Large-scale cancer gene profiling is feasible but faces barriers

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Researchers at Dana-Farber Cancer Institute and other institutions leading the largest genomic tumor profiling effort of its kind say such studies are technically feasible in a broad population of adult and pediatric patients with many different types of cancer. Credit: Dana-Farber

Researchers leading the largest genomic tumor profiling effort of its kind say such studies are technically feasible in a broad population of adult and pediatric patients with many different types of cancer, and that some patients can benefit by receiving precision drugs targeted to their tumors' mutations or being enrolled in clinical trials.

Published online by *JCI Insight*, it is the first report of "clinical implementation of tumor profiling in an enterprise-wide, unselected cancer patient population," according to the authors. The report contains data on 3,727 patients whose samples were analyzed during the first year of the Profile program at Dana-Farber/Brigham and Women's Cancer Center and Boston Children's Hospital. Unlike most other genomic testing programs, Profile tumor analysis is offered to all patients regardless of age, cancer type, or stage of the cancer.

While determining the genetic makeup of a patient's tumor is a critical tool for precision cancer medicine, the report's authors noted several challenges and unanswered questions about large-scale clinical application of the methods. Just over half of patients in the study who gave consent and had tumor profiling ordered by a physician actually received results, due to a variety of technical and logistical factors. For example, a patient's cancer sample might not have had sufficient material for study or for DNA sequencing.

And in only a minority of cases - about 10 percent across the cohort, the researchers estimated - was the test information used in caring for the patient, although in some cancer types genomic results were used in a much higher percent of cases. Reasons for the attrition rate included absence of effective drugs, timing of genomic testing in the course of a patient's disease, less-than-optimal access to targeted drugs or clinical trials, and patient and provider preferences. Identifying these barriers allows researchers to develop and implement new solutions, with the goal of improving the rate of use of the genomic results, the authors said.

Overall, the turnaround time from receiving the sample to issuing a report of the findings was 5.3 weeks - a timespan the researchers said they have since shortened to less than three weeks.

Profile tumor genotyping, which started in 2011, uses a platform called OncoPanel that comprehensively sequences hundreds of known cancer-related genes in a patient sample to look for mutations or other genetic alterations that drive tumors and which might be "actionable" - that is, potentially helpful in guiding the choice of a precision treatment or in enrolling the patient in appropriate clinical drug trials. Although 3,727 cases were reported in this paper, more than 15,000 individual tumors have been analyzed to date.

"A widespread genomic profiling initiative is expensive, and this cost has been borne by our institutions," said Laura MacConaill, PhD, of Dana-Farber Cancer Institute and Brigham and Women's Hospital (BWH), the scientific director of the Profile program and corresponding author of the publication. First author of the report is Lynette M. Sholl, MD, of BWH.

MacConaill noted that the results of Profile genomic testing are being used to further research within the institutions and are being shared more widely with initiatives like Project GENIE of the American Association

for Cancer Research (AACR), which will help advance the field of precision medicine.

The study wasn't designed to measure whether tumor profiling made a difference in how patients fared, but "it nonetheless lays the groundwork for more systematic study of the impact of genomics on clinical practice and patient outcomes," the report said.

According to the report, at least one actionable mutation was discovered in about two-thirds of patient samples. In 20 percent of cases, such mutations could inform treatment decisions, such as matching a patient's tumor profile to a targeted drug or improving the original diagnosis. In the remaining cases, the information could lead to referring the patient to clinical trials of approved or investigational drugs.

Tumor profiling can also reveal rare mutations and other changes that make some cancers unusually responsive to targeted drugs - knowledge that can be applied to patients with a variety of cancer types.

The report gave some examples of how genomic testing clarified or changed a patient's diagnosis, which in turn altered treatment and prognosis.

- A patient with blood cancer who had received several diagnoses was found, through testing, to have an unusual form of acute myeloid leukemia (AML), which predicted responsiveness to imatinib. He was treated with that drug and experienced a "dramatic and sustained clinical response."
- Testing revealed an ALK gene rearrangement when a sample of a patient's uterine leiomyosarcoma was profiled. Although she needed no further treatment, doctors would be prepared to give her an ALK inhibitor drug if needed later on.
- A patient's undifferentiated small bowel sarcoma was found to

contain a KIT gene deletion, resulting in a revised diagnosis of GIST (gastrointestinal stromal tumor) that was successfully treated with imatinib.

The authors concluded that "Genomic results may alter management in diverse scenarios; however, additional barriers must be overcome to enable precision cancer medicine on a large scale."

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