



# Establishing Expert Panels in ClinGen

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February 5, 2021

Laura V. Milko, PhD

ClinGen CDWG Oversight Committee



# ClinGen core curation activities

- Encourage sharing of genetic and phenotypic data globally
- Establish a robust informatics infrastructure to manage, store, and disseminate ClinGen work products
- Develop standardized, evidence-based evaluation frameworks to define clinically relevant genes and variants (gene/variant/dosage/actionability)
- Engage the international community to develop an expert curation ecosystem organized by broad over-arching “Clinical Domain Working Groups” and curation-focused Expert Panels



# ClinGen expert curation groups

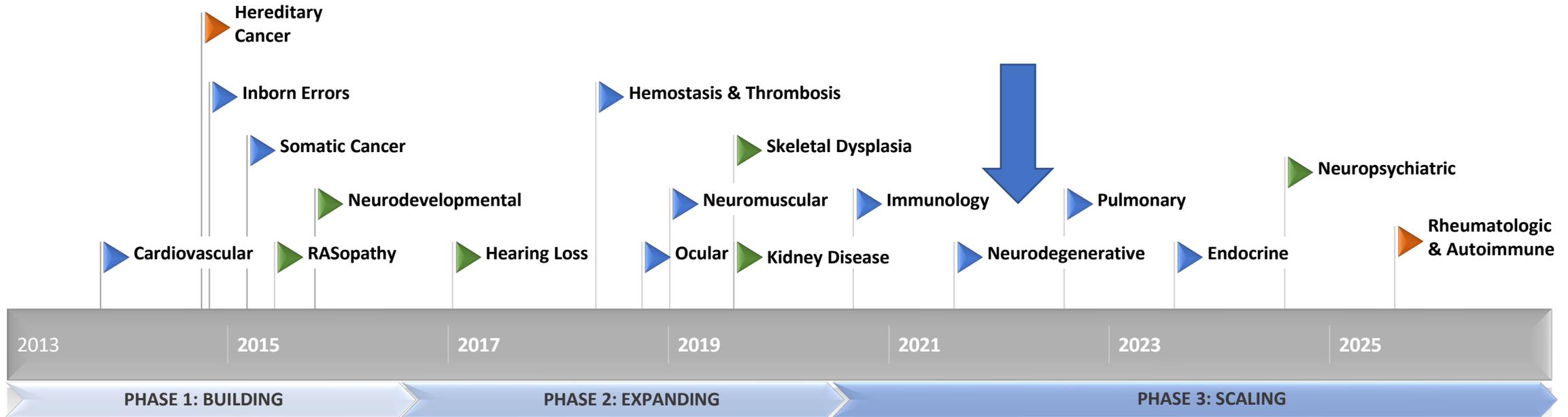
- **Clinical Domain Working Group (CDWG)**
  - Umbrella term that includes all members participating in curation activities in a particular clinical domain.
- **Gene Curation Expert Panel (GCEP)**
  - Focus on ClinGen gene validity curation process to determine the strength of association between a particular gene and disease.
- **Variant Curation Expert Panel (VCEP)**
  - Specify rules for variant curation for particular genes or gene families, and curate variants for expert Panel status recognized by ClinVar for 3-star submission



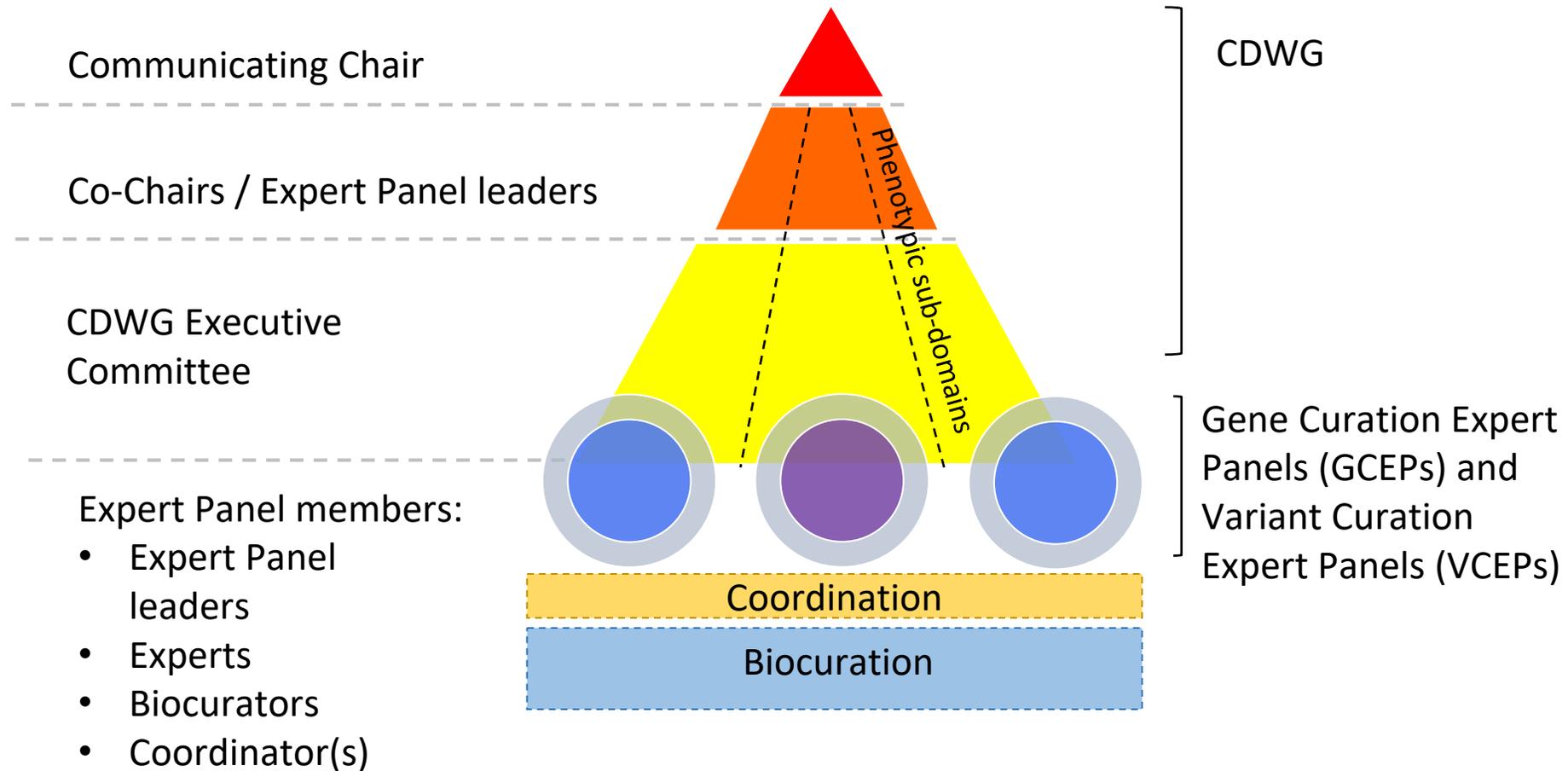
# Competencies for the physician medical geneticist in the 21st century

*Bruce R. Korf, MD, PhD<sup>1</sup>, Mira Irons, MD<sup>2</sup>, and Michael S. Watson, MS, PhD<sup>3</sup>*

▶ UNC/Kaiser    ▶ Broad/Geisinger    ▶ Baylor/Stanford



# CDWG Relationship with Expert Panels



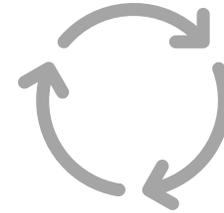
# CDWG Tasks

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## *Strategic efforts*

Foster data sharing  
Horizon scanning and planning  
Coordinate internal/external curation groups



## *Tactical efforts*

Develop Gene Curation Expert Panels (GCEPs)  
Develop Variant Curation Expert Panels (VCEPs)  
• Develop and test gene-specific ACMG rules

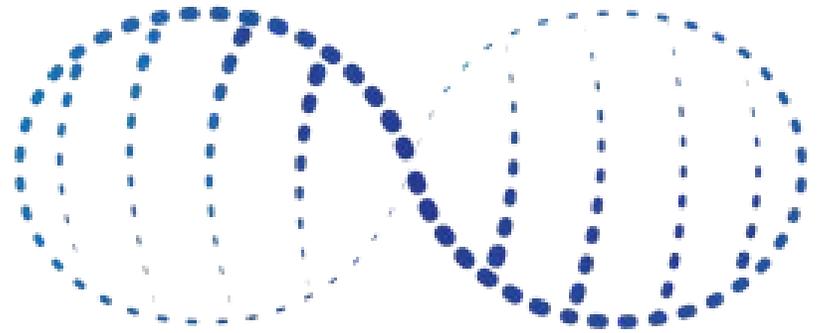


# CDWG Oversight Committee

Includes representatives/co-chairs from all 3 grants, NIH, various ClinGen WGs, and CDWGs and EPs

- to set priorities for future CDWG and Expert Panel development
- promote harmonization and standardization of activities
- facilitate interaction between the CDWGs, GCEPs, and VCEPs and the ClinGen consortium
- provide orientation and materials for CDWGs and EPs regarding their roles and responsibilities and general information about ClinGen and the processes they will be implementing
- provide a point of contact for new curation groups who wish to form Expert Panels and use ClinGen resources
- conduct outreach and foster relationships to accomplish our mutual objectives.





**ClinGen**  
Clinical Genome Resource



# Establishing Gene Curation Expert Panels (GCEPs)



# GCEPs curate gene-disease clinical validity

- How strong is the evidence that genetic alteration of a gene causes the disease in question?
- The Gene Curation Working Group developed a semi-quantitative framework to assess the strength of evidence supporting a gene-disease association
  - Defines criteria needed to demonstrate causality
  - Organizes and quantifies different types of evidence
  - Allows curators to systematically assign a clinical validity classification
- Data is reviewed by the expert panel for final classification.

Am. J. Hum. Genet. 100:895-906, 2017

ARTICLE

Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

Natasha T. Strande,<sup>1,14</sup> Erin Rooney Riggs,<sup>2,14</sup> Adam H. Buchanan,<sup>3</sup> Ozge Ceyhan-Birsoy,<sup>4,5,6,7</sup> Marina DiStefano,<sup>4</sup> Selina S. Dwight,<sup>8</sup> Jenny Goldstein,<sup>1</sup> Rajarshi Ghosh,<sup>9</sup> Bryce A. Seifert,<sup>1</sup> Tam P. Sneddon,<sup>8</sup> Matt W. Wright,<sup>8</sup> Laura V. Milko,<sup>1</sup> J. Michael Cherry,<sup>8</sup> Monica A. Giovanni,<sup>3</sup> Michael F. Murray,<sup>3</sup> Julianne M. O'Daniel,<sup>1</sup> Erin M. Ramos,<sup>10</sup> Avni B. Santani,<sup>11,12</sup> Alan F. Scott,<sup>13</sup> Sharon E. Plon,<sup>9</sup> Heidi L. Rehm,<sup>4,5,6,7</sup> Christa L. Martin,<sup>2,3,\*</sup> and Jonathan S. Berg<sup>1,\*</sup>

Definitive

Strong

Moderate

Limited

No Known Disease Relationship

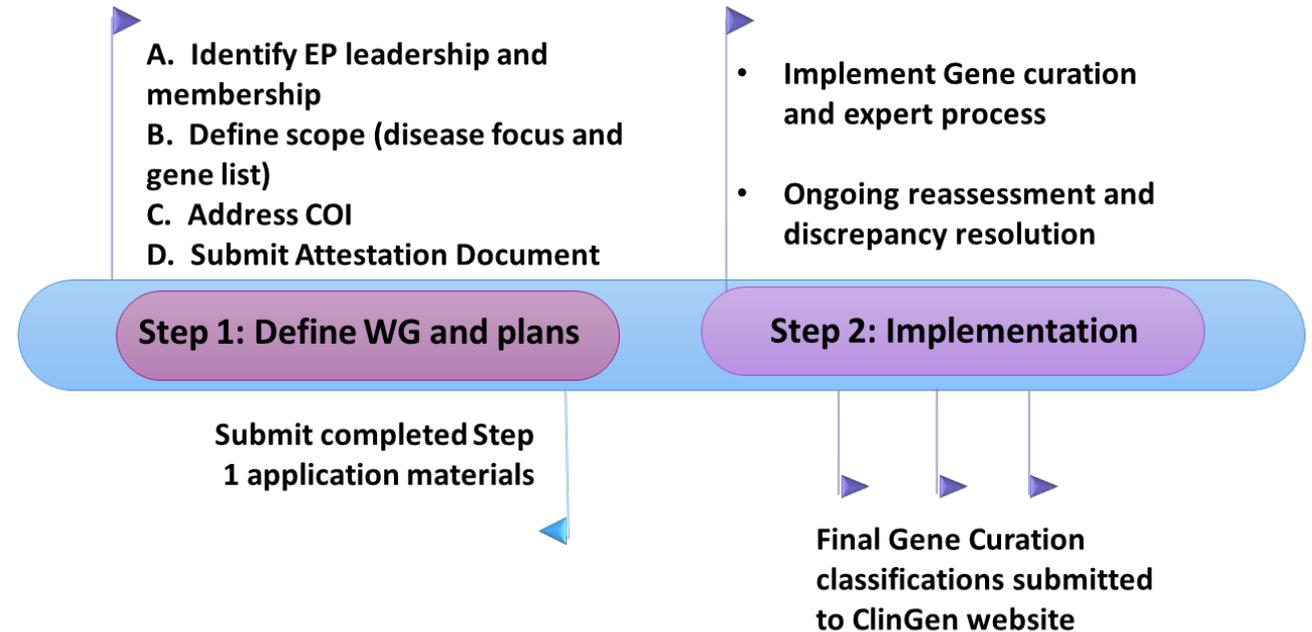
Conflicting Evidence Reported

Disputed

Refuted



# GCEP Approval Process



Average time to approval is 3 months



# Recommendations for GCEP Leadership & Membership

- At least 3 independent experts from different institutions.
  - ClinGen strongly recommends broad representation of the community of experts to ensure a wide range of opinions are reflected.
- At least one member should have expertise in the ClinGen clinical validity framework.
  - eg. A member of the Gene Curation WG and/or a ClinGen staff curator is embedded with the group.
  - For groups without ClinGen representation, there should be periodic interactions with the ClinGen Gene Curation WG.



# A: Define GCEP Leadership & Membership

Chair: A well-regarded expert(s) in the field with invested interest in success of the group.

Coordinator: Generally familiar with the focus area and empowered to help drive the GCEP work

Experts: scientists and clinician with well-developed expertise in the focus area and diversity at various levels:

- Areas of clinical, diagnostic laboratory, and basic research expertise.
- Institutionally
- Demographically
- Globally

Biocurators: May or may not be gene/disease experts; may or may not have experience in biocuration (ClinGen will provide training).



## **B: Define Scope, disease focus, and gene list**

Decide on the disease area(s) of focus and create a list of genes to be curated

Identify issues with Lumping & Splitting

Disease Focus:

- Clinically relevant disease entities that share common phenotypic features.

Gene List:

- Gene lists range anywhere from 40 genes to 400+ genes.
- Genes that fall on genetic testing panels are generally a good place to start.
- It is important to include ALL genes that you want to use in variant curation.



## C: Conflict of interest (COI) disclosures

- Members are expected to self-manage and declare COI on a survey sent by the coordinator.
  - Academic (discoverer of a gene that is relevant to their SOW)
  - Financial (lab director/employee of a commercial laboratory)
- All conflicts will be declared publicly on the group's roster on the [clinicalgenome.org](http://clinicalgenome.org) website.
- No special measures are needed if there is group consensus on a gene classification. Otherwise, those with relevant conflicts of interest should recuse themselves.
- Members are expected to disclose other existing or planned independent curation efforts that will potentially overlap with the scope of their ClinGen work.



## D: Attestations

- To utilize the ClinGen Gene Tracker for documentation of all precuration information, consistent with the current Lumping and Splitting working group guidance.
- To utilize the Gene Curation Interface (GCI) for curation and documentation of all gene-disease validity classifications.
- To make all curations publicly available through the ClinGen website immediately upon completion.
- To submit draft manuscripts to the ClinGen Gene Curation WG prior to submission.
- That the ClinGen publication policy has been reviewed and a manuscript concept sheet will be submitted to the NHGRI and ClinGen Steering Committee before the group prepares a publication for submission.
- That the ClinGen Gene-Disease Validity Recuration process has been reviewed and is acceptable to the GCEP.



# Select a Curation and Review Process

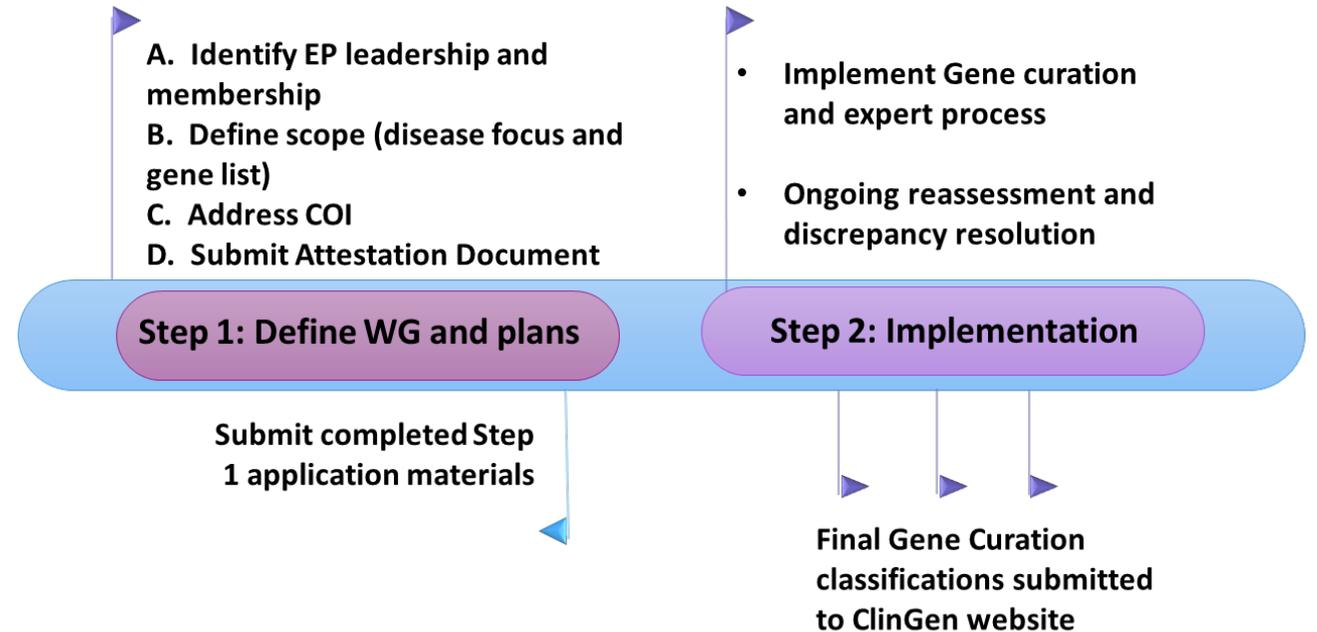
Examples of ClinGen-approved approaches:

1. Single biocurator curation with comprehensive GCEP review (presentation of all data on calls with GCEP votes).
2. Paired review (biocurator & domain expert) with expedited GCEP review.
3. Dual biocurator review with expedited GCEP review for concordant genes and full review for discordant genes



# Submit for Review by the CDWG Oversight Committee

Average time to approval is 3 months



# GCEP metrics

- 35 GCEPs
- 12 publications

1,017

- Total Gene-disease records in the GCI

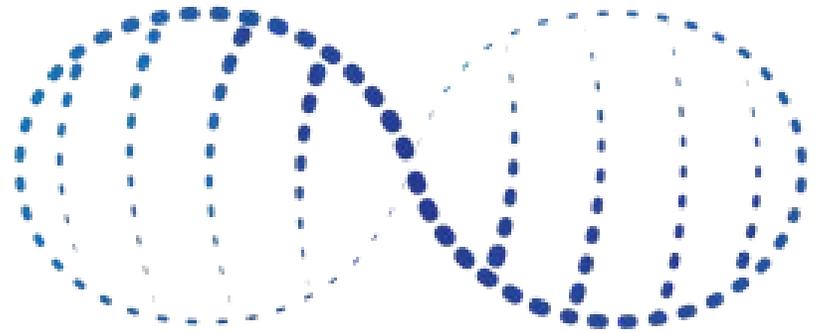
164

- Provisional gene-disease curations pending expert approval

1,220

- Approved gene-disease curations posted on the ClinGen website





ClinGen  
Clinical Genome Resource



Establishing  
Variant  
Curation Expert  
Panels (VCEPs)



# VCEPs curate and interpret variant pathogenicity

- Goal is to improve the quality of assertions and increase the numbers variants in ClinVar.
- Variants submitted to ClinVar from ClinGen are recognized as 3-star submissions.
- ClinGen submission to ClinVar are automatically FDA approved.

ClinGen as first FDA-approved public genetic variant database - how this will affect our VCEP processes

The collage features several key elements: the top left shows the U.S. Food & Drug Administration website with a search bar and navigation tabs; a central tweet from @US\_FDA (13m) announces the FDA's recognition of ClinGen as the first publicly-available human genetic variant database; a news article snippet on the right is titled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics" and "Guidance for Stakeholders and Food and Drug Administration Staff"; and a press release at the bottom is titled "ClinGen Receives Recognition Through New FDA Human Variant Database Program" and states that ClinGen variants are available for unrestricted use in the community via ClinVar.



# VCEP Approval Process

- A. Identify EP leadership and membership
- B. Define scope (disease focus and gene list)
- C. Address COI

## Step 1: Define WG and plans

Submit completed Step 1 application materials

- D. Specify ACMP/AMP rules for genes in scope
- Review SVI guidance and other EP disease-specific rule specification as examples

## Step 2: Develop Variant Classification Rules

Submit completed Step 2 application materials and present to the SVI WG

- E. Validate specified rules with known variants and refine as needed
- 10-12 P/LP per gene
- 10-12 B/LB per gene
- 10-12 VUS per gene

## Step 3: Pilot Rules

Submit completed Step 3 application materials

- F. Define plans for ongoing variant review and reanalysis and discrepancy resolution
- G. Provide example evidence summaries
- H. & I. Provide attestations for these sections

## Step 4: Final VCEP approval

Submit fully completed VCEP application and present to the CDWG OC

The VCEP Protocol is a companion guide to this process and can be found at:  
[https://clinicalgenome.org/site/assets/files/3635/vcep\\_protocol\\_v\\_8.pdf](https://clinicalgenome.org/site/assets/files/3635/vcep_protocol_v_8.pdf)



# 1A: Define VCEP Leadership & Membership

Chairs: 2 chairs is often helpful, experience with variant curation and the ACMG/AMP guidelines is strongly recommended

Experts:

- At least 3 board certified clinical genetics are required (FACMG equivalent if outside of U.S.)
- As with the GCEP, VCEPs are expected to represent the diversity of expertise in the field: **clinical, diagnostic laboratory**, and basic research.

Biocurators:

- Utilize genetic counselors and individuals familiar with ACMG guidelines.



## 1B: Define Scope, disease focus, and gene list

- Scope should focus on a single condition or highly related conditions.
- Typically select between 1-10 genes.
- Genes must be well-characterized with a strong/definitive disease association.
- Known clinical impact (actionable or impending actionable)
- Need to have known gold standard variants to use in pilot (+/-)



# 1C: Conflict of interest (COI) disclosures

- Members are expected to self-manage and declare COI on a survey sent by the coordinator.
- All conflicts will be declared publicly on the group's roster on the [clinicalgenome.org](http://clinicalgenome.org) website.
- No special measures are needed if there is group consensus on a variant classification. Otherwise, those with relevant COI should recuse themselves.
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## 2D: Specify ACMP/AMP rules for genes in scope

- Establish consensus decisions on ACMG/AMP guideline specifications for gene(s) within the VCEP's scope of work
- Review current recommendations from the Sequence Variant Interpretation (SVI) WG on broadly applicable specifications of the guidelines
- Follow the ClinGen General Sequence Variant Curation SOP for guidance on variant classification using ClinGen approved processes and tools, as well as additional resources identified by the SVI.
- VCEPs may proceed with rules specification using one or a combination of the following:
  - Approach 1: Subdivide the VCEP and assign a category from the guidelines to each subgroup; subgroups then bring their proposed specifications to the larger group for feedback and final consensus approval.
  - Approach 2: Develop and approve specifications to the guidelines all within the full VCEP.



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## 3E: Pilot rule specifications

- Validate specified rules with known variants and refine as needed, using at least:
  - 10 to 12 Pathogenic/Likely Pathogenic variants
  - 10 to 12 Benign/Likely Benign variants
  - 10-12 VUS variants or those with conflicting ClinVar interpretations
  - Variants with a variety of different evidence types for the gene to test all relevant criteria codes.
- Use of the Variant Curation Interface (VCI) is required for pilot (and all other) variant curation
- Refine rule specifications based on test curations.
- Validate final rule specifications by curating pilot variants



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# 4F: Ongoing Variant Curation and Review

- Define plans for ongoing variant review and reanalysis and discrepancy resolution
  - Process #1 – Biocurator review followed by VCEP discussion
  - Process #2 - Paired biocurator/expert review followed by expedited VCEP approval
- VCEPs are expected to keep their variant interpretations up-to-date
  - prioritize the re-review of variants with conflicting assertions in ClinVar within 6 months
  - LP and VUS classifications at least every 2 years to see if new evidence has emerged to re-classify the variants.
  - LB classifications when new evidence is available (e.g. new gnomAD releases or other large sources of population data).
  - any classifications when requested by the public via the ClinGen website.



# 4G: Evidence Summaries

- Elements to include:
  - The condition for which the variant is being assessed.
  - Each ACMG/AMP evidence code applied and the sources of evidence (e.g. PMIDs).
  - Highlight exceptions.

The c.2167C>T(p.Arg723Cys) variant in MYH7 has been reported in >20 individuals with hypertrophic cardiomyopathy (PS4; PMID:1430197; PMID:27532257; PMID:9829907; PMID:16199542; PMID:20359594; PMID:12707239; ClinVar SCV000059423.5; ClinVar SCV000212630.1). Five of these probands carried additional variants in sarcomere genes (BP2; PMID:20359594; PMID:12707239; ClinVar SCV000059423.5). This variant has been identified as a de novo occurrence in 1 proband with hypertrophic cardiomyopathy (PM6; PMID:1430197). This variant segregated with disease in 7 affected individuals (PP1\_Strong; PMID:9829907; ClinVarSCV000059423.5; ClinVarSCV000212630.1). This variant was identified in 2/66738 European chromosomes (PM2; <http://exac.broadinstitute.org>). This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be disease-associated (PM1;PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). A different pathogenic missense variant has been previously identified at this codon which may indicate that this residue is critical to the function of the protein (PM5; c.2167C>Gp.Arg723Gly -ClinVarVariation ID42885). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. The benign evidence code BP2 was not considered to be in conflict with this conclusion given that presence of a second variant can be seen in individuals with cardiomyopathy and may contribute to the severity of disease. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1\_Strong; PM1; PM2; PM5; PM6; PP3; BP2



# 4H & 4I: Attestations

## 4H: Designation of Biocurators, Biocurator Trainers, and Core Approval Members

- All variant curators must attest to having completed Level 1 training (provided by ClinGen) and Level 2 training and be enrolled in the ClinGen Community Curation database
- Biocurators who have completed the above are eligible to be designated biocurator trainers and each VCEP should designate at least 1 or 2.
- At least 3 core approval members (defined as those who regularly use the ACMG/AMP guidelines to classify and/or review variants during clinical laboratory case sign-out) are required for a final variant classification approval to be made.

## 4I: NHGRI Data Availability

- VCEPs must agree to disseminate their curation results via the ClinGen website and/or ClinVar immediately upon completion of expert review of each variant.
- If the VCEP is planning to publish its rule specifications in a peer-reviewed journal, a copy of the paper must be provided to the SVI with sufficient time for review before submission.
- VCEPs are expected to pre-publish their manuscripts on medRxiv.



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Submit completed Step 2 application materials and present to the SVI WG

Submit completed Step 3 application materials

Submit fully completed VCEP application and present to the CDWG OC

Average time to approval is  
18 months

# VCEP metrics

- 42 VCEPs
- 18 publications

4,049

- Variant records entered in the VCI

484

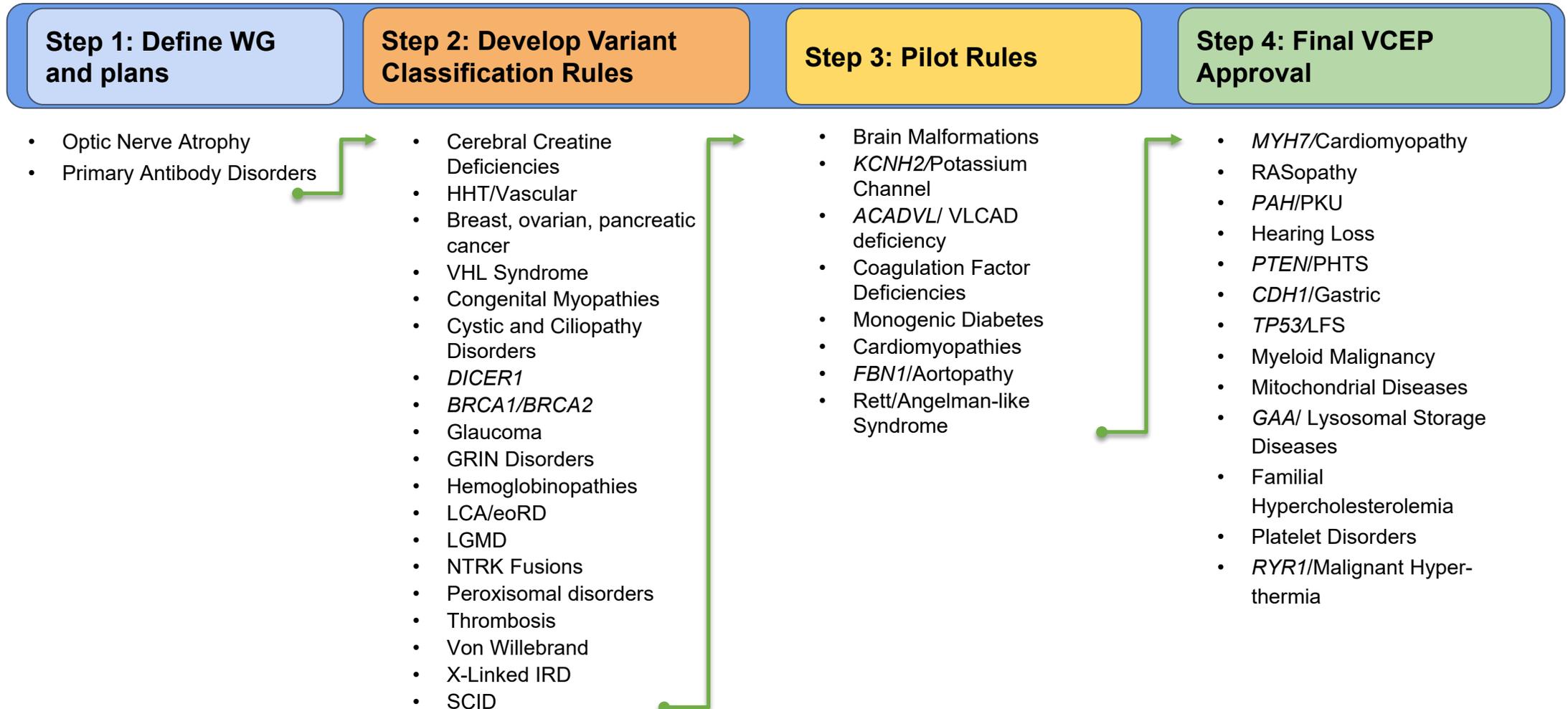
- Provisional variant interpretations

12,242

- Expertly curated variant classifications submitted to ClinVar



# ClinGen VCEP progress



# Thank you for listening!

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Questions Now?

Follow-up Questions Later??

- **Visit:** <https://clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/>
- **Contact** [laura\\_milko@med.unc.edu](mailto:laura_milko@med.unc.edu) with questions about the presentation –OR–
- [CDWG\\_OversightCommittee@clinicalgenome.org](mailto:CDWG_OversightCommittee@clinicalgenome.org) with questions about establishing a GCEP or VCEP

