The ACMG/AMP reputable source criteria for the interpretation of sequence variants

To the Editor: In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) promulgated recommendations for the interpretation of sequence variants.[1] These recommendations have been widely implemented and shown to be useful for improving variant classification consistency.[2–4] From the beginning, they were recognized to be a starting point for further future refinements and extensions. The Clinical Genome (ClinGen) Resource is focused on curating the genome for use in molecular diagnosis.[5] One such effort is the Sequence Variant Interpretation Working Group, which has taken on the task of refining and evolving the current ACMG/AMP recommendations. This working group meets regularly and also, as individuals, interacts widely with the clinical testing community. Through these interactions, the working group has received input from multiple sources that two related criteria in the original recommendations should be considered for removal from the ACMG/AMP framework:

- PP5 "Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation."
- BP6 "Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation."

It is our strongly held view that primary data are far preferable to expert opinion without access to primary data. The PP5 and BP6 criteria rely on assertions that are not directly linked to the evidence on which they were based. These criteria might have been appropriate in 2015 as they were originally intended as a bridge to allow the community to benefit from clinical laboratory expertise and locus-specific research databases, prior to the wider use of resources such as ClinVar that provide mechanisms for laboratories and researchers to share underlying primary data. Indeed, ClinVar has been even more successful than hoped and now includes 580,831 assertions for over 375,106 variants (ClinVar website accessed 8 January 2018). Submissions with "assertion criteria provided" review status, designating that the submitter either provided their evidence to ClinVar or indicated a willingness to provide evidence upon inquiry, account for 81% (470,245-/580,831) of all submissions to ClinVar (ClinVar website accessed 8 January 2018). Therefore, there is less need to rely on assertions from reputable sources in the absence of primary evidence.

A second rationale for these two criteria was to support the efforts of the Sharing Clinical Reports Project (https://www.clinicalgenome.org/data-sharing/sharing-clinical-reports-project-scrp/), in which clinicians collected the test reports (including variant interpretation) produced by a large commercial laboratory that for the past decade has consistently declined to share underlying data or to submit assertions to ClinVar. As data for hereditary breast and ovarian cancer susceptibility alleles have increasingly been forthcoming from other laboratories, the necessity of this secondary information has declined and the currency of these data has receded.

Finally, we are concerned that these two criteria may be commonly misused by laboratories that incorporate primary data into variant assessment (e.g., functional data, criteria PS3 and BS3) and at the same time invoke criteria PP5 and BP6 for existing classifications that are based on the same set of data, which may lead to double counting, and potentially lead to errors in classification.

Based on these considerations, we propose that laboratories discontinue the use of criteria PP5 and BP6 as soon as that is practically achievable. We have removed these criteria from the ClinGen Variant Curation Interface. However, as with all types of evidence, interpretation of variants is the responsibility of the clinical testing laboratory director, who should account for the entirety of evidence and the sources of the data, and these recommendations should not be interpreted otherwise.

DISCLOSURE

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