Title: Advancing clinical validity curation and disease naming in hereditary cancer: A comprehensive recuration of breast, ovarian, colon cancer and polyposis disease genes

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Introduction: Multigene panel testing (MGPT) is commonly used to evaluate at-risk patients for hereditary cancer predisposition syndromes, particularly for breast/ovarian and colon cancer/polyposis syndromes. The Clinical Genome Resource (ClinGen) has a standardized framework for gene-disease validity (GDV) curations including regular updating of this data with new evidence and updated curation frameworks.

Methods: The Hereditary Cancer Gene Curation Expert Panel (HC-GCEP) re-evaluated gene-disease pairs previously curated and published in 2018 by the Breast/Ovarian Cancer GCEP and Colon Cancer GCEP. We utilized updated ClinGen guidelines, including lumping and splitting criteria, dyadic gene-disease naming conventions and updated framework and standard operating procedures. The curation was performed in the ClinGen gene curation interface (GCI) and results displayed on clinicalgenome.org.

Results: We curated 58 genes for breast and ovarian cancer validity, with 20 gene-disease pairs keeping their previous classifications. Notably, 20 genes/disease relationships were downgraded including 15 pairs to Refuted categories based on contradictory evidence from recent large case-control studies. For colon cancer and polyposis syndromes, 42 gene-disease pairs were curated, with 22 maintaining their previous classifications and 20 undergoing changes. Four were upgraded to Definitive classifications based on new genetic and experimental data and three genes/disease relationships were downgraded. Of previously Limited curations (12 CRC and 15 BRCA/OV) were retired due to lack of new evidence. Dyadic disease naming was introduced, e.g. BRCA1-related or CHEK2-related cancer predisposition.

Discussion: This recuration effort demonstrates the dynamic nature of gene curation and the importance of continuous literature and evidence review. For breast/ovarian cancer the major motivation for change was new case-control studies refuting disease association whereas for polyposis/colon cancer there was new evidence supporting rare disorders. The importance of standardized curation frameworks and the integration of updated validity curation to validate or refute gene-disease associations should inform the selection of genes for hereditary cancer MGPT to improve clinical practice.