How I curate: applying American Society of Hematology-Clinical Genome Resource Myeloid Malignancy Variant Curation Expert Panel rules for *RUNX1* variant curation for germline predisposition to myeloid malignancies

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Supplemental Figure

Supplemental Figure 1: Overview of Clinical Genome Resource (ClinGen) and the American Society of Hematology (ASH) partnership and relationship to the Myeloid-Malignancy Variant Curation Expert Panel (MM-VCEP) and goals. (A) ASH and ClinGen co-sponsored MM-VCEP, convened in 2018 to develop gene- and disease-specific rules, to resolve inconsistent variant classification and to curate genomic variants. (B) Example screenshot of ClinGen Variant Curation Interface (VCI) for sequence variant interpretation and curation by the MM-VCEP.

ClinVar is a database in which gene variants along with clinical phenotypes are deposited (1). Clinicians, and/or clinical laboratories can deposit variants identified in their practice into ClinVar with associated clinical and phenotype data (https://www.clinicalgenome.org/share-your-data/laboratories/clinvar-instructions/). The ClinGen-designated Variant Curation Expert Panels (VCEP) curates variants in ClinVar, such as in our instance for *RUNX1*, the Myeloid-Malignancy VCEP (https://www.clinicalgenome.org/affiliation/50034/). Variants that are curated are those requested by the community members, and which are reviewed first by VCEP curators and then presented/discussed for approval with Expert Panel members. The goal is to curate all variants deposited in ClinVar over time. Additional details of the variant curation process are available at the ClinGen website, including standard-operating-procedures for variant curation:

- https://clinicalgenome.org/curation-activities/variant-pathogenicity/training-materials/

- https://clinicalgenome.org/site/assets/files/3677/clingen_variant-curation_sopv1.pdf

Expert Panel curated variants are recognized by the U.S. Food and Drug Administration (https://clinicalgenome.org/docs/fda-recognizes-clingen-assertions-in-clinvar-frequently-asked-questions/).

Supplemental Reference:

1. Landrum MD, Lee JM, Riley GR et al., ClinVar: public archive of relationships among sequence variation and human phenotype. Nucleic Acids Res. 2014:42(Database issue):D980-985).

Suppl. Figure 1A: Schematic for ASH/ClinGen & MM-VCEP

AMERICAN SOCIETY OF HEMATOLOGY ®

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ClinGen
Clinical Genome Resource

NIH-funded program

Clinical Domain Working Group

Myeloid Malignancy Variant Curation Expert Panel

Affiliated to Hereditary Cancer Clinical Domain Working Group

- 2 Co-Chairs (clinical & laboratory, MD/PhDs)
- 3 Variant Lead Scientists for curation (MD and PhDs)
- 29 clinicians, geneticists, molecular biologists, scientists, genetic counselors, or research scientists (MDs and PhDs and others)
- 34 total participants from academia and industry from 6 countries
- Established in 2018; group picture above from ASH Annual Meeting 2018, San Diego, CA; not all members are pictured.

- **Develop** gene- and disease-specific rules
- **Serve** as authoritative central resource
- **Resolve** inconsistent or inaccurate variant classification
- **Curate** genomic variants

Deposit curated germline variants for *RUNX1* and others genes for hematologic malignancies

NCBI ClinVar

Database of genomic variants for precision medicine

★★★☆ reviewed by expert panel FDA RECOGNIZED DATABASE

Suppl. Figure 1B: Example of ClinGen Variant Curation Interface for variant curation