



AI-Based Liquid Biopsy May Detect Liver Fibrosis, Cirrhosis and Chronic Disease Signals

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Researchers at the [Johns Hopkins Kimmel Cancer Center](#) report that an artificial intelligence (AI)-based liquid biopsy test using genome-wide cell-free DNA (cfDNA) fragmentation patterns and repeat landscapes can detect early liver fibrosis and cirrhosis, and may also reveal signals of broader chronic disease burden.

The research was supported in part by the National Institutes of Health, and the findings, published March 4 in [Science Translational Medicine](#), represent the first time this fragmentome technology, initially studied in cancer, has been applied systematically to detection of chronic noncancer conditions.

Liquid biopsies based on cfDNA have shown success in detecting cancer, but their potential in other diseases has remained largely unexplored. In the new study, investigators used whole-genome sequencing to analyze cfDNA fragmentomes from 1,576 people with liver disease and other comorbidities, examining DNA from across their entire genomes. They examined fragment size and how the fragments were distributed across the genome, including in previously uncharacterized repetitive regions, to look for signs of disease.

In each analysis, roughly 40 million fragments spanning thousands of genomic regions were evaluated — more data than almost any other liquid biopsy test. Machine-learning algorithms were used to sort through these large-scale data to identify disease-specific fragmentation signatures. This AI technology allowed the team to zero in on the most informative patterns and develop a classifying system that detected early liver disease, advanced fibrosis and cirrhosis with high sensitivity.

“This builds directly on our earlier fragmentome work in cancer, but now using AI and genome-wide fragmentation profiles of cell-free DNA to focus on chronic diseases,” says [Victor Velculescu, MD, PhD](#), co-director of the cancer genetics and epigenetics program at the Johns Hopkins Kimmel Cancer Center and co-senior author of the study. “For many of these illnesses, early detection

could make a profound difference, and liver fibrosis and cirrhosis are important examples. Liver fibrosis is reversible in early its stages, but if left undetected, it can progress to cirrhosis and ultimately increase the risk of liver cancer.”

Unlike other liquid biopsy technologies that look for cancer-related gene mutations, the fragmentome analyzes how DNA pieces are cut, packaged and distributed across the genome, which is applicable to diseases beyond cancer, including underlying health conditions that can eventually lead to cancer development, explains the team, which was also co-led by [Robert Scharpf, PhD](#), professor of oncology, and [Jill Phallen, PhD](#), assistant professor of oncology.

“The fact that we are not looking for individual mutations is what makes this study so powerful,” says first author Akshaya Annapragada, an MD/PhD student working in the Velculescu lab. “We are analyzing the entire fragmentome, which contains a tremendous amount of information about a person’s physiologic state. The scale of these data, coupled with machine learning, enables development of specific classifiers for many different health conditions.”

An estimated 100 million people in the United States have liver conditions that put them at high risk for cirrhosis and cancer, says Velculescu. However, he notes, existing blood-based markers for fibrosis have limited sensitivity, particularly in early disease. Current blood testing does not detect early fibrosis, and detects cirrhosis only about half the time, while available imaging tools require specialized ultrasound or magnetic resonance equipment, which may not be accessible to all patients.

“Many individuals at risk don’t know they have liver disease,” Velculescu says. “If we can intervene earlier — before fibrosis progresses to cirrhosis or cancer — the impact could be substantial.”

In some cases, he says, early detection of these precursor conditions could have an even greater impact, alerting doctors to treatable conditions that, through intervention, could prevent the development of cancer.

The origins of the study trace back to a [2023 Cancer Discovery liver cancer fragmentome study](#) by Velculescu and team. When analyzing patients with liver cancer, the team observed individuals with fibrosis or cirrhosis whose fragmentation profiles appeared largely normal but showed subtle signals of disease-related changes. That observation prompted a focused investigation into the fragmentome of liver fibrosis and cirrhosis to uncover the disease-specific patterns used in the current study.

In a cohort of 570 individuals presenting with suspected serious illness, the team developed a fragmentation comorbidity index that distinguished individuals with high versus low Charlson Comorbidity Index scores, a common tool used by doctors and researchers to estimate how other health conditions may affect a person’s risk for death. The fragmentome index independently predicted overall survival and, in some analyses, proved more specific than traditional inflammatory markers. The researchers also found that some specific fragmentation signatures correlated with worse clinical outcomes.

“The fragmentome can serve as a foundation for building different classifiers for different diseases, and importantly, these classifiers are disease-specific and do not cross-react,” Annapragada says. “A liver fibrosis classifier is distinct from a cancer classifier. This is a unique, disease-specific test built from the same underlying platform.”

Beyond liver disease, the study examined a population at high risk for other conditions. The researchers also detected fragmentomic signals associated with cardiovascular, inflammatory and neurodegenerative conditions. The researchers point out that the study did not include sufficient numbers to develop disease-specific classifiers for each of these conditions, but rather suggest broader applicability, which will be one focus of ongoing research.

The researchers note that the liver fibrosis assay described in the study is a prototype and not yet a clinical test. They say next steps include further development and validation of the liver disease classifier as well as exploration of fragmentome signatures in additional chronic conditions.

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