ClinGen Variant Curation Expert Panel Application

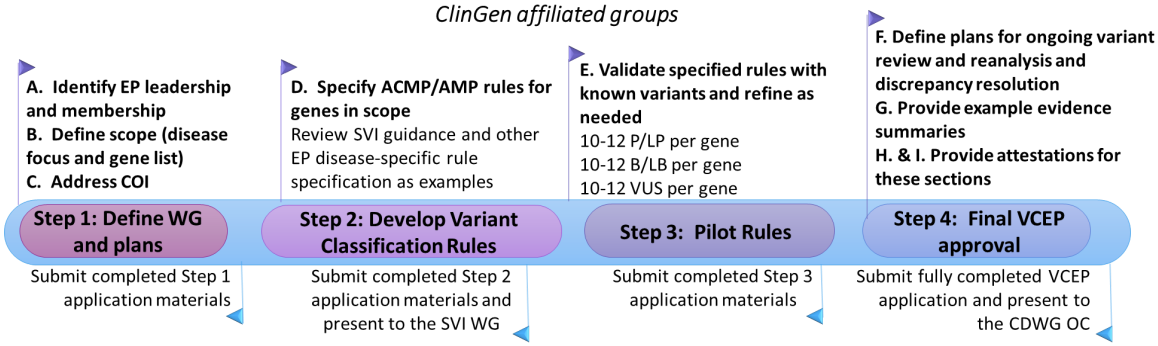
Submitter Information	
Full Base Name of Expert Panel:	
Short Base Name of Expert Panel (≤15 characters):	
Expert Panel Coordinator:	
Email address:	**Phone**:
Expert Panel Member Responsible for ClinVar Submission:	
Email address:	**Phone:**

ClinGen Variant Curation Expert Panels (VCEPs) must fulfill the stepwise requirements in accordance with the diagram shown below to become an approved ClinGen VCEP with the resulting classified variants meeting FDA recognition. For detailed guidance on completing the ClinGen VCEP application and approval process, please refer to the ClinGen VCEP Protocol which can be found at: VCEP V9 Protocol . Additional pages may be used for all Sections A-I, if needed.

External VCEP applicants (not subject to FDA requirements but wishing to obtain ClinVar 3-star status) are also encouraged to use the same stepwise process for their VCEP application. We encourage these groups to begin communication early in the application process (prior to submitting Step 1) with the Sequence Variant Interpretation WG (SVI) and Clinical Domain Working Group (CDWG) Oversight Committee (OC). All VCEP applicants are required to submit for final VCEP approval by the CDWG OC.

Expert Panel Approval Steps

ClinGen affiliated groups



Expert Panel Submission Details

A Composition of the Expert Panel (STEP 1)

Expert Panels are expected to represent the diversity of expertise and backgrounds in the field and should refer to Section 2.1 of the VCEP Protocol and the NIH Scientific Workforce Diversity Toolkit for guidance to complete the Member List below. Please list the VCEP Chair(s) and Coordinator(s) first.

*The column on the far right should be completed in Step 4 prior to the final approval presentation to the CDWG OC. Refer to Section 2.4 of the VCEP Protocol for a definition of core approval members.

Member List

Name, credentials, and email	Institution	Area and Type of Expertise	VCEP role	Indicate Step 4 core approval members*
Joanna Doe, PhD, FACMG jsmith@clingen.edu	ClinGen University	Clinical Molecular Geneticist; Inherited Cardiovascular Disorders	Chair	☐
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Describe the expertise of VCEP members who regularly use the ACMG/AMP guidelines to classify variants and/or review variants during clinical laboratory case sign-out.				

B. Scope of Work

Describe the scope of work of the VCEP and list the disease areas and gene(s) being addressed and which genes are likely to be worked on first. Refer to Section 2.1 of the VCEP Protocol for guidance and the established VCEP webpages on clinicalgenome.org for examples.

C. Conflict of Interest (COI) and Competing Activities Management

The ClinGen Expert Panel Conflict of Interest Policy can be viewed here: https://www.clinicalgenome.org/docs/clingen-expert-panel-conflict-of-interest-policy/. Refer to Section 2.1 of the VCEP Protocol for additional information.

ClinGen uses a standardized form to collect COI and competing activities disclosures through the Expert Panel Application Management (EPAM) system. Contact ***CDWG_OversightCommittee@clinicalgenome.org*** to request a unique COI url for the VCEP.COI surveys must be complete for each member before submission of the Step 1 application.

End of Step 1 VCEP application

Stop here and submit completed Step 1 application materials to (CDWG_OversightCommittee@clinicalgenome.org) for review in fulfillment of the requirements for Step 1.

Note: After Step 1 approval, you will be contacted to set up an affiliation in the Variant Curation Interface and an VCEP webpage on clinicalgenome.org. At this time, you will be ready to begin the ACMG/AMP specification process

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D. ACMG/AMP Guideline Specifications (STEP 2)

ClinGen Expert Panels are required to use the ACMG/AMP variant assessment criteria as their starting point for a framework to classify variants into the five categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign).

Follow the detailed instructions and the Step 2 checklist found in Section 2.2 of the VCEP Protocol to draft your ACMG/AMP rule specifications for the genes/disease pairs within your scope of work. When draft specifications are completed, email them to CDWG_OversightCommittee@clinicalgenome.org for review by the SVI VCEP Review Committee.

End of Step 2 VCEP application

Stop here and submit completed Step 2 application materials to (CDWG_OversightCommittee@clinicalgenome.org) for review in fulfillment of the requirements for Step 2.

Note: The SVI VCEP Review Committee provides written feedback to the VCEP with a summary of recommendations to address prior to beginning the pilot. The VCEP responds in writing to the SVI VCEP Review Committee points. Finally, the SVI co-chairs approve the VCEP to move on to Step 3 and piloting the specified rules once all feedback has been addressed.

E. Validation of ACMG/AMP Guideline Specifications (STEP 3)

Apply specified variant classification rules to known variants for pilot testing and validation and submit pilot results and final, refined specifications for review following detailed instructions in Section 2.3 of the VCEP Protocol

Note that VCEPs are required to use the ClinGen Variant Curation Interface (VCI) according to the detailed ClinGen General Sequence Variant Curation Process Standard Operating Procedures, though tracking your pilot variant classifications in a spreadsheet for ease of submission and review is recommended. A template spreadsheet with sample data can be found here.

End of Step 3 VCEP application

Stop here and submit completed Step 3 VCEP application materials to CDWG_OversightCommittee@clinicalgenome.org for review in fulfillment of the requirements for Step 3.

Note: The SVI VCEP Review Committee reviews the updated specifications and pilot results. The SVI VCEP Review Committee may request additional information on pilot variants. The VCEP should respond in writing to any SVI VCEP Review Committee points. Finally, the SVI VCEP Review Committee approves the VCEP's specifications and the VCEP can move on to Step 4.

F. Define Plans for Ongoing Variant Review and Reanalysis and Discrepancy Resolution (STEP 4)

VCEPs are expected to define and present their plans for sustained variant curation and review (after Step 4 approval), including work schedules, standard review process in Part I and reanalysis and discrepancy resolution in Part II. A detailed description of ClinGen-approved processes are outlined in Section 2.4 of the VCEP Protocol

Part I: Ongoing Variant Curation and Review:

- **Meeting/call frequency:** Click here to enter text.
- **VCEP Standardized Review Process:** (check one)
  - ☐ Process #1: Biocurator review followed by VCEP discussion
  - ☐ Process #2: Paired biocurator/expert review followed by expedited VCEP approval

For all variants approved by either of the processes described above, a summary of approved variants should be sent to ensure that any members absent from a call have an opportunity to review each variant. The summary should be emailed to the full VCEP after the call and should summarize decisions that were made and invite feedback within a week.

Part II: Reanalysis and Discrepancy Resolution:

Expert Panels are expected to keep their variant interpretations up-to-date and to expedite the re-review of variants that have a conflicting assertion submitted to ClinVar after the Expert Panel submission. Please check all 3 boxes below to attest that the VCEP will follow the ClinGen-approved schedule described below and in Section 3.3 of the VCEP Protocol -or- describe other plans at the bottom of the section.

☐ VCEPs are expected to reassess any newly submitted conflicting assertion in ClinVar from a one star submitter or above and attempt to resolve or address the conflict within 6 months of being notified about the conflict from ClinGen. Please reach out to the submitter if you need additional information about the conflicting assertion.

☐ VCEPs are expected to re-review all LP and VUS classifications made by the EP at least every 2 years to see if new evidence has emerged to re-classify the variants

☐ VCEPs are expected to re-review any LB classifications when new evidence is available or when requested by the public via the ClinGen website.

☐ Check box if plans differ from the expectations above, and describe below:

G. Example Evidence Summaries

Provide at least 5 written evidence summaries that represent examples of the content that will be submitted to ClinVar to support variant classifications. Use the standardized summary text for each ACMG/AMP code as described in this document and in Section 2.4 of the VCEP Protocol

H. Designation of Biocurators, Biocurator Trainer(s) and Core Approval Members

Trained variant biocurators (*list below*)

The following VCEP members will be designated biocurators following Step 4 approval and have completed Level 1 and Level 2 training, filled out an attestation, and are enrolled in the ClinGen Community Curation Database:

Biocurator Trainer(s) (*list below*)

The following VCEP members will be the designated biocurator trainer(s) following Step 4 approval:

Core Approval Members (*check boxes in Step 1: Section A*)

Prior to submitting the Step 4 application, please return to Section A. “Composition of the Expert Panel” and designate via the checkboxes which VCEP members will serve as core approval members for ongoing final approval of variant classifications following Step 4 approval.

I. NHGRI Data Availability

Curated variants and genes are expected to be approved and posted for the community as soon as possible as described in Section 2.4 VCEP Protocol. Note that upon approval, a VCEP must finalize their set of variants for upload to the ClinGen Evidence Repository within 30 days.

☐ Check box to confirm your understanding that once a variant is approved in the VCI it will become publicly available in the Evidence Repository. They should not be held for publication.

Please review the ClinGen Publication Policy and refer to guidance on submissions to a preprint server (e.g. bioRxiv or medRxiv).

End of Step 4 VCEP application

Stop here and submit completed Step 4 VCEP application materials to CDWG_OversightCommittee@clinicalgenome.org for review in fulfillment of the requirements for Step 4

Note: Fully completed VCEP applications (Section A and Sections F-I) must be presented for Step 4 final approval to the CDWG OC. If possible, contact CDWG_OversightCommittee@clinicalgenome.org with at least two months' notice for scheduling to avoid delays. Send the fully completed VCEP application materials (including Steps 1-4 of the application) at least two weeks prior to the call for circulation to the OC.
