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Title: Expanding Preventive Genomics: Observations from the Mass General Brigham Preventive Genomics Clinic

Authors:
Stephanie Coury, MS, CGC- Ariadne Labs, Brigham and Women's Hospital, Broad Institute
Sheyenne Walmsley, MS, CGC- Ariadne Labs, Brigham and Women's Hospital, Broad Institute
Janelle Shea, MS, CGC- Ariadne Labs, Brigham and Women's Hospital
Carrie Blout Zawatsky, MS, CGC- Ariadne Labs, Brigham and Women's Hospital, Broad Institute
Bethany Zettler, MS, CGC- Ariadne Labs, Brigham and Women's Hospital
Robert C. Green, MD, MPH- Brigham and Women's Hospital, Ariadne Labs, Harvard Medical School, Broad Institute

Introduction: Genomic screening to detect genetic risks in healthy individuals allows for early risk stratification, surveillance, treatment and possible prevention. The Preventive Genomics Clinic (PGC) at Mass General Brigham builds upon our NIH- funded research to offer comprehensive screening options to healthy adults and their families. Here we report uptake and results from individuals seen in the PGC over the past 5 years, and compare gene-disease risks identified in PGC patients who underwent whole genome sequencing with interpretation of ~6000 genes to what would have been found using more limited screening panels such as the CDC Tier 1 conditions (10 genes) and the ACMG 3.2 secondary findings list (81 genes), in all cases returning only pathogenic and likely pathogenic variants.

Methods: Healthy individuals self- or physician-referred to PGC had telehealth consultations with a genetic counselor who collected personal and family health histories and advised on multiple out-of-pocket genomic screening options as described below.

Results: 278 of 299 individuals (92.9%) chose one or more screening options. The majority opted for WGS (90.3%) and/or a gene panel (47.8%), with significant uptake of pharmacogenomic analysis (71.2%) and polygenic risk scores (88.0%). Results disclosed for 212 patients to date revealed that 18.9% of patients carried monogenic disease risks, 87.7% were carriers of recessive conditions (range 1-9 conditions), 27.8% had at least one common risk allele, with 17.5% carrying at least one APOE e4, all had actionable variants affecting current/future medication use and 22.5% had elevated polygenic risk of prostate/breast cancer, type 2 diabetes, coronary artery disease, or Alzheimer's disease. Of the 40 PGC patients with monogenic disease risks identified, 11 had variants in genes included in the ACMG v3.2 secondary findings list, and 3 had variants related to genes associated with CDC Tier 1 conditions.

Summary: Comprehensive genomic screening identifies meaningful genetic risks in a substantial proportion of healthy individuals. In this series monogenic disease risks were identified in 18.9% of patients tested with WGS and an expanded gene panel whereas ACMG

and CDC gene lists would have identified only 5.2% and 1.4% respectively. These results support the potential for wider implementation of preventive genomic screening in clinical practice, highlighting its role in enhancing personalized healthcare and preventive strategies.