Impact of concurrent DNA and RNA genetic testing on variant classification and medical management in a cohort of 40,000 patients undergoing hereditary cancer testing

Author: Carrie Horton

Background: When paired with DNA genetic testing (DGT) RNA genetic testing (RGT) may improve identification of individuals with cancer predisposition by aiding variant classification and increasing detection range; however, reports have been limited by small sample size or targeted towards highly selected cohorts.

Methods: In this retrospective study, test results, clinical data, and variant classification history were curated for all patients undergoing paired DGT+RGT for hereditary cancer from October 2019 through April 2020. We evaluated the overall results by variant type, the effect of RGT on variant classification and the potential impact on medical management.

Results: A total of 43,599 individuals were eligible for this study. Of 15,411 reported variants (pathogenic and likely pathogenic variants (P/LPV), and variants of uncertain significance (VUS)) in the 18 genes covered by RNA, 6.1% were potential splicing variants. Evidence obtained from RGT impacted variant classification in 549 individuals. Medically significant upgrades were made in 97 individuals, including 70 individuals who had a variant reclassified from VUS to P/LP and 27 individuals who had a newly detected deep intronic P/LPV. This led to eligibility for increased surveillance and surgical options in 69.0% (n=78) and 28.3% (n=32) of individuals with medically significant reclassifications (MSR), respectively. Conversely, 16 of the impacted cases (2.9%) had MSR in which variants were downgraded from LP to VUS, eliminating prophylactic surgery recommendations in 11.5% (n=13) of individuals with MSR. VUS were downgraded to likely benign or benign (LB or B) in 45.5% of impacted variants (n=250). RNA evidence reinforced a classification in a third of impacted cases (n=186; 33.9%), resulting in a reclassification from LP to P or LB to B. Amongst potential splicing variants, 57.7% (545 of 943) were P/LPVs and 17.8% of P/LP splicing variants were dependent on RGT results for classification. Nearly 1 in 50 individuals with P/LPVs would have received results with misclassified or undetected variants without RGT.

Conclusion: Our results from high-volume paired DGT+RGT at a single diagnostic laboratory demonstrate that RNA evidence improves results interpretation and accuracy by strengthening confidence in previous classifications made with more limited evidence, resolving inconclusive results, and identifying previously undetected pathogenic variants. The addition of RGT can decrease ambiguity in counseling and informs medical management recommendations.