Supplementary Materials

Supplementary Methods

Among probands, sequencing of a 47 gene panel was performed using a short-read next-generation sequencing (NGS) assay that used genomic DNA extracted from blood or saliva samples as reported previously. (Lincoln et al. 2015; Haverfield et al. 2021) A bioinformatics pipeline was used to align sequencing reads and utilized community standard and custom algorithms to identify single nucleotide variants (SNVs), small and large insertions or deletions (indels), structural variants, and exon-level copy-number variants (CNVs). (Lincoln et al. 2015, 2021; Truty et al. 2019)

The clinical significance of variants was interpreted using Sherloc (Nykamp et al. 2017), which uses a point-based system incorporating the joint consensus statement guidelines from the American College of Medical Genetics and the Association of Molecular Pathology. (Richards et al. 2015) Based on the evidence, variants were classified as benign or likely benign (B/LB), variant of uncertain significance (VUS), pathogenic or likely pathogenic P/LP. Clinically significant P/LP variants that did not meet stringent NGS quality metrics were confirmed by an orthogonal assay prior to reporting. (Lincoln et al. 2019) For probands, variants classified as P/LP and VUS were reported to the ordering healthcare provider, who then oversaw results disclosure to the individual and advised which at-risk relatives should undergo cascade testing.Post-test genetic counseling was available to all individuals, regardless of result (e.g., no clinically significant result, medically actionable result) through Invitae.

If a proband harbored at least one clinically significant variant (including carrier status), then the proband's relatives were eligible for cascade testing for the identified variant(s). A clinically significant variant was defined as a P/LP variant, a pathogenic-low penetrance (P[LP]) variant, or an increased risk allele (IRA). P(LP) variants are less penetrant compared to other P/LP variants in the same gene and may result in a less obvious Mendelian pattern of inheritance (e.g., *CHEK2* p.Ile157Thr). IRAs are variants in genes that increase the risk for a condition and have stringent criteria (Ioannidis et al., 2008), but are not associated with a Mendelian inheritance pattern (e.g., *APC* p.Ile1307Lys). Testing was offered at no charge to the relatives for the gene in which the proband's P/LP, P(LP), and/or IRA was identified for up to 90 days following the proband's test report date, though the cascade testing window was extended to 150 days after March 30, 2020, due to the COVID-19 pandemic. However, at the discretion of the ordering healthcare provider, at-risk relatives could undergo cascade testing via a multigene panel to assess for PGVs in the same gene as the proband as well as others.Cascade testing performed via a multigene panel was either billed to the relative's health insurance or paid for by the relative. The analyses in this paper were limited to those at risk relatives who underwent cascade testing via multigene panel testing. Relatives who were tested for the purposes of reclassifying variants of uncertain significance (VUS) in probands were excluded from the analysis.

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Supplementary figure 1. Flow-chart detailing size of MGPT panels and results in relatives undergoing cascade testing. While all probands were testing using the 47 gene Invitae Common Hereditary Cancers panel, choice of MGPT panel for the relative was at the discretion of the ordering provider with half (1861/3696) ordering the same Common Hereditary Cancers panel as the probands. Changes in management would be recommended for 50% (6/12), 38% (51/136) and 31% (22/70) of relatives with unexpected PGV identified with MGPT panels with 11-39, 40-79 and ≥80 genes, respectively. uPGV = unexpected PGV, H/M PGV = high or moderate risk PGV