averaged 77.3 percent sensitivity plus or minus about 9 percent.

In the race to develop blood-based cancer screening tests, specificity is immensely important because of the negative impact of false-positive results. But equally crucial is the ability to detect cancers at their earliest stages.

In the study, the UCLA team also looked at the performance of the method in the 25 subjects who had early-stage liver cancers, showing that CancerDetector still maintained its nearly 95 percent sensitivity in this group.

Another potentially important aspect for a future clinical test is the ability to differentiate cancer from other conditions or illnesses that might have similar clinical signs and symptoms.

The authors argued that the results seen for the hepatitis B samples were especially promising in this regard. The CancerDetector method predicted near-zero tumor fractions for all eight HBV samples in the study, clearly differentiating them from the cancer subjects.

The UCLA team is far from alone in looking to methylation, or other epigenetic processes, for potential early cancer detection. Commercial firms now operating with huge financial backbones, like Grail, have incorporated methylation sequencing into their programs. Unfortunately, they have shared little data so

far about whether they have been able to define or create specific methylation-based predictors.

Other companies have adopted specific epigenetics-based methods, including a firm called Singlera, which is advancing a methylation haplotype method initially described by authors from the University of California, San Diego.

IvyGene, a holding of the Laboratory for Advanced Medicine, has also cited the same UCSD work as a basis for the test it is commercializing.

In their study this week, the UCLA team also did some rough comparisons of CancerDetector with some of these other methods as published.

According to the authors, the UCSD haplotype approach, much like CancerLocator, only reached about 70 percent sensitivity at 100 percent specificity.

The investigators are now seeking grant funding for continued exploration of the method, Zhou said, with goals to both refine the approach itself, and to conduct validation that the group hopes will recapitulate these early results in a larger group of patient samples.

To translate their method to a clinical test, the team will also need to show that they can establish a set cutoff point for tumor fraction that can accurately divide cancer and non-cancer subjects when applied prospectively. In the current study, the calculations of sensitivity were not based on this type of specific cutoff.

This will require cross-validation using a large number of non-cancer samples to build a reliable upper-limit for a non-cancer signal, the authors wrote.

Filed Under Cancer Sequencing liver cancer UCLA cancer screening early detection methylation bisulfite sequencing

We recommend

CancerLocator Tool Aims to Non-Invasively Diagnose Cancer, Pinpoint Tissue of Origin
GenomeWeb

Methylation-Specific PCR Helps Uncover Potential cfDNA Biomarker for Lung Cancer Prognosis
GenomeWeb

New Protocol for Sequencing Small Amounts of Methylated Free Circulating DNA May Help with Cancer Dx
GenomeWeb

Archived Cancer Samples Yield DNA Methylation Insights
GenomeWeb

Lung Cancer Study Provides Clinical Validation for Digital PCR-Based Liquid Biopsy
GenomeWeb

MSKCC Researchers Debut High-Intensity Liquid Biopsy Method Developed With Funding from Grail
GenomeWeb

Powered by