ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2

This version specified for the following gene: *APC*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50099

RULES FOR COMBINING CRITERIA

Important notes:

As per the SVI Working Group's recommendations, in addition to the original rules for combining pathogenic criteria, these additional rules apply for variant curation in the *APC* gene.

1) The combination of one Pathogenic-Very Strong criterion and one Pathogenic-Supporting criterion reach a classification of Likely pathogenic.

2) The fulfillment of one Benign-Strong criterion reaches Likely Benign.

3) If a rare variant fulfilling only PM2_Supporting but not any other pathogenic codes also meets criteria for classification as (Likely) Benign, the population data is not considered conflicting and the variant can be classified as (Likely) Benign.

4) PVS1 cannot be applied in conjunction with splicing predictions (PP3) or RNA assays (PS3).

5) If RNA assay findings conflict with splice predictors, RNA findings overrides computational predictions (i.e., BS3 over PP3, and PS3 over BP4).

6) PS4_Variable and PP1_Variable should not be applied to a variant if BS1 is met; meeting PM2_Supporting is not required so that clinical criteria may apply for pathogenic variants with some population data.

Related publication(s): PMIDs 30192042, 33348689, 4843792