How Liquid Biopsies Can Reveal Cancer Subtype

Researchers developed a new tool, the EPIC-seq, that can diagnose cancer subtypes from patient blood samples.

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Damon Runyon alumni Ash Alizadeh, MD, PhD, and David Kurtz, MD, PhD, and others have shown that cancer can be detected via blood sample by measuring circulating tumor DNA (ctDNA). This approach, however, requires high concentrations of tumor DNA in the bloodstream and provides low resolution—in other words, it can detect cancer but cannot identify a specific cancer subtype.

Now, the pair of Stanford researchers has developed a new diagnostic tool that still only requires a blood sample, but can extract much more specific information. The tool uses cell-free DNA (cfDNA), a term that refers to all free-floating DNA in the bloodstream, to infer which genes are expressed in the DNA's tissue of origin. This allows for cancer subtyping and other predictions about clinical outcome. To make such inferences, the tool relies on epigenetic features of the cfDNA—hence its name, EPIC-seq, short for "epigenetic expression inference from cell-free DNA-sequencing."

"Epigenetic" refers to how DNA is packaged. In order to fit six feet of DNA into a cell's nucleus, DNA must be condensed into nucleosomes, which resemble beads along a string. The exposed string between beads are the "promoter" regions of DNA, where transcription factors bind to start transcription.

CfDNA molecules circulating in the bloodstream arise from the DNA fragmentation that accompanies cell death, when proteins called nucleases chop up the carefully packaged DNA. In developing EPIC-seq, Dr. Alizadeh and Dr. Kurtz hypothesized that they would observe more random chopping activity in fragments of active promoters, because they less protected than other regions of DNA. Random chopping, as indicated by fragments of different lengths, would be the epigenetic feature that indicated gene expression.

Their hypothesis was correct. Using EPIC-seq to sequence these promoter regions, the researchers were able to infer which genes were expressed in the tissue where the DNA came from, allowing them to diagnose lung cancer and lymphoma subtypes from patient blood samples. Further, by applying EPIC-seq to blood samples from patients receiving immunotherapy, they showed that individuals' gene expression profiles could be used to predict therapy response.

With this tool, Dr. Kurtz and Dr. Alizadeh have expanded the diagnostic, prognostic, and therapeutic potential of the liquid biopsy (blood sample). The team is now working to bring this test to the clinic, potentially sparing patients more invasive testing without sacrificing precision.

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