# ClinVar/ClinGen Enhance Representation of the Status of Variant Assessment

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**ClinGen:** The Clinical Genome Resource (ClinGen), launched in 2013, is an NIH-supported program to build an authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research. www.clinicalgenome.org

**ClinVar:** A database at NCBI that archives information submitted about variants with medical relevance. It is an integral part of ClinGen and serves as ClinGen's public portal for the deposition and retrieval of variants and their clinical significance. www.ncbi.nlm.nih.gov/clinvar/

ClinVar validates and standardizes the content of submissions but does not review variant interpretations for accuracy or resolve differences form submitters, which is a function of other activities within ClinGen.

To increase the utility of the ClinVar database, ClinGen developed a tiered rating system to designate the review level of each variant in ClinVar (Fig 1).

Fig 1. Current and New ClinVar Review Levels


## Refining the Review Levels of Variant Assessments

Currently, only 2.2% of all variants with assertions are from Practice Guidelines or Expert Panels submissions, with the remaining 97.8% of variant assertions coming from single sources, such as clinical and research labs. To help users assess the quality and consistency of variant assertions from single submitters, ClinGen created two sub-categories, those who attest to certain approaches and provide documentation of methods, and those who do not. The new category "Single Submitter – Criteria Provided" requires:

1. **Attesting to a comprehensive review of variant evidence**
2. **Use of a scoring system with at least 3 levels (e.g. pathogenic, uncertain significance, benign for Mendelian disease variants)**
3. **Posting of criteria used to assign a variant to each category**
4. **Inclusion of supporting evidence or a rationale for the classification of variants and/or willingness to be contacted by ClinVar users to provide supporting evidence.**

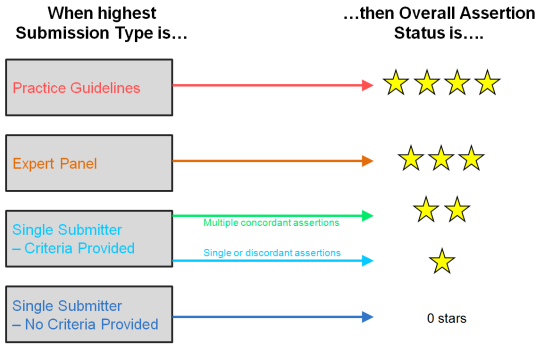
Fig 2. New Design for Assertions Table in ClinVar (coming soon…)

| Clinical Significance (Date last evaluated) | Condition(s) (Mode of inheritance) | Submitter (Last Submitted) | Submission Type (Context) | Citations | Evidence Links | Submission Accession |
|---|---|---|---|---|---|---|
| Pathogenic (March 3, 2010) | Breast-ovarian cancer, familial 1 | Submitter A (Sep 1, 2011) | Practice Guidelines Guideline (Curation) | PubMed (3) | Summary Evidence Case Observations | SCV00001 |
| Pathogenic (Sep 5, 2013) | Breast-ovarian cancer, familial 1 | Submitter B (Dec 2, 2013) | Expert Panel Criteria (Curation) | PubMed (3) | Summary Evidence Case Observations | SCV0002 |
| Pathogenic (May 30, 2012) | Breast-ovarian cancer, familial 1 | Submitter C (Aug 10, 2013) | Single Submitter - Criteria Provided Criteria (Clinical Testing) | PubMed (2) | Summary Evidence Case Observations | SCV0003 |
| Pathogenic (Aug 26, 1998) | Breast-ovarian cancer, familial 1 | Submitter D (Mar 28, 2014) | Single Submitter – Criteria Provided Criteria (Clinical Testing) | PubMed (3) | | SCV0004 |
| Pathogenic (Jun 11, 2013) | Neoplastic Syndromes, Hereditary | Submitter E (Jul 25, 2014) | Single Submitter - No Criteria Provided (Clinical Testing) | PubMed (2) | Summary Evidence | SCV0005 |
| Pathogenic (Jan 1, 2012) | Breast cancer | Submitter F (Aug 18, 2014) | Single Submitter - No Criteria Provided (Research) | | Summary Evidence | SCV0006 |
| Not provided | | Submitter G (Mar 30, 2013) | Single Submitter – No Assertion (Literature Only) | PubMed (1) | | SCV00007 |

A link to the submitter's variant assessment criteria will provided in the 'Submission Type' column in the redesigned ClinVar assertion table.

These modifications will also change the aggregate review level (Fig 3). Now, one star will only be assigned to variants with at least one submission from a "Single Submitter - Criteria Provided" submitter. Two stars will only be assigned when a variant has ≥2 concordant Single Submitter – Criteria Provided assertions and no conflicting assertions.

Fig. 3: Overall Assertion Status based on Review Level




## Conclusions

The ClinVar database is intended to be a robust resource for researchers, clinical laboratories and healthcare providers. By ClinVar requesting documentation that describes variant assertion methods, and making it clearer which records are based on assessments that are well documented, users can more readily determine the support and evidence for a variant interpretation.