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CORRESPONDENCE

Response to Biesecker et al.

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We thank Biesecker et al. for their correspondence regarding our article proposing the incorporation of clinical response to treatment in the interpretation of genomic variants.[1] Appreciation of the comprehensive nature of the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) Guidelines[2] and their foundational status in variant interpretation, infused with the wealth and breadth of expertise of the Working Group in its formulation, was pervasive throughout the conceptualization and drafting of our article,[3] and continues in this cogent correspondence. We acknowledge the examples provided from the mitochondrial Variant Curation Expert Panel (VCEP) that components of treatment response are included in PP4 and PP1 criteria for Leigh syndrome and *SLC19A3*-related biotin-responsive basal ganglia disease, respectively, and note our mutual agreement that clinical information is valuable in genomic bioinformatics.

The discrepancy between our views, and between the examples each of our groups have submitted, may lie in the interpretations of the strength of evidence ascribed to an observed clinical response to treatment. We emphasized that "the value of the treatment response in providing functional evidence of variant pathogenicity is tied to and proportional to how specific and targeted the therapeutic option is to the affected gene product, molecular pathway, and suspected diagnosis."[3] Relating to the diseases referenced by Biesecker et al.,[1] we note that biotin is not only a cofactor that functions with different carboxylases involved in gluconeogenesis, fatty acid metabolism, and branched chain amino acid catabolism, it also has been shown to modulate immunological and inflammatory functions through several different transcriptional factors and have roles in other cellular regulatory pathways.[4] Thiamine and its metabolism and transport have been implicated in diseases involving at least four genes to date, including *SLC19A2*, *SLC25A19*, *TPK1*, in addition to *SLC19A3*-related biotin-responsive basal ganglia disease. We further note that the molecular mechanism as to why this thiamine transporter disorder is responsive to biotin has yet to be elucidated, thiamine is in the "mitochondrial cocktail" commonly provided in the empiric treatment of mitochondrial dysfunction indicative of its broad but less specific usefulness, and not all patients with *SLC19A3*-related disease respond to treatment.[5,6] Thus, although biotin and thiamine administration certainly have led to remarkable clinical improvement in many patients, these supplements are not narrowly targeted.

In contrast, the prescribed treatments in our families were only known to be targeted to the molecular pathways at which they were aimed. Family 1 received replacement therapy involving a specific enzyme, while the suspected diseases in family 2, family 3, and family 5 were in well-circumscribed and delineated biochemical pathways.[3] Moreover, implicit in the standard to which we wanted to claim treatment response to justify inclusion in our article, the affected individuals needed to exhibit improved and, ideally, normalized clinical and biochemical parameters. Objective data underscoring this standard include the proband in family 1 having her triglyceride level halved and liver transaminases brought into the normal range, the proband in family 2 reaching normal weight, family 3 assessing as normal neurodevelopmentally along with seizure resolution, and the proband in family 5 demonstrating normal hemoglobin levels with no further transfusion dependency.[3]

Our primary intent in these families was patient-focused medical care and not variant reclassification. However, during the diagnostic odysseys, we were constrained by the available clinical and molecular data within the framework of the guidelines, being impeded by the inability to utilize in vitro functional assays (PS3) in family 1 and family 3, clinical phenotype (PP4) in family 2 and family 4, and variant filtering in family 5.[3] Positive responses to treatment decreased the time and cost in confirming the suspected diagnoses, subsequently allowing the clinically beneficial therapeutic interventions to be justified and continued with sustainable access and reimbursement in the ongoing medical care of these families.

We generally echo the sentiment that the overall goal would be to aim for guideline simplification and not to split or add criteria.[1] However, we also feel that a PP code and the pathogenic supporting level of evidence that it represents are insufficient and incompletely encapsulate the human-based, in vivo physiologic functional assay that clinical response to a specific and targeted treatment embodies, which we demonstrated in our families. It is our opinion that utilizing guideline simplification as an argument to not adequately capture the strength of this type of evidence would be unjust in the diagnosis and subsequent clinical care of those with genetic disorders. In fact, separate (pathogenic strong) criteria, rather than an extension of existing criteria, may even be useful because it could represent "refined and more accurately quantitated evidence" as noted in the Bayesian classification framework article by Tavtigian et al.[7] and in line with principles of medicine based evidence,[8–10] thus decreasing the number of circumstances in which "expert judgement is always necessary" and lessening "the need for clinical judgement during variant classification using the existing system."[7] The addition of clinical response to specific treatment as independent criteria and documentation of this evidence in databases such as ClinVar then can help laboratories, clinicians, and patients. We wholeheartedly welcome and it is our expectation that additional examples are forthcoming not only as a continuation of academic discourse, but also because as we collectively aim for the goal of the International Rare Diseases Research Consortium to develop treatments for 1,000 rare diseases by 2027, this would mean that more therapeutic options are available for patients and families with genetic disorders.

In summary, we have demonstrated multiple examples, from lysosomal storage diseases, mitochondrial disorders, and several other different defined biochemical pathways, in which elements from the existing guidelines that could have assisted with variant classification did not do so, whereupon administration of narrowly targeted therapeutic interventions resulted in positive clinical effects. The treatment responses in these families could be characterized objectively, including with normalization of aspects of the disease phenotypes, and represent human physiologically relevant in vivo functional assays in clarifying variant pathogenicity. Ongoing advancements in personalized medicine initiatives primarily aiming for therapeutic benefit secondarily will lead to further similar opportunities for variant resolution. We maintain our position that positive clinical response to specific and targeted

treatment merits continued academic communication and consideration as additional, separate, pathogenic strong level criteria.

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COMPETING INTERESTS

C.D.C. and M.R.H. are employed by PerkinElmer Genomics. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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