ClinGen Curation Activities:

How will they support the clinical genomics community?

For more information, visit www.clinicalgenome.org.

ClinGen
Clinical Genome Resource

Gene Curation

Can variation in this gene cause disease?

By reviewing genetic and experimental data in the scientific literature, ClinGen is working to identify genes in which pathogenic variants clearly cause disease. Some gene-disease pairs, such as *BRCA1* and hereditary breast cancer, have extensive evidence, while others have less. The ClinGen Gene Curation working group has defined 6 classification categories (below) describing the level of evidence supporting a given gene-disease relationship.

Laboratories may use this type of information when deciding which genes to include in clinical testing panels, and which genes require more research studies.

Clinicians may use this type of information when interpreting test results for their patients – they may be less likely to recommend medical management for variants in genes with insufficient evidence.

Definitive · **Strong** · **Moderate** · **Limited** · **Disputed** · **Refuted**

Variant Curation

Which changes in the gene cause disease?

All genes have variants. If a variant significantly changes how a gene functions, it can cause disease (pathogenic); if it does not, the variant may have no impact on overall health (benign).

The ClinGen variant curation process combines clinical, genetic, population, and functional evidence with expert review to classify variants into 1 of 5 categories (below) according to ACMG guidelines (Richards et al. 2015). The results of these analyses are deposited in ClinVar for community access.

Laboratories and Clinicians may use ClinGen's variant curation tools to evaluate evidence for a variant that has not yet undergone expert review, or has a discrepancy in classification that requires resolution.

Pathogenic · **Likely Pathogenic** · **Uncertain** · **Likely Benign** · **Benign**

Actionability Curation

How does this impact medical management?

Certain genetic diseases have medical interventions that can improve outcomes for patients. In these cases, pathogenic variants in genes that underlie these diseases are considered "actionable." The interventions may be substantial (risk-reducing surgeries for individuals with *BRCA1*-related hereditary breast cancer) or non-invasive (routine breast surveillance).

The ClinGen Actionability curation process evaluates the efficacy and nature of available interventions in the context of the likelihood and severity of a particular outcome (below).

Laboratories may use this type of information to determine which results to report back to clinicians and patients.

Clinicians may use this type of information to determine the utility of ordering genetic testing, and to develop appropriate treatment plans for patients with certain genetic diseases.

Severity and Likelihood of Disease · **Efficacy and Nature of Intervention**