Researchers develop machine-learning tool to detect cancer earlier via liquid biopsy

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"A huge body of evidence shows that cancer caught at later stages kills people. This new technology gets us closer to a world where people will receive a blood test annually to detect cancer earlier when it is more treatable and possibly curable," said Cristian Tomasetti, Ph.D., corresponding author of the new study and director of City of Hope's Center for Cancer Prevention and Early Detection.

Tomasetti explained that 99% of people diagnosed with Stage 1 breast cancer will be alive five years later; however, if it is found at Stage 4, when disease has spread to other organs, the five-year survival drops to 31%.

The technology City of Hope, TGen and colleagues developed was able to identify half of the cancers in the 11 studied types. The test was highly accurate with a false positive in only one out of every 100 tested. Importantly, most of the cancer samples originated from people with early-stage disease, who had few or no metastatic lesions at diagnosis.

Working in the background was an algorithm they developed called Alu Profile Learning Using Sequencing (A-Plus). It had been applied to 7,657 samples from 5,980 people—2,651 of whom had cancer of the breast, colon and rectum, esophagus, lung, liver, pancreas, ovary or stomach.

When a cell dies, it breaks down and some of the DNA material of the cell leeches into the bloodstream. Cancer signals can be found in this cell-free DNA (cfDNA). The cfDNA of normal cells breaks down at a

typical size, but cancer cfDNA fragments break down at altered spots. This alteration is hypothesized to be more present in repetitive regions of the genome.

So instead of analyzing specific DNA mutations by looking for one misarranged letter out of billions of letters, researchers led by City of Hope and colleagues at John Hopkins University came up with a new way to detect the difference in fragmentation patterns in repetitive regions of cancer and normal cfDNA. As a result, fragmentomics requires about eight times less blood than required by whole genome sequencing, Tomasetti said.

"Our technique is more practical for clinical applications as it requires smaller quantities of genomic material from a blood sample," said Kamel Lahouel, Ph.D., an assistant professor in TGen's Integrated Cancer Genomics Division and the study's co-first author. "Continued success in this area and clinical validation opens the door for the introduction of routine tests to detect cancer in its earliest stages."

Tomasetti is poised to open a clinical trial in summer 2024 to compare this fragmentomics blood testing approach with standard-of-care in adults aged 65–75. The prospective trial will determine the effectiveness of the biomarker panel in detecting an earlier stage of cancer when it is more treatable.

City of Hope's Center for Cancer Prevention and Early Detection is focused on producing key research findings and technologies based on noninvasive blood tests and imaging to detect cancers years before conventional diagnostic methods.

More information: Christopher Douville et al, Machine Learning to Detect the SINEs of Cancer, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adi3883.

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