

***RPE65* Rules for Combining Codes**

For *RPE65* variants where criteria codes for benign and pathogenic evidence apply, these variants are not subjected to a variant of uncertain significance (VUS) classification. Instead, we recommend application of the rule combination point system described by Tavtigian, et al. 2020 (PMID: 32720330). We also recommend a general comparison of the point system calculation to that produced by the VCI and if there is a conflict, the point system classification will be applied.

Use the Tavtigian, et al. Table 2 below to determine how many points that each evidence code is worth and sum those point values:

TABLE 2 Point values for ACMG/AMP strength of evidence categories

Evidence Strength	Point scale	
	Pathogenic	Benign
Indeterminate	0	0 ^a
Supporting	1	-1
Moderate	2	-2 ^b
Strong	4	-4
Very strong	8	-8 ^b

Then, use the Tavtigian, et al. Table 3 below to determine which variant classification corresponds to the summed point value.

TABLE 3 Point-based variant classification categories

Category	Point ranges
Pathogenic	≥10
Likely Pathogenic	6 to 9 ^a
Uncertain	0 to 5
Likely Benign	-1 to -6 ^a
Benign	≤ -7