RULES FOR COMBINING PATHOGENIC/BENIGN CRITERIA

The Antibody Deficiencies VCEP will adopt the Bayesian points scale for all criteria combinations (PMID: 29300386), including in scenarios where a variant has met a combination of pro-pathogenic and pro-benign evidence codes. The two figures below showing the points scale and the corresponding classification categories come from Tables 2 and 3 of PMID: 32720330.

Point values for ACMG/AMP strength of evidence categories

Evidence Strength	Point Scale: Pathogenic	Benign
Indeterminate	0	0 §
Supporting	1	−1
Moderate	2	−2 †
Strong	4	−4
Very Strong	8	−8 †

PMID: 32720330

Table 3.

Point based variant classification categories

Category	Point ranges
Pathogenic	≥ 10
Likely Pathogenic	6 – 9 ¥
Uncertain	0 – 5
Likely Benign	−1 – −6 ¥
Benign	≤ −7

Open in a separate window

¥Operationally, the prior probability should be understood to be infinitesimally greater than 0.10. This has two effects. First, it makes the posterior probability of the ACMG likely pathogenic combining rules infinitesimally greater than 0.90, so that the likely pathogenic rules work properly. A specific value of 0.102 would have the added benefit that 7 points would meet the IARC likely pathogenic threshold of 0.95. Second, it enforces a requirement for some evidence of benign effect for sequence variants to be classified as likely benign. One could also argue that the point threshold for likely benign should really be −2. This would match the ACMG rule "Likely Benign (ii)" rather than the simple numerical requirement that the posterior probability be <0.10.