Mutation Spectrum Identified by Germline Testing in a Pancreatic Cancer Cohort
Carmelina Heydrich, Cynthia L. Neben, Anjali Zimmer, Robert O’Connor, Jack Ji, Alicia Y. Zhou
Color Genomics, Burlingame, CA

Introduction
Pancreatic cancer accounts for an approximately 7% of all cancer-related deaths in the United States and has been associated with several hereditary cancer syndromes. Recent studies have estimated that between 4% and 11% of pancreatic cancer patients carry a germline pathogenic variant associated with increased risk for hereditary cancer.

The discrepancy in frequency of pathogenic variants between these two studies is likely due to differences in cohort size, ethnic background, and/or selection criteria. To further investigate the frequency and spectrum of pathogenic variants found in pancreatic cancer patients, we studied a cohort of individuals with a personal history of pancreatic cancer who were referred for multi-gene next generation sequencing panel testing for hereditary cancer risk. Here, we describe the demographics and results obtained from these 107 individuals who received the Color Hereditary Cancer Test. We also present three case studies of individuals who carry pathogenic variants associated with hereditary pancreatic cancer risk, including one individual who would not have met the current recommendations for genetic testing provided by the National Comprehensive Cancer Network (NCCN).

Methods
All individuals were referred by physician order for the Color Hereditary Cancer Test which analyzes 30 genes in which pathogenic variants have been associated with increased risk for hereditary breast, ovarian, uterine/endometrial, colorectal, melanoma, pancreatic, prostate, and stomach cancer (APC, ATM, BAPI, BARD1, BMPRIA, BRCA1, BRCA2, BRIPI, CDH1, CDKN2A, CDKN2B, CHEK2, EPCAM, GREM1, MUTYH, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, and TP53). The majority of these genes were assessed for variants within all coding exons and non-canonical splice regions. Laboratory procedures were performed at the Color laboratory under CLIA and CAP compliance.

Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation, and all variant classifications were approved by an American College of Medical Genetics and Genomics board certified medical geneticist. Pathogenic and likely pathogenic (hereafter referred to as pathogenic) variants were confirmed by an orthogonal technology (Sanger sequencing, aCGH, or MLPA). Ethnicity assignments and personal history of cancer were based on self-reported information.

Conclusions
- Of the 7 BRCA1 and BRCA2 carriers identified in our cohort, one individual (14.3%) would not have met current recommendations for genetic testing provided by the NCCN.
- Excluding alleles not closely associated with pancreatic cancer, the overall frequency of pathogenic variants in the cohort was 10.3% (11/107).
- This frequency of pathogenic variants of 10.3% exceeds the often cited 10% desired diagnostic yield for genetic testing.
- Further testing of a larger number of individuals with a history of pancreatic cancer is warranted to identify genes associated with pancreatic cancer risk and determine the most appropriate testing guidelines to identify pathogenic variant carriers.

References