Concurrent RNA and DNA sequencing improves variant detection

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Performing RNA sequencing concurrently with DNA sequencing improves detection of novel variants and classification of existing variants, according to a study published online Nov. 4 in *JAMA Oncology*

to coincide with the annual meeting of the American Society of Human Genetics, held from Nov. 1 to 5 in Washington, D.C.

Carolyn Horton, from Ambry Genetics in Aliso Viejo, California, and colleagues performed paired DNA and RNA testing on individuals undergoing germline testing for a hereditary cancer indication at a single diagnostic laboratory. A total of 43,524 individuals were included, with 43,599 tests. The main outcomes examined included an increase in diagnostic yield and reduction in the rate of variants of uncertain significance (VUS).

The researchers found that variant classification was impacted in 1.3 percent of participants (549 individuals). Overall, 97 individuals had medically significant upgrades made, including 70 who had a variant reclassified from VUS to pathogenic/likely pathogenic (P/LP) and 27 who had a novel deep intronic P/LP variant that would not have been identified using DNA sequencing alone.

Overall, 17.1 percent of 545 P/LP splicing variants were dependent on RNA evidence for classification and 71.1 percent of 439 existing splicing VUS were resolved by RNA evidence. Compared with White individuals, Asian, Black, and Hispanic individuals combined had a higher increase in positive rate and decrease in VUS rate (3.1 versus 1.6 percent and −3.9 versus −2.5 percent, respectively).

"This diagnostic study highlights the importance of RNA sequencing in precision medicine to improve the identification of high-risk individuals missed by DNA-only diagnostic approaches and the medical management of tested patients," the authors write.

More information: Carolyn Horton et al, Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Testing, *JAMA Oncology* (2023). DOI:

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