Detecting Cancer With Cell-Free Fragmentation

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Genome-Wide Cell-Free DNA Fragmentation: A Potential Low-Cost Cancer Screening Method

By Peggy I. Wang

Imagine, taking a simple blood draw to find out if you have cancer, and if so, the cancer's location and molecular type. While this scenario may have sounded like science fiction not long ago, liquid biopsies are now an exciting, tangible, area of cancer research.

I spoke with two researchers who have developed an approach to detect cancer from cell-free DNA by looking at DNA fragmentation: Robert B. Scharpf, PhD, associate professor of oncology at the Sidney Kimmel Cancer Center and Biostatistics at the Johns Hopkins Bloomberg School of Public Health and Victor E. Velculescu, MD, PhD, professor of oncology, pathology, and medicine at the Johns Hopkins University School of Medicine.

Their study, published in Nature earlier this year, demonstrates the feasibility of liquid biopsies using DNA fragmentation profiles. They show that their machine learning-based method works to detect breast, colorectal, lung, ovarian, pancreatic, and gastric or bile duct cancer.

Peggy I. Wang: Starting with the very basic: what exactly is cell-free DNA (cfDNA)?

Victor Velculescu: DNA released into blood circulation is considered cfDNA. Most cfDNA is derived from non-cancerous cells, typically as a result of cell death of blood cells. In cancer patients, however, there is also a small amount of cfDNA derived from cancer cells that can be detected in the blood.

What is DNA fragmentation and how are you defining a DNA fragmentation profile?

VV: DNA is broken into pieces, or fragmented, as part of normal processes when cells die or when cfDNA is cleared from the blood. Different parts of the genome may be more susceptible to fragmentation depending on its packaging within the nucleus—and packaging can vary among different cell types or as a result of disease such as cancer.

Robert Scharpf: The “fragmentation profile” is something we developed to measure these potential differences in the packaging of DNA, defined as the ratio of the number of short fragments to the number of long fragments in non-overlapping bins across the genome.

So for each segment of DNA across the genome, we have a number that tells us something about how DNA is getting broken up there. Since we performed low-coverage whole genome sequencing (1-2X coverage), we found 5 Mb bins to provide sufficient numbers per window and resolution of the genome.

What happens to the cfDNA fragmentation profile in cancer patients?

VV: Since most cfDNA is derived from turnover of blood cells, the fragmentation profiles of healthy individuals reflect the chromatin structure of hematopoietic cells. In our study, we found these profiles to be remarkably consistent across 215 healthy individuals.

In contrast, fragmentation profiles from individuals with cancer were distinct from that of healthy individuals. Their cfDNA does not seem to be derived from only blood cells, but instead from a mixture of blood cells and the cancer tissue of origin.

RS: By looking at the fragmentation profiles, we were able to detect chromosome arm-level changes in the short to long fragment ratios, reflecting gain or loss of chromosomal copy number.

We also found bin-level changes in the fragmentation profiles, indicating the presence of smaller scale, copy-neutral alterations.

Overall, the cancer profiles were much more heterogeneous than that of healthy samples, with differences in coverage as well as fragment lengths in many regions of the genome. We think this reflects the aberrant nuclear packaging of cancer genomes.

How did you incorporate DNA fragmentation profiles into a cancer screening technique?

RS: We developed a machine learning model called “DNA evaluation of fragments for early interception,” or DELFI. Using 10-fold cross validation on DNA fragmentation profiles from 208 patients, we trained DELFI to classify whether a sample of cfDNA is from a healthy individual or a patient with cancer.

We trained DELFI on short and long fragment counts for each bin, along with chromosome arm and mitochondrial copy numbers. The patients with breast, lung, ovarian, colorectal, bile duct, or gastric cancer were gathered from various hospitals in Denmark, the Netherlands, and the United States.

Our method detected 73% (152 out of 208) cancer patients. When combined with information about mutations (identified through targeted sequencing), DELFI detected 82% of cancer cases. It misclassified as cancer 4 cases of 215.

As mentioned earlier, we think the cfDNA from cancer patients is from a mixture of blood cells and

cancer tissue of origin. Thus, we trained DELFI to further classify the tissue type of origin and were able to achieve a 61% accuracy.

With more data and a better understanding of how DNA fragmentation profiles behave in different types or stages of cancer, and also other diseases, we think DELFI could be further improved.

What kinds of things can we learn by monitoring DNA fragmentation profiles during treatment? E.g., will we be able to know more quickly if a patient is responding to treatment?

VV: We looked at DNA fragmentation profiles of 19 non-small-cell lung cancer patients with targetable mutations in EGFR or ERBB who were undergoing treatment. We previously showed that by sequencing these genes in cfDNA, we can measure the mutant allele fraction as a way to monitor the response to treatment.

Excitingly, the abnormality in the fragmentation profiles tracked well with the mutant allele fractions. There's a lot of potential here, but the use of DELFI to monitor disease requires further study.

How does looking at DNA fragmentation profile compare with other methods for detecting cancer from cfDNA, like looking at mutations or copy number changes?

RS: Our method has the potential to be very sensitive—we've detected cancers with tumor fraction levels below 0.1% as estimated by the mutant allele fraction by targeted sequencing.

It's also cost-effective, since we use low-coverage whole genome sequencing. Mutation-based approaches, in contrast, require very deep sequencing. Targeted sequencing is one way to get around the cost, but typically these approaches target fewer than 100 well-known drivers of human cancer. Many cancers do not have alterations in these genes, especially at the early stages of disease.

VV: Although we were able to detect altered profiles across all of the cancer types we've tested so far, one thing to keep in mind is that certain cancers are more likely to shed DNA into the blood stream. So some cancer types may be better suited for cfDNA assays, whether fragmentation- or mutation-based.

What are some of the next steps with this work and questions you're excited to answer?

RS: We are excited to evaluate DELFI in large-scale prospective studies and learn what DNA fragmentation can tell us about the biology of different cancers and other diseases. While these first results are promising, it was a pilot study with a couple hundred patients. We are currently working on analyzing a much larger number of healthy individuals patients with various common cancers.

VV: Another question we have is whether patients with other conditions would have altered DNA fragmentation profiles. We are further evaluating this aspect as this could potentially affect the specificity of the method. Alternatively, DELFI could emerge as a way to detect diseases beyond

cancer.

We’re also excited about the translational potential for DELFI. We were able to detect a wide range of abnormalities—changes in chromatin structure, copy number, and mutations—using very low sequencing coverage. This means it’s feasible to develop DELFI into a cost-effective screening mechanism for high-risk populations.

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