A systematic approach for applying disease-specific phenotype in clinical variant interpretation

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Introduction: The 2015 ACMG/AMP clinical variant interpretation guidelines incorporate an individual's phenotype, including presenting features and family history consistent with a particular genetic cause of disease, across multiple pathogenicity criteria. However, they do not give detailed guidance on how to define or weight such disease-specific features, leading to uncertainty and discordant use in clinical variant interpretation. Here, we assessed the recommendations of existing ClinGen Variant Curation Expert Panels (VCEPs) for applying phenotypic data for their associated gene-disease pairs, and used this to create a broader framework to support more systematic use of phenotypic features in clinical variant interpretation.

Methods: We evaluated the recommendations for applying disease-specific phenotype from the sixteen ClinGen VCEPs with formally approved variant interpretation guidelines, encompassing the clinical domains of cardiovascular disease, hemostasis/thrombosis, malignant hyperthermia, hearing loss, hereditary cancers, RASopathies, neurodevelopmental disorders, and inborn errors of metabolism. We compared VCEPs' specifications regarding: when disease-specific phenotype could be applied; the sources used to identify disease-specific features; which general categories of features were chosen and the strength level/s assigned to them; and whether there were additional requirements to use disease-specific phenotype as evidence (eg, exclusion of alternate genetic causes, population allele frequency). We then used our comparative review of these VCEP specifications to identify key aspects for applying disease-specific phenotype in clinical variant interpretation.

Results: Unsurprisingly, VCEPs' specifications varied substantially regarding when disease-specific phenotype could be applied, which categories of features were chosen, and need to exclude alternate genetic etiologies, reflecting differences in the clinical and genetic heterogeneity of their associated disease. Diseasespecific features were largely drawn from VCEPs' review of existing clinical diagnostic criteria. Of note, across multiple clinical domains, the majority of VCEPs used non-quantitative approaches to select disease-specific features and determine the strength level to assign them. From this analysis, we identified four key aspects that can be used as a framework for applying disease-specific phenotype in clinical variant interpretation: (1) establishing the clinical context of testing; (2) assessing the nature of the given disease; (3) selecting consistent phenotypic features and assigning strength level; and (4) determining the need for additional evaluation, including formal exclusion of alternate genetic causes of the disease via further genetic testing.

Conclusion: Applying phenotype-related evidence in clinical variant interpretation frequently requires integrating existing knowledge of the clinical and genetic features of the particular disease with the clinical context of genetic testing. Existing VCEP recommendations provide a useful model for identifying

relevant resources to help define these features. However, our work suggests that a more detailed framework that incorporates the clinical context of testing and