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CORRESPONDENCE

Correspondence on "The role of clinical response to treatment in determining pathogenicity of genomic variants" by Shen et al.

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On behalf of the American College of Medical Genetics and Genomics (ACMG)/ClinGen/Association for Molecular Pathology (AMP) Interpreting Sequence Variant Working Group, we are pleased that *Genetics in Medicine* is supporting academic communications regarding the vital work necessary for the ongoing improvement of variant interpretation. Recently, Shen et al.[1] have proposed addition of two novel evidence codes to the Richards et al. ACMG/AMP recommendations.[2] Briefly, they propose that a novel pathogenic criterion of strong weight be added if an individual has evidence of response to a therapeutic agent and that a novel benign criterion of supporting weight be added if the individual does not have a response.

The general concept of using a response to treatment has been endorsed by the ClinGen Sequence Variant Interpretation Working Group. The first example was that of the mitochondrial Variant Curation Expert Panel (VCEP), which has incorporated the following specification for the determination of criterion PP4 (phenotype highly specific for a disease with a single genetic etiology): "patient has/had MRI features of Leigh syndrome with clinical response to biotin/thiamine" and for criterion PP1 (cosegregation with disease): "a person with neurodevelopmental regression or MRI lesions compatible with *SLC19A3*-related biotin-responsive basal ganglia disease who had significant clinical improvement in either symptoms or MRI lesions from treatment with biotin and thiamine." We expect that other VCEPs will do the same and we welcome this as an aspect of clearly and specifically defining a phenotype. In addition to criteria PP4 and PP1, phenotypes should be clearly defined for counting de novo occurrences (PS2 and PM6), case counting (PS4), and nonsegregation (BS4). We would support consideration of the principle espoused by Shen et al. for these other criteria as well. It is worth emphasizing, as Shen et al. state, the specificity of drug response as a phenotypic attribute is a crucial consideration and data on this question are typically lacking. We know very little about the utility of most drugs for most conditions. That many genetic disorders have overlapping genetic architecture and the existence of the entire drug repurposing effort should suggest a healthy dose of skepticism for claims of specificity in the absence of evidence. That being the case, we do agree that as a component of a broad phenotypic descriptor, drug response can be a useful addition, as was done for *SLC19A3*-related biotin-responsive basal ganglia disease. The strength of the PP4 criterion applied, for example, would then relate to the specificity of the treatment response in the context of other phenotypic attributes and to the gene and variant identified.

We would not, however, endorse the specific recommendation to create new pathogenicity criteria and instead encourage integration of this concept into the existing criteria as described above. Overall, the committee is moving toward consolidation of pathogenicity criteria rather than splitting out new criteria. These efforts are based on a general desire to simplify the criteria, but more fundamentally, a recognition that some of the criteria may not be probabilistically independent, an essential feature of a naïve Bayesian classifier, as the Richards et al. recommendations have been shown to be.[3,4] Response to therapy can be a useful component of the specific delineation of phenotypes, applicable to a number of existing pathogenicity criteria, but we do not anticipate that addition of novel criteria based on drug response would be useful in the foreseeable future.

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Variant Curation Expert Panel https://clinicalgenome.org/affiliation/50027/.

DISCLOSURE

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Leslie G. Biesecker, MD[1]✉, Steven M. Harrison, PhD[2] and Heidi L. Rehm, PhD[2,3]

[1]*Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA.* [2]*Broad Institute of MIT and Harvard, Cambridge, MA, USA.* [3]*Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA.* ✉*email: lesb@mail.nih.gov*

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to L.G.B.

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