Mendelics ClinVar Assertion Criteria

For a variant to be classified as a pathogenic variant it must be located in a gene associated with Mendelian disease. Additionally, the phenotype of the patient being tested must be consistent with that disease.

Pathogenic Variant:

- Variants predicted to result in the loss of protein function in a gene for which this is a known mechanism of disease (may or may not have been previously reported in patients with disease)

1. frameshift (an insertion or deletion that is not a multiple of 3 nucleotides)

2. nonsense not located in the end of the gene (introduction of a premature stop codon)

3. change in an initiation codon if an initiation codon change has been shown to be a disease mechanism

4. change in the termination codon if previously demonstrated to be associated with disease

- Variants predicted to result in an amino acid replacement (missense) with one of the following conditions met:

1. variant demonstrated to result in reduced protein function (loss of function), or aberrant protein function (gain of function) in an appropriate functional assay

2. common disease causing pathogenic variant in a specific population based on evidence in the literature

3. variant reported in multiple affected individuals and demonstrated to segregate with disease in multiple families (Note: the number of families depends on the gene and the disease it is associated. The mode of inheritance of the disease is also considered; e.g. autosomal recessive vs dominant.)

4. Variants demonstrated to result in aberrant splicing in an appropriate functional assay (e.g. intronic or silent) or located in splice junction (at positions +1,+2, -1 and -2 in an intron unless there is data from the literature or databases to suggest the change is not pathogenic)

Likely Pathogenic Variant:

Biallelic conditions: (all the following conditions must be met)

1. diagnosis has been confirmed by functional/biochemical testing or patient phenotype is specific for disease

2. variant located in trans from a known disease causing pathogenic or likely pathogenic variant and algorithmically predicted to be deleterious

3. variant not present in GnomAD or other publically available database at a frequency consistent with being a benign variant

Monoallelic conditions: (all of the following conditions must be met)

1. variant segregates with phenotype in the family being tested (Note: reduced penetrance is considered in the evaluation.) **OR** testing parental samples demonstrates that the variant occurred de novo

2. variant not present in GnomAD or other publically available database at a frequency consistent with being a benign variant

Benign Variant:

One of the following conditions must be met:

1. variant present in GnomAD or other publically available database at a population frequency higher than expected given the prevalence of the disease and mode of inheritance.

2. Variant reported in a control population at a frequency inconsistent with being causative of disease

3. Other evidence from published literature that indicates the variant has no effect on function or constitutes a pseudodeficiency allele

Likely Benign Variant:

One of the following conditions must be met:

1. Variant found heterozygous (for dominant) or homozygous (for recessive) in multiple unaffected individuals at an allele frequency inconsistent with clinical significance based on mode of inheritance and severity of disorder

2. Variant found in *cis* with a pathogenic variant in multiple unrelated individuals

3. Variant found in unaffected family members (for monoallelic)

*Benign and likely variants are interpreted as described above and not reported in clinical reports. A list of these variants is available upon request.

Variant of Unknown Significance (VUS):

Either condition must be met:

1. Variant not clearly categorized as benign, likely benign, likely pathogenic or pathogenic.

2. Evidence from multiple sources is conflicting (i.e. evidence for both a pathogenic and benign classification exists)