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An initial step toward blood tests for early detection of cancer

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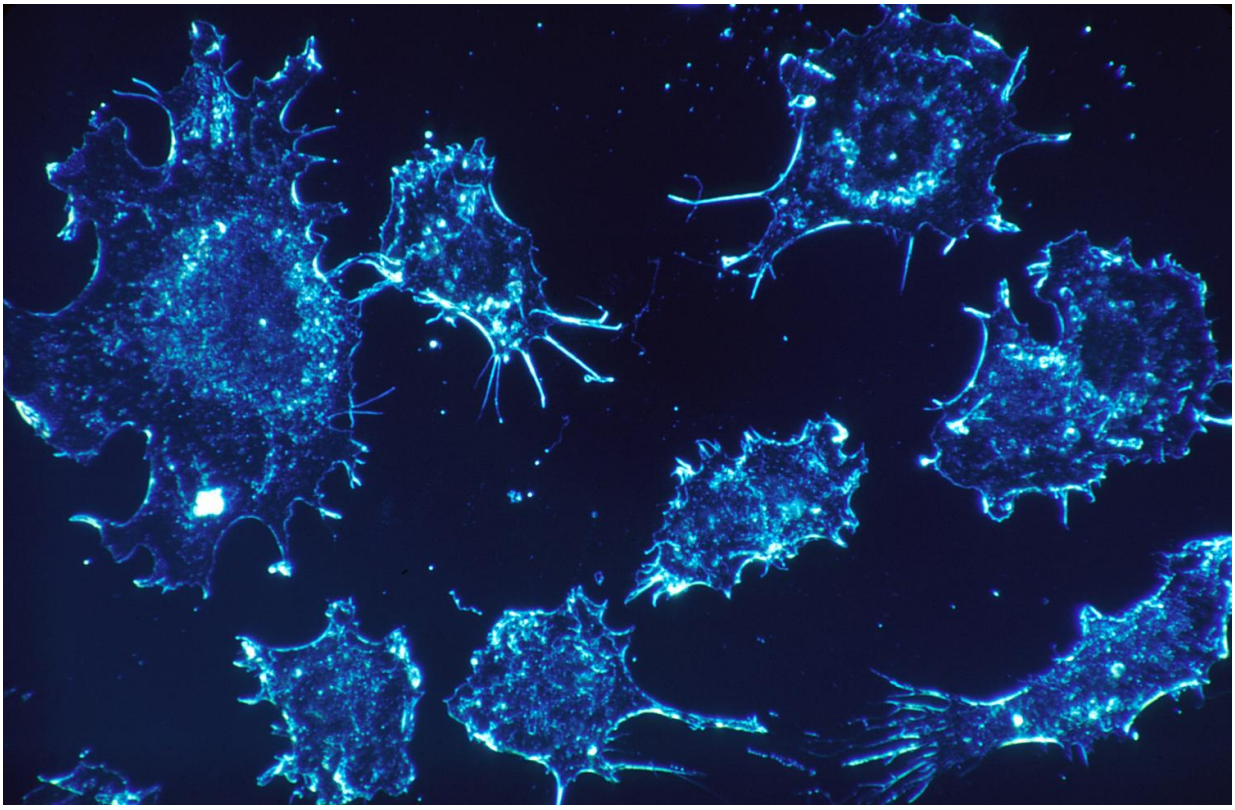

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In a study of 124 patients with advanced breast, lung, and prostate cancers, a new, high-intensity genomic sequencing approach detected circulating tumor DNA at a high rate. In 89 percent of patients, at least one genetic change detected in the tumor was also detected in the blood.

Overall, 627 (73 percent) genetic changes found in tumor samples were also found in blood samples with this approach.

The study will be featured in a press briefing today and presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting.

This innovative approach – using high-intensity sequencing to detect cancer from circulating tumor DNA in the bloodstream – heralds the development of future tests for early cancer detection.

The high-intensity sequencing approach used in this study has a unique combination of breadth and depth. It scans a very broad area of the genome (508 genes and more than two million base pairs or letters of the genome, i.e. A, T, C, and G) with high accuracy (each region of the genome is sequenced or "read" 60,000 times), yielding about 100 times more data than other sequencing approaches. This enormous amount of data will be instrumental in developing a blood test to detect cancer early.

This approach, however, differs from liquid biopsies, including commercial tests, which only profile a relatively small portion of the genome in patients already diagnosed with cancer for the purpose of helping monitor the disease or detect actionable alterations that can be matched to available drugs or clinical trials.

"Our findings show that high-intensity circulating tumor DNA sequencing is possible and may provide invaluable information for clinical decision-making, potentially without any need for tumor tissue samples," said lead study author Pedram Razavi, MD, PhD, a medical oncologist and instructor in medicine at Memorial Sloan Kettering Cancer Center (MSK) in New York, NY. "This study is also an important step in the process of developing blood tests for early detection of cancer."

Circulating tumor DNA is a term used to describe the tiny pieces of genetic material that dying cancer cells shed into the blood circulation. To create a picture of the entire genomic landscape of the tumor from circulating tumor DNA, scientists "read" each tiny fragment and then piece them together as a puzzle. In the bloodstream, circulating tumor DNA is only a small subset of the total cell-free DNA, as most circulating fragments of genetic material come from normal cells.

About the Study

The researchers prospectively collected blood and tissue samples from 161 patients with metastatic breast cancer, non-small-cell lung cancer (NSCLC), or castration-resistant prostate cancer. Thirty-seven patients were excluded due to unavailability of the results of the genetic analysis of the tumor or cell-free DNA samples. For 124 evaluable patients for concordance analysis, researchers compared genetic changes in the tumors to those in circulating tumor DNA from the blood samples.

Tumor tissues were analyzed using MSK-IMPACT, a 410-gene diagnostic test that provides detailed genetic information about a patient's cancer. In each blood sample, the researchers separated the plasma, the liquid part of the blood, from the blood cells. The cell-free DNA extracted from the plasma and, separately, the genome of white blood cells were then sequenced using the high-intensity, 508-gene sequencing assay.

"Finding tumor DNA in the blood is like looking for a needle in a haystack. For every 100 DNA fragments, only one may come from the tumor, and the rest may come from normal cells, mainly bone marrow cells," said Dr. Razavi. "Our combined analysis of cell-free DNA and white blood cell DNA allows for identification of tumor DNA with much higher sensitivity, and deep sequencing also helps us find those rare tumor DNA fragments."

Patients' tumors may have various genetic changes; there can be different changes in different parts of the same tumor, as well as in different sites where the tumor spreads in the body. For these reasons, sequencing over very broad regions of the genome is critically important to identify the multitude and diversity of genetic changes in the tumor.

Key Findings

In 89 percent of patients, at least one genetic change detected in the tumor was also detected in the blood (97 percent in metastatic breast cancer patients, 85 percent in those with NSCLC, and 84 percent in those with metastatic prostate cancer). Overall, including all genomic variations present in most if not all tumor cells (clonal) as well as those present only in subsets of the cancer cells (subclonal) from tumor tissue, the researchers detected a total of 864 genetic changes in tissue samples across the three tumor types, and 627 (73 percent) of those were also found in the blood.

Importantly, without any prior knowledge from the analysis of tumor tissue, 76 percent of "actionable" mutations (genetic changes that can be matched to an approved targeted therapy or one being tested in clinical trials) detected in tissue were also detected in blood.

"Prior research in the field has primarily focused on using knowledge from tumor tissue sequencing to identify specific changes to look for in circulating tumor DNA. This approach allows us to detect, with high confidence, changes in circulating tumor DNA across a large part of the genome without information from tumor tissue," said Dr. Razavi. While circulating tumor DNA tests targeting a smaller set of cancer genes are already available for use in routine practice to guide care, by covering a much larger number of cancer genes, this high-intensity sequencing approach may enable development of future tests for early detection of cancer.

Next Steps

The high-intensity sequencing approach used in this study is a research platform and is not intended to be commercially available to patients. To understand the current performance and potential of this assay, the researchers first tested it in advanced cancer, an area where circulating tumor DNA has been previously characterized.

"This study will inform development of technology for a future test that could eventually be used as a blood test for early cancer detection. In patients undergoing cancer screening, tumor tissue is not available, and we will need to detect changes in circulating tumor DNA without prior knowledge of tissue analysis results," said Dr. Razavi.

Advantages of Liquid Biopsy

Genomic changes can differ between various areas within a tumor, as well as among the different organs where the cancer has spread. A circulating tumor DNA test provides a "summary report" of all the genomic changes in the primary tumor and metastases. In contrast, a tissue biopsy, which typically takes only a small piece of the tumor, sometimes misses key genetic changes that fuel cancer growth.

Another advantage of liquid biopsy is its ability to capture genomic changes in real time, helping guide treatment planning without the need of additional conventional tissue biopsies. Genomic changes evolve as the cancer grows and spreads. New changes may lead to cancer recurrence or resistance to treatment. A liquid biopsy test requires only a simple blood draw. It is generally safe and convenient to repeat, allowing doctors to keep easier track of new mutations.

More information: New Technology Dives Deep Into the Cancer

Genome: An Initial Step Toward Blood Tests for Early Detection of Cancer. www.asco.org/about-asco/press- … s-deep-cancer-genome

Provided by American Society of Clinical Oncology