

Novel sequencing approach seeks to detect cancer's genomic alterations

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Findings from an early study evaluating a sophisticated new genomic-sequencing approach that analyzes cell-free DNA (cfDNA) in the blood of people with advanced cancer will help inform development of a future assay that could potentially detect cancer in its earliest stages, according to research presented today by a Memorial Sloan Kettering Cancer Center (MSK) investigator at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.

The study's lead author, Pedram Razavi, MD, PhD, a medical oncologist at MSK, reported that the new sequencing approach was able to identify at least one [tumor](#)-derived genomic alteration—even if it occurred in very low levels in the tumor—in the blood of 89 percent of patients in the study, all of whom had advanced breast, lung, or prostate [cancer](#). Notably, the approach detected alterations independently, without relying on tumor tissue sequencing results to guide the search for alterations.

The sequencing approach used in this study has a unique combination of breadth and depth: It scans a sizable portion of the genome (508 genes) and sequences each location an average of 60,000 times. This unprecedented combination of breadth and depth, dubbed "high-intensity" sequencing, yields about 100 times more data than other sequencing approaches.

According to Dr. Razavi, this huge amount of data is necessary because a successful blood-based screening test would need to be able to provide a

comprehensive genomic picture of early cancer in the absence of tumor tissue. The genomic profiles of tumors differ greatly between patients and even within tumors themselves, and the level of tumor signal in the blood can be very low.

"Prior research in this field has primarily focused on using knowledge from tumor tissue sequencing to choose which specific changes to test for in cell-free DNA or to cover small portions of genome suitable for detection of actionable alterations," said Dr. Razavi. "But at the earliest stages of cancer, a doctor would not necessarily know which alterations to look for. Our findings demonstrate that a high-intensity sequencing approach allows us to detect, with high confidence, changes in cfDNA across a large part of the genome without information from tumor tissue."

As little as 0.1 percent of all cfDNA is shed from a tumor, so the more of a genome an assay covers and the deeper it reads, the higher the chances of discovering elusive DNA from the cancer, he added.

About the Study

To test the approach, Dr. Razavi and his team collected blood from 124 evaluable patients with metastatic breast, non-small cell lung, or [prostate cancer](#); the study examined [genomic alterations](#) in people with advanced cancers because the mutational landscape in that population is already well characterized and they are expected to have tumor DNA circulating in their bloodstream. The team extracted cfDNA from each person's plasma and sequenced it using the high-intensity approach. The team also sequenced the DNA in patients' white blood cells as a control since these cells can also develop mutations with age and having this information helps eliminate non-cancer-related alterations, as noted in a separate ASCO abstract from Dr. Razavi (abstract #11526).

To confirm that the high-intensity sequencing approach was detecting DNA shed by the tumor, the team then compared the alterations identified in the cfDNA with those identified in each person's tumor tissue by MSK-IMPACT, a powerful 410-gene diagnostic test developed at MSK that provides detailed genomic information about a person's cancer and is used to analyze tumors from most people with advanced cancer treated at MSK. To date, more than 10,000 tumors have been sequenced using MSK-IMPACT, and this data is made available to the larger scientific community via a database developed at MSK called cBioPortal.

Overall, investigators detected 864 clonal (common) and subclonal (less common) genomic alterations in tissue samples across the three tumor types, and 627 (73 percent) of these alterations were found in the blood. Clonal alterations were significantly more likely to be detected in the cfDNA than subclonal alterations. In 89 percent of the study's patients, at least one of the alterations identified in the tumor tissue was also found in the blood (97 percent for those with metastatic breast cancer, 85 percent for those with non-small cell lung cancer, and 84 percent for those with metastatic prostate cancer). Most actionable mutations detected in tissue were also detected previously in the blood (76 percent).

The high-intensity nature of this sequencing approach—and the fact that it does not rely on tumor [tissue](#) sequencing to guide its search for genomic alterations—distinguishes it from the more widely known liquid biopsy approach, which scans a small amount of confirmed cancer genes in people already diagnosed with cancer to help monitor their disease or detect actionable mutations that can be matched to available drugs or clinical trials.

The sequencing [approach](#) used in this study is a research tool and not currently available to patients.

More information: Cell-free DNA (cfDNA) mutations from clonal hematopoiesis: Implications for interpretation of liquid biopsy tests.
abstracts.asco.org/199/AbstView_199_193109.html

Provided by Memorial Sloan Kettering Cancer Center

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