Summary of updates to the ClinGen Gene Clinical Validity Curation SOP

Note: Significant updates were included in version 7, including several new sections and the rearrangement of prior sections. It is highly recommended for all curators (new and existing) to read version 7 in full.

Updates from Version 6 to Version 7 (08/2019):

- **Table of Contents (p2):** The Table of Contents is now interactive and "clickable." Clicking on a section title will take the reader to the section of interest.
- **Hypothes.is Gene Annotation SOP (p3):** Information on Hypothes.is and a hyperlink to the Hypothes.is Annotation SOP is now included. This web-based annotation tool is used by many GCEPs, and has been shown to significantly reduce curation time.
- **Overview of Gene Curation (p4):** This section has been updated to reflect our current curation workflow.
- **Gene Curation Workflow-Figure 1 (p5):** This figure has been updated to reflect the current curation workflow and approval process.
- **Figure 2-Clinical Validity Classifications (p7):** The classification of "No reported Evidence" has been updated to "No known disease relationship" in order to align with the new terminology recommendation from the international Gene Curation Consortium (GenCC) (see footnote 3).
- **Establishing the Gene-Disease-Mode of Inheritance (p9):** This is a new section outlining the process of selecting a gene, disease, and mode of inheritance. Hyperlinks to supportive resources, such as the ClinGen Lumping and Splitting guidelines, GeneTracker, etc. are provided.
- **Mode of inheritance (p9-11):** New section that outlines the current "Mode of inheritance" (MOI) options available in the GCI and how they affect the ability to score and/or publish gene-disease validity classifications to the website. A new table visually outlines the MOIs and scoring, approving, and publishing capabilities (Table 1).
- **Evidence Collection (p11-12):** This section has been updated to include additional useful publication search engines.
- **Scoring Genetic Evidence: Default and Range score per case(p14):** New section that outlines the purpose of the default and range scores per case.
- **Genetic evidence matrix footnotes (Figure 3, p17-18):** New section that outlines important information on the matrix including max points per variant type and category, and information on how to manually override a calculated gene-disease validity classification in the GCI (visual representation on **Figure 4, p18**).
- **Recurrent Variants (p20):** New section that provides examples, guidance and recommendations for the evaluation of recurrent variants, or variants that have been observed multiple times for a given gene-disease relationship.
- **Founder Variants (p21):** New section that provides guidance and recommendations for scoring founder variants in a given gene-disease relationship.
- **General Consideration for Variant Level Evidence Scoring (p22-25):** Updated section that provides guidance and recommendations for upgrading and downgrading default

variant scores based on several lines of evidence, including mode of inheritance, computational predictors, population frequency, disease mechanism, phenotype, and constraint metrics.

- **Summary and Final Matrix (p42-43):** This section has been updated to reflect the current curation workflow using the GCI.
- **Clinical Validity Summary Matrix footnotes (p44, Figure 10):** New section that outlines additional information to consider for the final classification summary.
- **Recuration Procedure (p45):** New section that outlines the procedures for all GCEPs to follow for recuration of gene-disease relationships under their purview. A hyperlink to the full recuration document is included.
- **SOP References (p46):** This section was updated to reflect new references.
- **Appendix A (p47-50):** This section was updated to include new useful websites, including PMIDs to use for curation purposes on websites that may house important evidence (e.g. The Human Protein Atlas, MGI, IMPC, etc). A new section entitled Case-Level databases was added to provide curators with information on well-known sites containing case-level genetic evidence that may be applicable to scoring for a given gene-disease relationship.
- **Appendix C (p55-57):** New section that outlines examples on how to score semidominant mode of inheritance in the GCI.