Gene-Specific Criteria for PTEN Variant Curation

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The PTEN Expert Panel was the first ClinGen group assembled within the Hereditary Cancer domain, with a primary goal to tailor the 2015 ACMG/AMP Variant Interpretation Guidelines specific to PTEN. The group, which meets monthly, includes clinicians, researchers, and diagnostic laboratory members with a special interest in and experience with PTEN. We present our finalized benign and draft pathogenic criteria, which after evaluating with a test variant curation set will be finalized and incorporated into the group's curation process as part of the ClinGen Expert Panel application. The group developed and tested draft benign criteria on a set of 15 variants classified as benign/likely benign (BEN/LBEN) per multiple ClinVar submitters, and were advised that a concordance of 80% would prove acceptable. Using these criteria the group arrived at a BEN/LBEN classification for 13 (86.7%). The two variants not meeting criteria for BEN/LBEN included a promoter variant, c.-1311T>C, and a synonymous variant c.75G>A (p.L25L). Although c.-1311T>C is present in 23/1618 (1.4%) East Asian alleles per gnomAD, the allele denominator in this subpopulation is below the recommended 2,000 minimum threshold, leaving us unable to apply criteria that would otherwise lead to a BEN classification. PTEN c.75G>A is near a predicted U12-dependent splice donor for which in silico tools are not available. The group has also drafted pathogenic criteria. Current ACMG/AMP pathogenic criteria optimized for PTEN include phenotype criteria for PP4, boundaries for use of PVS1 vs. PM4 for truncating variants not predicted to undergo nonsense-mediated decay, functional domain definitions, functional assays qualifying for use of PS3 as well as supporting level evidence, numbers of meioses and families for segregation criteria, and use of strong criteria for more than one de novo occurrence without maternity/paternity confirmed. These criteria will be tested on a set of 15 variants classified as pathogenic/likely pathogenic per multiple ClinVar submitters. Should a concordance of 80% again be achieved, the criteria will be considered final and be incorporated along with the curation process into the expert panel application. These criteria will be compared with gene-specific optimizations developed

by other ClinGen expert panels to identify common and unique modifications to the ACMG/AMP guidelines.