Tumor-Only Sequencing Plagued by False Positives

By Lori Solomon, Editor, Diagnostic Testing & Emerging Technologies

Many of the genetic changes detected by sequencing tumor tissue are not actually associated with the cancer, but reflect inherited germline mutations that are also present in non-cancer cells of the patient, according to a study published April 15 in *Science Translational Medicine*. As a result, matched "normal" DNA may need to be tested along with tumor tissue in order to effectively personalize therapy selection, the study authors suggest.

While it is known that tumors contain both inherited (germline) and tumor-specific (somatic) variants, tumor DNA is not usually compared to normal DNA during molecular workups of cancer patients. Cancer diagnostic assays, the authors say, only examine tumor DNA likely as a result of logistical challenges, the increased cost, and "an underappreciation" of the potential value of the matched normal DNA.

"These data suggest that matched tumor-normal sequencing analyses are essential for precise identification and interpretation of somatic and germline alterations and have important implications for the diagnostic and therapeutic management of cancer patients," writes study co-author Luis A. Diaz Jr., M.D. from Johns Hopkins University (Baltimore).

The researchers, from Personal Genome Diagnostics (PGDx; Baltimore) and Johns Hopkins University, evaluated 815 tumor-normal paired samples from patients with 15 different tumor types. Genomic alterations were assessed using next-generation sequencing of whole exomes or a targeted analysis of 111 clinically relevant genes in order to identify somatic mutations and predisposing alterations.

On average, analyses detected 140 somatic mutations with exome analysis and 4.3 somatic mutations with targeted analysis. More than three-quarter of cases (77 percent) had somatic alterations in genes associated with targeted therapies. When analyzing matched normal DNA, germline alterations were detected in 85 cancer-predisposing genes in 3 percent of patients with apparently sporadic cancers. Only one of these 27 patients was previously known to have a cancer-predisposing alteration in their germline, yet, 15 mutations were predicted to be pathogenic or likely pathogenic.

"We have shown, without analysis of germline DNA, cancer patients cannot be accurately screened for hereditary mutations in cancer predisposition genes that could inform the clinical management of the patient and indicate additional family members that could benefit from regular cancer screening," write the authors.

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Return to top of page