Utility of RNA testing in Individuals at Increased Risk for Hereditary or Familial Pancreatic Cancer

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Background
PRECEDE is an international consortium designed to improve pancreatic cancer (PC) survival. Participants are offered DNA and RNA testing of 37 cancer susceptibility genes. We hypothesize that RNA testing will improve the classification of pathogenic variants (PV) in PC susceptibility genes and decrease the variant of uncertain significance (VUS) rate associated with panel testing.

Methods
The 37 gene DNA/RNA panel was completed for 616 individuals. Results were reviewed to determine the number of variant classifications that were affected by RNA data. Calculations were performed to determine the percent increase in PV detection in PC susceptibility genes.

Results
In total, 167 individuals had a PV or likely pathogenic (VLP) variant identified through testing, 151 of which were in a PC susceptibility gene. Three individuals had PV/VLP variants identified that would have been classified as VUS without RNA data, representing a 2.1% increase in detection of PV/VLP in pancreatic cancer susceptibility genes; additionally, three individuals had a PV identified that would have been classified as VLP without RNA data (see Table 1). One variant was reclassified from VUS to likely benign with RNA data; another 16 variants outside of reporting range were determined to be benign with RNA data.

Conclusions
In a cohort of individuals with or at risk for hereditary pancreatic cancer, data from RNA testing aided in the classification of splice site, deep intronic, and silent variants. Though underpowered, this study suggests that deep intronic variants could be more common in this cohort (1 in 300 samples) than in all-comers who have RNA testing (1 in 1500 samples). Additionally, the number of typically unreported intronic variants that were determined to be benign through RNA data indicates that RNA analysis may be useful if whole genome testing for cancer susceptibility becomes more commonplace.