# Personalized Cancer Therapy Pilot Points to Integrated Genomic Profiling Potential

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NEW YORK (GenomeWeb) – Results from a prospective study suggest that integrated genomic profiling can provide clues to personalized cancer treatment or prognoses in the majority of adult patients with solid tumor types.

As they reported today in Genome Medicine, researchers from the Icahn School of Medicine at Mount Sinai used a combination of exome sequencing, SNP array-based genotyping, and RNA sequencing, when possible, to develop personalized cancer therapy plans for 46 individuals with breast, colorectal, thyroid, and other solid cancer types.

The team identified genetic alterations that led to therapeutic recommendations for 42 of the patients, or 91 percent. Four patients reportedly had significant changes to their treatment based on the results.

"We launched this program with the idea that a more comprehensive view of [each tumor's] variant signature would make a difference in patient treatment, but even we were surprised by just how much is being missed with current testing," co-senior author Rong Chen, director of genome informatics at Mount Sinai's Icahn School of Medicine, said in a statement.

As part of a pilot effort exploring the potential clinical utility of a personalized cancer therapy program, the team enrolled individuals being treated for colorectal cancer, breast cancer, medullary thyroid carcinoma, and other primary solid tumors.

Though the technology used to profile patient samples varied somewhat for the first five individuals enrolled, tumor and normal samples from the remaining 41 participants were assessed using a single pipeline, using Illumina arrays and sequencing platforms at a CLIA-certified lab at the Icahn School of Medicine genomics core.

Using exome sequencing and SNP array genotyping on frozen or formalin-fixed paraffin-embedded samples — coupled with RNA sequencing on available frozen tumor samples — the team searched for gene mutations, expression shifts, gene fusions, or copy number patterns that might impact tumor treatment or anticipated outcomes.

"The primary goal of our integrative approach was to utilize multi-platform genomic profiling data to generate, at the cellular level, molecular portraits of the oncogenic signaling networks underlying these cancers," Chen and co-authors wrote.

When they compared the mutations that could be identified by exome sequencing with those that were found by targeted panel sequencing, the researchers saw 85 percent concordance in somatic single nucleotide variant and small insertion and deletion calls between both approaches. The targeted panel

sequencing method was more sensitive for picking up these types of alterations, they noted, likely due to the increased sequence depth they afforded.

For the copy number analyses, the team saw consistent results using the exome sequence data compared with SNP genotypes. Using RNA sequence data, gene fusions were also detected in 14 of the tumors, including one fusion event that they validated using PCR-based breakpoint mapping.

The number of mutations detected overall varied both within and across tumor types — from just a few identifiable somatic alterations per megabase of DNA in one tumor to more than two dozen mutations per megabase in another, with a mean of more than 17 somatic mutations per patient with potential cancer relevance.

The team estimated that the integrated exome sequencing-centered approach picked up between five and 13 times as many somatic mutations per patient, on average, as the FoundationOne, Oncomine Comprehensive, and Ion AmpliSeq Cancer Hotspot panels. Potentially actionable mutations appeared in 42 of the patients — roughly two to eight-fold the number identified using the panel-based approaches.

"The argument against this integrated approach is the added cost of using multiple analysis platforms," co-senior author Eric Schadt, founding director of the Icahn Institute for Genomics and Multiscale Biology, said in a statement. "But for patients battling cancer, it's hard to put a price on information that may lead to more successful outcomes."

Benefit to patients could be maximized, he added, by starting with targeted panels and adding more comprehensive testing for patients lacking actionable variants.

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