Adapted from:
http://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/ (University of Maryland, School of Medicine)

Patient ID:
Variant ID:

Criteria for pathogenic classification

☐ PVS1 null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease

☐ PS1 Same amino acid change as a previously established pathogenic variant regardless of nucleotide change

☐ PS2 De novo (both maternity and paternity confirmed) in a patient with the disease and no family history

☐ PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product

☐ PS4 The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls

☐ PP1 (Strong evidence) Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease

☐ PM1 Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation

☐ PM2 Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium

☐ PM3 For recessive disorders, detected in trans with a pathogenic variant

☐ PM4 Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants

☐ PM5 Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before

☐ PM6 Assumed de novo, but without confirmation of paternity and maternity

☐ PP1 (Moderate evidence) Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease

☐ PP1 Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease

☐ PP2 Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease

☐ PP3 Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.)

☐ PP4 Patient's phenotype or family history is highly specific for a disease with a single genetic etiology

☐ PP5 Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation

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Criteria for benign classification

☐ BA1 Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium

☐ BS1 Allele frequency is greater than expected for disorder

☐ BS2 Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age

☐ BS3 Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing

☐ BS4 Lack of segregation in affected members of a family

☐ BP1 Missense variant in a gene for which primarily truncating variants are known to cause disease

☐ BP2 Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern

☐ BP3 In-frame deletions/insertions in a repetitive region without a known function

☐ BP4 Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.)

☐ BP5 Variant found in a case with an alternate molecular basis for disease

☐ BP6 Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation

☐ BP7 A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved

☐ Sequencing artifact as determined by depth, quality, or other previously reviewed data