The PTEN Gene ClinGen Expert Panel: A model for creating a framework for gene specific criteria using ACMG guidelines.

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ClinVar is a publicly available resource of genetic variants along with evidence supporting each assertion submitted by clinical and research laboratories. Different groups using their own approaches and available evidence for variant interpretation often results in conflicting assertions. To help ClinVar users understand the level of evidence behind each assertion, ClinGen developed a hierarchical 4-star rating system where more stars indicate a greater level of review, with ClinGen-designated Expert Panels at 3 stars. For some genes an expert group already existed; for others, ClinGen is facilitating their development. PTEN, associated with Cowden, Bannayan-Riley-Ruvalcaba, and other syndromes caused by germline PTEN mutation, is the first gene in the Hereditary Cancer domain for which an expert panel has been developed within the ClinGen framework. The group's first meeting in Dec 2014 included ClinGen staff as well as experts in PTEN clinical care and research. The group was tasked with creating an expert panel drawn from both research and diagnostic groups and developing gene-specific criteria for PTEN based on the 2015 ACMG/AMP Variant Interpretation Guidelines, which will be submitted as part of the group's formal ClinVar Expert Panel application. To develop the criteria for PTEN, working groups were assembled around the following evidence types: population frequency, splicing, computational/predictive, functional, phenotype, and segregation/de novo data. The group decided to first define benign criteria, then pathogenic, and will then curate a test set of variants. Here we present proposed PTEN-specific benign criteria the group has decided upon to date. Stand-alone: allele frequency $\geq$ 1%. Strong: allele frequency 0.1-1%, homozygous (hmz) observation in 1 unaffected individual with hmz status confirmed, 2 without confirmation. Supporting: 1 observation in trans with a pathogenic variant or 3 observations in cis/phase unknown with different pathogenic variants, 2 hmz observations without clinical data. The computational/predictive working group was challenged by the paucity of known benign PTEN missense variants, and was unable to validate use of *in silico* predictors for this purpose. A formal evaluation of criteria for pathogenic variants is in progress. We hope this

outline of our process and challenges for creating gene-specific criteria will be helpful to other expert panels as they develop and establish their variant interpretation guidelines.