The ClinGen-InSiGHT *MUTYH* Variant Curation Expert Panel: Lessons learned and a call to action.

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The ClinGen-InSiGHT Hereditary Colon Cancer/Polyposis Variant Curation Expert Panel (VCEP) was formed in 2021 to create variant curation specifications for the known genes causing these conditions. The *MUTYH* subcommittee of this VCEP is nearing the release of gene-specific recommendations for ACMG variant classification. *MUTYH*-associated polyposis (MAP) is an autosomal recessive disorder caused by germline biallelic variants in the base excision repair gene *MUTYH*. *MUTYH* encodes a glycosylase that identifies and excises adenines mispaired with the oxidation product 8-oxo-deoxyguanosine (OG), which, if left incorporated, lead to somatic G>T transversions (Brinkmeyer 2015). Through developing ACMG criteria for *MUTYH*, experts from functional, clinical, and computational fields have identified key gaps in understanding transcript expression, functional studies, and clinical features, plus inadequate communication among researchers in these fields. We first identified nomenclature discrepancies because of confusion in application of the Matched Annotation from NCBI and EMBL-EBI (MANE) *MUTYH* transcript. The *MUTYH* MANE Select transcript encodes a 521 AA protein. However, a transcript encoding a 549 AA protein is the most used by clinical labs. Our VCEP successfully had this second transcript officially recognized as MANE Plus Clinical, harmonizing historical data with current clinical reports. Another issue the VCEP addressed was establishing specific phenotypic descriptions of affected individuals. These are needed since MAP patients present with a variable number of polyps, age of onset, extracolonic features, and association with colorectal carcinoma. Somatic genomic analysis for G>T transversions, mostly done in colorectal cancer, provides strong support for MAP diagnosis, but these tests are rarely done, so data for MAP-specific cohorts are lacking. For ClinGen, *MUTYH* is the first autosomal recessive cancer gene assessed which requires additional ACMG criteria. Per ACMG guidelines (Richards 2015, Brnich 2020), only evidence from “well-established” functional assays can be used for applying criteria PS3 and BS3. Satisfactory functional assays are lacking due to inadequate use of controls and inattention to statistical principles that establish the strength of evidence, despite years of research on *MUTYH*. Improved communication among academics, clinicians, and industry labs is needed. Here, we identify the knowledge gaps in developing *MUTYH*-specific ACMG recommendations in the hopes of galvanizing these communities to generate the needed data for this routinely assessed cancer susceptibility gene.