



ClinGen Variant Curation Expert Panel (VCEP) Protocol

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Abbreviations:

- VCEP - Variant Curation Expert Panel
- FDA - US Food and Drug Administration
- CDWG - Clinical Domain Working Group
- OC - CDWG Oversight Committee
- SOP - Standard Operating Procedure
- C3 - ClinGen Community Curation Working Group
- VCI - Variant Curation Interface
- ECT - Education, Coordination and Training Working Group
- SVI - Sequence Variant Interpretation Working Group
- WG - Working Group
- COI - Conflict of Interest
- P - Pathogenic
- LP - Likely Pathogenic
- VUS - Variant of Uncertain Significance
- LB - Likely Benign
- B – Benign

INTRODUCTION

All ClinGen Variant Curation Expert Panels (VCEPs) wishing to apply for ClinGen approval to submit to ClinVar at the 3-star level must fulfill all the stepwise requirements described within this VCEP Protocol. Public access and transparency to the variant-level evidence, assessment process, and classifications are central to the mission of ClinGen and a requirement of the US Food and Drug Administration (FDA) Recognized Human Variant Database (<https://www.clinicalgenome.org/about/fda-recognition/>). As such, the VCEP Protocol outlines the processes of formation, approval, curation, assessment, and publication of variant classifications of pathogenicity by ClinGen VCEPs. All final, approved variant classifications made by approved VCEPs and the curated evidence supporting those classifications are part of the ClinGen Human Variant Database.

The VCEP's specified criteria for evaluating pathogenicity and the process for curation and expert review must be provided with the application for final approval. This detailed variant classification criteria will accompany ClinVar submissions in addition to a summary of the individual assessment for each variant. The evidence assessed in the classification of individual variants will be available to external users via the public [ClinGen Evidence Repository](#). Lastly, the approved VCEP application materials will be available on the VCEP's ClinGen webpage to ensure transparency about the group's process.

1. Guidance for Application and Approval of ClinGen VCEPs

1.1 Membership and Training

Variant Curation Expert Panel Membership

VCEP membership is expected to include individuals with diverse areas of expertise including medical professionals caring for patients relevant to the disease gene in question, medical geneticists when the diseases span multiple organ systems, clinical laboratory diagnosticians and/or molecular pathologists who report such findings and appropriate researchers relevant to the disease, gene, functional assays, and statistical analyses. VCEP members should represent at least three or more academic or commercial institutions and global participation is strongly encouraged. ClinGen strongly supports inter-institutional collaboration and recommends reaching out to international colleagues and collaborators within their area of focus to maximize the ability to represent experts in the disease area across multiple institutions and to build consensus and data sharing.

- One or more co-chairs who are respected international authorities in the field based on publication record and professional experience should be selected.
- Membership should encompass disease/gene expert members as well as biocurators (see below for additional information).

- There is no predefined number of members for a VCEP, though as described above the panel should represent the diversity of expertise in the field.
- Each panel should include independent participants from at least three institutions; inclusion of more than two senior members who are affiliated with the same institution is discouraged, unless they bring distinct experience, though members may invite additional staff from their groups to support projects and engage in curation.
- It is strongly recommended to consult with your parent Clinical Domain Working Group (CDWG) and ClinGen parent grant, if one exists, for guidance on your proposed VCEP membership.

Biocurator Proficiency Training

Each VCEP will consist of both domain experts and biocurators. Biocurators are not required to be gene/disease experts and will be primarily responsible for aggregating the available evidence for subsequent expert member review. All biocurators must have a minimum number of variants approved by the VCEP, dependent on initial skill level, to be considered fully trained and able to work independently. Designation of at least one “biocurator trainer” within the VCEP is required to ensure understanding of and adherence to the ClinGen variant curation method and frameworks as outlined in the [Variant Curation Standard Operating Procedures \(SOP\)](#).

Volunteer biocurators may be recruited through the [ClinGen Community Curation \(C3\) Working Group](#) or by the VCEP itself and/or the parent CDWG. Domain experts in the VCEP may also choose to participate in biocurator training and biocuration activities. All VCEP members who plan to curate in the [Variant Curation Interface \(VCI\)](#) must take the [biocurator survey](#) to schedule and attest to the FDA-required training.

- All VCEP biocurators are required to complete general [Level 1 Variant Curation Training](#). Level 1 training is coordinated by the [Education, Coordination, and Training \(ECT\) Working Group](#), and is the same for all VCEP biocurators, regardless of level of experience. Level 1 training orients the biocurator to ClinGen-specific procedures, tools, and resources, such as use of the VCI. Once all training materials listed have been completed/reviewed, the biocurator will attest that they have completed Level 1 training and they may begin curation activities.
- After completion of Level 1, VCEP biocurators move on to [Level 2 Variant Curation Training](#). This training is VCEP-specific and designed to ensure that each biocurator is proficient in their VCEP’s variant curation procedures. The VCEP is responsible for ensuring all their biocurators receive Level 2 training, and that completion of this training is documented.
 - Ongoing proficiency is evaluated through the regular variant curation review activities of the VCEP during variant assessment. Final variant review and classification approval always includes at least three designated VCEP experts or the full VCEP.
 - Each VCEP may provide additional training beyond what is specified in the ClinGen Level 2 training protocol at their discretion. Practice curations can be conducted in the VCI demo version <https://curation-test.clinicalgenome.org/>

The [Biocurator Working Group](#) provides curation training assistance and a forum to discuss process questions and relevant updates to ClinGen frameworks and policies. The Biocurator WG also provides general training materials that outline approaches for evidence searches and data documentation required for each variant. Diverse and highly relevant topics are discussed on the calls such as [Sequence Variant Interpretation Working Group \(SVI\)](#) updates, use of the ClinGen interfaces (including the VCI), and presentations from experts on relevant resources such as Ensembl, ClinVar, gnomAD, etc. Recordings of all calls and relevant slide sets are accessible on the [Biocurator Educational Materials page](#) and important updates, such as new guidance from the SVI, are disseminated via the listserv to ensure that biocurators stay current with ClinGen best practices.

- All VCEP biocurators should join the ClinGen Biocurator WG. The WG meets by conference call twice a month. The VCEP coordinator can request that members be added to this group via Confluence, and instructions can be found in the [Coordinator Resource](#).
- If you have any questions about any aspect of the training process, please contact clingen@clinicalgenome.org.

HIPAA Training

All VCEP members are responsible for obtaining HIPAA and human subjects training based on their home institutional/affiliation guidelines and the level of access to human subject data. VCEP leadership and coordinators should ensure that members do not inadvertently share data that has not been stripped of protected health information (PHI) or other identifiers. Identifiable and/or protected health information is not necessary for variant curation and should not be stored in the VCI or variant evidence summary. More information can be found in the [VCI User Agreement](#).

1.2 Overview of the Stepwise Application for VCEP Development

All ClinGen VCEPs wishing to apply for approval and FDA recognition of their classified variants are required to follow the stepwise procedure outlined in Figure 1, by fulfilling and documenting the requirements described in detail below. VCEPs must prepare submission materials for review and approval at the end of each step of the 4-step application process, including approval of ACMG/AMP rule specifications by the [SVI VCEP Review Committee](#). After Step 4 approval by the [CDWG Oversight Committee](#) (OC), the VCEP is ClinGen-approved to submit variants to ClinVar with 3-star, FDA-recognized status. Frequent communication with the CDWG OC is encouraged if questions arise during the process.

Expert Panel Approval Steps

ClinGen affiliated groups

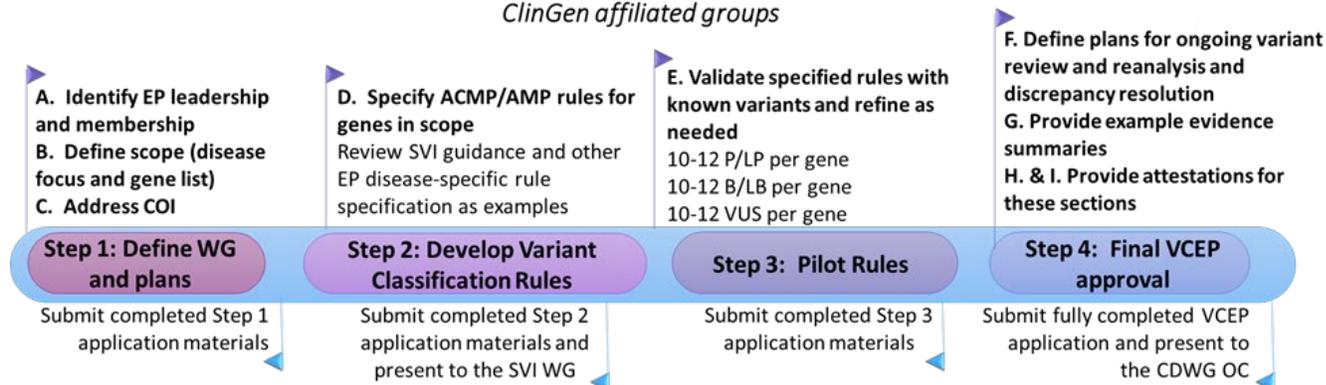


Fig. 1. Stepwise process for ClinGen Variant Curation Expert Panel application submission and review

Following approval, the full application document, including rule specifications, is made publicly available on the ClinVar Submitter page under “Expert panel documentation”. See <https://www.ncbi.nlm.nih.gov/clinvar/submitters/506439/> for an example. The newly approved ClinGen VCEP is also encouraged to publish their gene/disease-specific ACMG/AMP criteria and validation in a peer-reviewed journal (see Data Sharing under section 2.4 below), either after their pilot or once a larger set of variants has been expertly classified.

The 4-step [VCEP application](#) includes the following sections which are described in detail on pages 7-18.

STEP 1 (approved by the CDWG Oversight Committee)

- A. Composition of the Expert Panel
- B. Scope of Work
- C. Conflict of Interest Management

STEP 2 (approved by the SVI VCEP Review Committee)

- D. ACMG/AMP guideline specifications, including:
 - a. Pathogenicity assertion criteria, and
 - b. Any changes to the criteria combining rules to achieve overall classification categories

STEP 3 (approved by the SVI VCEP Review Committee)

- E. Validation of ACMG/AMP guideline specifications, including:
 - a. Submission of pilot results, including a list of the example variant set with original classification, VCEP classification, codes applied, text-based evidence summary
 - b. Refined specifications, including supporting evidence and rationale

STEP 4 (approved by the CDWG Oversight Committee)

- F. Define plans for ongoing variant classification and reanalysis and discrepancy resolution
- G. Example Evidence Summaries
- H. Designations for Biocurators and Minimum Approval Members
- I. NHGRI Data Availability

2. Expert Panel Submission Details

2.1 Step 1: Define Working Group and Plans

A. Composition of the Expert Panel

Before beginning Step 1 (Sections A-C) of the VCEP application, the VCEP Chair(s), Coordinator(s), Scientific Lead(s), and other key personnel should review this VCEP Protocol, and the ACMG/AMP guidelines ([PMC4544753](#)). Then, if the VCEP falls under a parent [CDWG](#), the CDWG's Executive Committee should be contacted to provide input on group composition (based on interactions within their professional societies, NIH institutes, etc.). ClinGen VCEPs may also be formed outside of the current CDWGs if there is no relevant CDWG at the time; these VCEPs will receive guidance directly from the CDWG Oversight Committee. See Section 1.1 above for a description of VCEP membership.

VCEP chairs should discuss and invite members with all major areas of expertise (clinical, diagnostic laboratory, and basic research), including several members who regularly use the ACMG/AMP guidelines to adjudicate and sign-out sequence variants. Please refer to the following when completing this section of the VCEP application:

- Please include board certifications along with other credentials (e.g. CGC, FACMG)
- Be specific in describing area and type of expertise (e.g. ABMGG laboratory diagnostician and type of lab; clinical geneticist with a focus on cancer genetics).
- Options for VCEP role include: primary biocurator, expert reviewer, scientific lead, biocurator trainer, coordinator, and/or chair. Multiple roles can be listed.
- Do not appoint Step 4 core approval members during Step 1. This column should be left blank in Steps 1-3. More information can be found in Section 2.4.H.
- At the bottom of the membership list, please note which VCEP members regularly use the ACMG/AMP guidelines to classify variants and/or review variants during clinical laboratory case sign-out.

The VCEP leadership should establish and circulate expectations for attendance and accomplishments for their members.

B. Scope of Work

The overarching parent CDWGs, if existing, will provide guidance as needed for the creation, development, and direction of VCEPs within their domains (e.g. *PTEN* VCEP within the Hereditary Cancer CDWG) and will lead the VCEP in focusing on specific areas and developing the policies and procedures necessary to accomplish certain tasks ([PMC6401338](#)).

In many cases, a VCEP will examine a single gene or a set of genes associated with a single condition or related conditions, and focus on the curation of variants in those genes (e.g., RASopathy and specific genes: *BRAF*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *PTPN11*, *RAF1*, *SHOC2* and *SOS1*). We expect that a VCEP will begin with one or several genes or gene families that are the highest contributors to disease or the target of therapies or clinical trials, within their area of focus for variant curation and steadily enlarge the scope of the project over time. Priorities for variant classification are discussed in Section 3.1.

For this section please define and list: 1) any specific rationale for choosing the condition or related conditions and/or the gene(s) of interest; 2) the specific gene or set of genes on which the VCEP is requesting approval to initiate work (each gene should have a Strong or Definitive disease association); 3) optional inclusion of future plans, possibly including an expanded list of genes, for the VCEP (requires an updated application before pursuing).

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

VCEPs should be composed with COI in mind to ensure that there is a sufficient number of eligible expert reviewers across institutions to broaden perspective. ClinGen defines the following two types of COI as:

- I. Academic COI: Authors of literature about relevant variants may serve on the VCEP and are welcome to voice their opinion but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that individual or the individual's lab group.
- II. Financial COI: Individuals with financial COIs may participate in the VCEP but should not be the major arbiter of a variant classification when the majority of evidence was provided by that individual or the individual stands to gain financially if a variant or set of variants are classified in a specific manner (e.g. variant specific therapies made by the individual's company or covered by a patent they hold, commercial genotyping tests involving the variant(s) etc.).

Members must disclose the following:

- If they work for a laboratory that offers fee-for-service testing related to the work of the Expert Panel.
- If they have made substantial contributions to the literature implicating a gene:disease relationship or defining pathogenicity of one or more variants that relates to the work of the Expert Panel.
- If they have any other existing or planned independent efforts that will potentially overlap with the scope of the ClinGen work.
- If they have any other relevant conflicts of interest (e.g. patents, intellectual property ownership, or paid consultancies related to any variants or genes associated with the work of your Expert Panel).

All conflicts will be declared publicly on the clinicalgenome.org website and reported in publications as appropriate. No special measures are needed if there is group

consensus on a variant classification; however, if a vote is needed, those with relevant conflicts of interest should recuse themselves.

- Coordinators should note potential academic conflicts of interest when relevant as noted above.
- Individual COI such as stock ownerships, patents, etc. are declared by authors in publications.
- VCEP coordinators will collect COI disclosures via the COI form and maintain a list along with the membership.
- VCEP members who are also ClinGen CDWG OC members will not participate in the review of the VCEP application.

Competing Activities

Expert Panel members are asked to disclose to their group about other pre-existing activities or new initiatives, such as independent gene or variant curation efforts, that may overlap with their involvement in ClinGen. For example, a lab preparing to publish their specific assertions about variant pathogenicity, internal gene curation efforts, or development of disease or gene-specific specifications of the ACMG/AMP guidelines. The member(s) and the VCEP and CDWG chairs should come to an agreement on how to manage the overlap.

ClinGen uses a standardized form to collect COI and competing activities disclosures through SurveyMonkey. Please contact CDWG_OversightCommittee@clinicalgenome.org to create a COI SurveyMonkey for the VCEP and to access results once complete. COI surveys must be complete for each member before submission of the Step 1 application. Please include the Excel file with your 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 (VCI) and an VCEP webpage on clinicalgenome.org. At this time, you will be ready to begin the ACMG/AMP guideline specification process.

2.2 Step 2: Develop Variant Classification Rules

D. ACMG/AMP Guideline Specifications

A primary task of the VCEPs is developing disease-gene specifications to the Richards et al. ACMG/AMP guidelines ([PMC4544753](#)), and then determining how the specified rules are combined to classify sequence variants (as in Table 5 of Richards et al. 2015, pictured below) according to the five Mendelian classification criteria: pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB), and benign (B). Although most VCEPs use the general rules for combining criteria (as shown left), some VCEPs may wish to propose modifications for approval by the SVI VCEP Review Committee. A common example is allowing a single strong piece of benign evidence to reach a Likely Benign classification. Any modifications to the rules for combining criteria must be included in Step 2 of the VCEP application along with the gene-disease specifications to the criteria and the VCEP should plan to apply all criteria and combining rules consistently.

Table 5
Rules for Combining Criteria to Classify Sequence Variants

Pathogenic	
1	1 Very Strong (PVS1) <i>AND</i>
	a. ≥ 1 Strong (PS1–PS4) <i>OR</i>
	b. ≥ 2 Moderate (PM1–PM6) <i>OR</i>
	c. 1 Moderate (PM1–PM6) and 1 Supporting (PP1–PP5) <i>OR</i>
	d. ≥ 2 Supporting (PP1–PP5)
2	≥ 2 Strong (PS1–PS4) <i>OR</i>
3	1 Strong (PS1–PS4) <i>AND</i>
	a. ≥ 3 Moderate (PM1–PM6) <i>OR</i>
	b. 2 Moderate (PM1–PM6) <i>AND</i> ≥ 2 Supporting (PP1–PP5) <i>OR</i>
	c. 1 Moderate (PM1–PM6) <i>AND</i> ≥ 4 Supporting (PP1–PP5)
Likely Pathogenic	
1	1 Very Strong (PVS1) <i>AND</i> 1 Moderate (PM1–PM6) <i>OR</i>
2	1 Strong (PS1–PS4) <i>AND</i> 1–2 Moderate (PM1–PM6) <i>OR</i>
3	1 Strong (PS1–PS4) <i>AND</i> ≥ 2 Supporting (PP1–PP5) <i>OR</i>
4	≥ 3 Moderate (PM1–PM6) <i>OR</i>
5	2 Moderate (PM1–PM6) <i>AND</i> ≥ 2 Supporting (PP1–PP5) <i>OR</i>
6	1 Moderate (PM1–PM6) <i>AND</i> ≥ 4 Supporting (PP1–PP5)
Benign	
1	1 Stand-Alone (BA1) <i>OR</i>
2	≥ 2 Strong (BS1–BS4)
Likely Benign	
1	1 Strong (BS1–BS4) and 1 Supporting (BP1–BP7) <i>OR</i>
2	≥ 2 Supporting (BP1–BP7)

In addition, VCEPs may make case-by-case variant-level decisions to override the calculated classification based on the full set of criteria. An example of this is in the case of VUSs with conflicting evidence. The VCEP may choose to discount certain pieces of evidence thereby allowing a P/LP/LB/B classification. The reasoning for these exceptions must be described in the relevant variant classification summary (see Section 2.4.D)

The Sequence Variant Interpretation Working Group (SVI) VCEP Review Committee

The ACMG/AMP guideline specification process (Step 2 and Step 3 of the VCEP application) is overseen by the SVI VCEP Review Committee. The SVI VCEP Review Committee consults with VCEPs to ensure uniformity and consistency of the VCEP specifications across ClinGen.

Variant Curation Interface (VCI) training

ClinGen VCEPs are required to curate in the VCI as stated in the FDA recognition process. After submitting the initial draft of the VCEP-specified ACMG/AMP sequence variant guidelines to the SVI VCEP Review committee, contact the C3 (volunteer@clinicalgenome.org) to see if any VCI

training sessions are scheduled. If not, a C3 representative will work with you to set up appropriate training for your biocurators. A training session should be scheduled while the SVI is reviewing the rules and the group is incorporating feedback, to complete VCI training before the pilot variant curation process begins.

The VCI aggregates external evidence about variants and supports the manual curation of variant information. The data fields (tabs) within the VCI are defined by the evidence categories provided by the ACMG/AMP guidelines. Dynamic links to external information sources are also embedded within the relevant evidence category tabs. VCEP members may also manually enter additional supporting evidence, such as evidence from the literature, internal clinical data, external case repositories like LOVD or DECIPHER, etc., though embedded sources should be used whenever possible. For manually entered data, provide the provenance, PMID, and a justification for any change in strength. Note that this type of supporting evidence is accessible to all VCI users; therefore, do not enter anything that should not be available to the public. Please see the [VCI user agreement](#) for further information on what is and is not appropriate for inclusion in the VCI.

[The ClinGen General Sequence Variant Curation SOP](#) is designed to provide guidance on variant classification using ClinGen approved processes and tools, as well as additional resources identified as valid sources by the SVI.

Rules Specification Process

VCEPs may choose to proceed with rules specification using one or a combination of the following organizational methodologies.

- Approach 1: Subdividing the VCEP and assigning 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: Developing and approving specifications to the guidelines all within the full expert panel.

Step 2 Checklist

- Draft your ACMG/AMP specifications for the gene/disease pairs within your scope of work. Refer to the general recommendations on the SVI webpage for using the ACMG/AMP criteria to improve consistency in usage and transparency in classification rationale. This page also includes specifications for currently approved VCEPs; new VCEPs are strongly recommended to review the work of those groups and utilize already approved specifications that may be relevant to their group.
- Prepare your draft specifications using the SVI template and include evidence and rationale to support the rule specifications. The SVI template and other supporting materials are available [here](#).
- Highlight new combining criteria for a given classification if any are being proposed (e.g. BS1 meeting Likely Benign without other criteria; PVS1 and

PM2_Supporting meeting Likely Pathogenic based on a Bayesian model ([PMC6336098](#)).

- Arrange a call with representatives from the SVI VCEP Review Committee by emailing CDWG_OversightCommittee@clinicalgenome.org. VCEP presentations typically take place on the Genomic Variant WG call on the 2nd Friday of the month at 11-12am ET. If possible, please give at least two months' notice for scheduling to avoid delays.
- Send your draft specifications to CDWG_OversightCommittee@clinicalgenome.org at least two weeks prior to the call for circulation to the SVI VCEP Review Committee or your presentation will be rescheduled.
- For the presentation to the SVI VCEP Review Committee, please focus on the specifications themselves and the rationale behind them, particularly for rules that differ from SVI's general recommendations and what other VCEPs have done or areas where you have questions for the SVI.

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.

2.3 Step 3: Pilot Rules

E. Validation of ACMG/AMP Guideline Specifications

Apply specified variant classification rules to known variants for pilot testing and validation using the following criteria:

1. Use at least 10 to 12 Pathogenic/Likely Pathogenic variants, 10 to 12 Benign/Likely Benign variants and 10-12 Uncertain Significance variants or those with conflicting interpretations in ClinVar. If you have more than one gene, make sure to have a minimum of 5 variants per gene.

2. Use variants with a variety of different evidence types for the gene to test all relevant criteria codes.
3. Refine rule specifications based on test curations.
4. All pilot variants must be curated on the final specifications to confirm validation.

ClinGen VCEPs are required to use the VCI according to our detailed [Standard Operating Procedures](#), but we do recommend tracking your pilot variant classifications in a spreadsheet for ease of submission and review. Refer to the [VCEP ACMG/AMP SVI Resources folder](#) for a template spreadsheet with sample data.

VCEP Rule Specification Review

After completing the pilot, the VCEP sends their pilot results, and final, refined specifications to the CDWG_OversightCommittee@clinicalgenome.org for review. Please note if any ACMG/AMP specifications have been changed as they will need re-review by the SVI VCEP Review Committee. In addition to final specifications, also include the following information (at a minimum) for the pilot set of variants that have been curated in a spreadsheet, an example of which can be found [here](#):

- Variant name, c. and p.
- ClinVar overall interpretation and review status
- List of the criteria applied to the variant
- VCEP classification
- Evidence Summary (if available)
- Relevant comments if the committee disagreed with the submitted interpretation

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.

2.4 Step 4: Final VCEP Approval

F. Define Plans for Ongoing Variant Review and Reanalysis and Discrepancy Resolution

Part I: Ongoing Variant Curation and Review:

For Step 4 approval, VCEPs will select a Standard Review Process from one of the two ClinGen-approved processes below to use for variant assessment. The VCEP will also define a schedule for reviewing and resolving differences in interpretation.

Standard Review Process - Final Approval

(Choose One on VCEP application)

Process #1 Biocurator review followed by VCEP discussion

- Biocurator performs a complete variant evaluation and presents the following evidence on a call live in the VCI or via slides.
 - Full evidence curation in VCI
 - Provisional classification
 - Preliminary evidence summary
- At least 3 core approval members (as identified on the VCEP application in Step 4) need to be present on the call for a classification decision to be made.
 - Core approval members are defined as having substantial experience interpreting and/or signing out variants, e.g. lab director, molecular geneticist and will be reviewed during the Step 4 approval process.
- If there is disagreement among VCEP members, then voting is required, and classification is determined by majority vote by voice or poll. Disagreements should be recorded.

-OR-

Process #2 Paired biocurator/expert review followed by expedited VCEP approval

- Biocurator/expert pair assigned to each variant
 - Asynchronous or synchronous interactions depending on level of difficulty
- Biocurator performs complete variant evaluation and sends to expert reviewer
 - Full evidence curation in VCI
 - Provisional classification
 - Preliminary evidence summary
- Expert independently reviews evidence and classification
- Expert makes assessment
- Final approval requires at least 3 core approval members (as identified on the VCEP application in Step 4) and can include the assigned expert providing initial review.

- Core approval members are defined as having substantial experience interpreting and/or signing out variants, e.g. lab director, molecular geneticist and will be reviewed during the Step 4 approval process.
- If there is disagreement among VCEP members, then voting is required, and classification is determined by majority vote by voice or poll. Disagreements should be recorded.

If a majority vote is not obtained, the VCEPs should err on the conservative side in these situations and classify using the more conservative class (e.g. agree that a variant will be considered VUS if a majority vote is not obtained for a LP or LB classification).

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 (see example below).

“Dear ClinGen [Disease] VCEP,

In our last meeting we approved the following variant classifications with the minimum required members to approve. If anyone else on the VCEP, who was unable to attend, disapproves of any of these classifications, please let us know. Otherwise we will go forward with final approval and submission to ClinVar.

Thank you, [co-chairs or coordinator]

Variant X, Classification

Include text-based evidence summary of the rationale for classification.

An export from the VCI of the evidence codes used and comments on each code can also be included if any additional notes are relevant.

Variant Y, Classification

The approval of the classification is recorded in the VCI and the variant record is labeled as “Approved”. Approved variants are submitted to ClinVar on a regular basis (at least once per quarter).

Part II: Reanalysis and Discrepancy Resolution

VCEPs are expected to keep their variant interpretations up-to-date and to prioritize the re-review of variants that have a conflicting assertion submitted to ClinVar after the VCEP submission. The ClinGen-approved schedule is described below and should be attested to on the VCEP Step 4 application.

- VCEPs are expected to reassess any newly submitted conflicting assertion in ClinVar from a one-star submitter or above (and consider whether to address zero-star submitters) and either resolve or note the basis for the conflict within 6 months of being notified about the conflict. ClinGen VCEPs that have submitted to ClinVar will automatically receive a quarterly Variant Prioritization Report. More information about this report can be found [here](#).

- Please reach out to the submitter if you need additional evidence. If the variant is not updated by the VCEP or the conflicting source to resolve the conflict, please track that it was addressed.
- VCEPs are expected to re-review all their LP and VUS classifications 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 (e.g. new gnomAD releases or other large sources of population data)
- VCEPs are expected to re-review any classifications when requested by the public via the ClinGen website, assuming the volume of requests can be handled by the VCEP.

G. Example Evidence Summaries

To promote understanding and enable external review, all finalized/approved variant classifications must be accompanied by brief, yet comprehensive evidence summaries. These evidence summaries will include the pathogenicity classification, the evidence category codes applied and the reasons for applying each code. These statements should include, where applicable, reference to external data sources such as PMIDs, ClinVar SCVs, gnomAD, etc. These evidence summary statements must be provided by the VCEP within the summary evidence tab in the VCI and will be accessible within publicly accessible ClinGen databases such as the Evidence Repository. The full VCEP should have an opportunity to review, edit, and approve the evidence summaries.

Elements to include with a variant evidence summary include:

- The condition for which the variant is being assessed. Of note, some variants in genes associated with multiple conditions may have evidence such as very high population allele frequencies that support the conclusion that they are benign for all conditions currently associated with that gene. This additional information could be noted in the summary where applicable, including using a more generalized condition name for the classification (e.g. RASopathies, instead of Noonan syndrome).
- Each evidence code applied. The evidence codes and the VCEP's specified rules may not be well known. Thus, VCEPs should include brief descriptions to support why a particular evidence code was applied and may reference the VCEP's rules. These can be initially entered during curation and review on the individual Evidence Tabs in the VCI. Reference supporting data with PMIDs, SCVs, or other indicators. These should be included within the final summary statement.
- Highlight exceptions. Statement(s) should be added to describe the instance when a piece of evidence or evidence category is "overruled" when applying or combining evidence codes. The reason for the exception should be clear and support the final conclusion regarding pathogenicity classification. For subjective pieces of evidence (e.g. the validity of a functional assay), this can be done by not applying the code and noting the reason it was not applied in the VCI, or, for

objective pieces of evidence (e.g. allele frequency meets a threshold defined by the VCEP) where the code is automatically applied, describing in the final evidence summary why the evidence is not being considered (e.g. reduced penetrance variant). Another example is the case of an autosomal dominant condition where the reviewed variant has been reported to occur along with a second P/LP variant, but the VCEP chooses not to apply the benign code (e.g. because the case had more severe disease) when calculating the final pathogenicity.

Example of Summary Description with exception highlighted:

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

For the Step 4 application, VCEPs should provide at least 5 written evidence summaries as examples of the content that will be submitted to ClinVar to support variant classifications. These example summaries should include references to the ACMG codes applied and the sources of evidence (PubMed IDs and/or the sources of unpublished data (e.g. clinical lab name or PI name for research data). More example evidence summaries can be found [here](#).

H. Designation of Biocurators, Biocurator Trainers, and Core Approval Members

Trained Variant Biocurators

All variant curators performing sustained variant curation must have completed Level 1 and Level 2 training (training materials listed [here](#)). Once the training is complete, an attestation will

be filled out by the curator and they will be enrolled in the ClinGen Community Curation Database. Additional information on biocurator training can be found in Section 1.1 above.

Biocurator Trainers

Biocurators who meet the criteria above are also eligible to train new biocurators. Each VCEP should designate which biocurator(s) will train new biocurators.

Core Approval Members

Prior to submitting the Step 4 application, return to Section A “Composition of the Expert Panel” and fill in the checkboxes to designate VCEP members who will serve as the core approval members for final variant classification approval following Step 4 approval. Core approval members are defined as those who regularly use the ACMG/AMP guidelines to classify and/or review variants during clinical laboratory case sign-out. At least 3 core approval members need to be present on the call for a final variant classification approval to be made.

I. NHGRI Data Availability

Data Sharing

According to the ClinGen publication policy, all ClinGen Expert Panels must agree to disseminate their curation results via the ClinGen website and/or ClinVar immediately upon completion of expert review of each variant, gene, genomic region, or topic (See Section 3.1 for information regarding ClinVar submission). Individual curation results cannot be held for publication. Data will be exported in either real time (VCI to ClinVar) or on a regular basis (at least quarterly). Additionally, all variant level evidence used in the curation of the approved variant will be available to the public through the Evidence Repository. It is the responsibility of the Expert Panel leaders to confirm that, upon publication in journal articles, the data is available through ClinVar and ClinGen.

Publication

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.

Furthermore, all ClinGen Expert Panels are expected to pre-publish their manuscripts on bioRxiv or medRxiv within one month of having a final draft. If the authors do not anticipate submitting their manuscript to bioRxiv or medRxiv they must provide a written justification in the Step 4 VCEP application.

Rule specifications must be posted on the ClinGen website in advance of paper submission so there are no copyright issues. When your VCEP is approved, you will be sent a version of your specifications in standardized ClinGen format to be posted on your VCEP’s page.

Presentation for ClinGen VCEP Step 4 Approval

- Arrange a call with representatives from the CDWG OC by emailing CDWG_OversightCommittee@clinicalgenome.org. VCEP presentations for Step

4 approval typically take place on the OC call on the 3rd Wednesday of the month at 12-1pm ET. If possible, please give at least two months' notice for scheduling to avoid delays.

- Send the fully completed VCEP application materials (including Steps 1-4 of the application) to CDWG_OversightCommittee@clinicalgenome.org at least two weeks prior to the call for circulation to the OC.
- For the presentation to the OC for Step 4 Approval, prepare to scroll through Step 1: Section C (core approval members) and Step 4: Sections F-I on the call and answer any questions. A slide presentation is not necessary. Presentations generally take about 15-20 minutes if the fully completed VCEP application is submitted at least two weeks prior to the call.

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 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.

Notification of approval from the CDWG Oversight Committee at this step signifies the group as a fully approved ClinGen VCEP. The newly approved ClinGen VCEP should format their first ClinVar submission, following the instructions outlined below.

2.5 Post Approval Requirements

Format for submission to ClinVar

Note that upon approval, a VCEP must finalize their set of variants for upload to the Evidence Repository within 30 days. The VCEP is responsible for coordinating the ClinVar submission process. All variants curated, evaluated, summarized, and assigned a final pathogenicity assertion, including those evaluated during the validation process, are submitted to ClinVar. This process is initiated by the VCEP once a set of variant classifications has been approved within the VCI. The VCI supports downloading variant curations including the variant, classification, condition and inheritance, and summarized

curation evidence out of the VCI and into a ClinVar submission format. The ClinVar submission data is reviewed by the VCEP for accuracy against the variant records in the VCI. Once approved, the VCEP is responsible for submitting the formatted data to ClinVar.

- VCEP SOP for ClinVar registration and submission can be found at: <https://docs.google.com/document/d/1CsczQMyC3aHqjZgsZD5DUXEIFWIGdigFDKfn7Qr2q6Y/edit>
- Contact the VCI help desk if assistance is needed: clingen-helpdesk@lists.stanford.edu

VCEPs are expected to maintain ongoing curation and variant classification resulting in submissions to ClinVar at least quarterly.

Annual Update Form

All ClinGen VCEPs are expected to submit an annual update form to the CDWG OC (CDWG_OversightCommittee@clinicalgenome.org). These reports are due on May 1 of every year and should include a summary of the prior year's progress, plans for the coming year including any changes or additions to the scope of work and any changes to the VCEP panel members.

If there are significant changes during the year, such as changes in Chair(s), significant changes in scope of work, or if the group is no longer able to follow the rules as written in the VCEP Protocol, the chair or coordinator should immediately notify the OC.

3. Variant Prioritization and Reanalysis

The following sections describe the processes for selecting and prioritizing variants and requirements for reanalysis.

3.1 Selection and Prioritization of Variants

Selection of variants for curation and evaluation will be made by consensus discussion by the VCEP membership. Variants are prioritized based on conflicting interpretations in ClinVar, variants that are major contributors to disease, including those that are major contributors to disease in underrepresented populations, variants that are VUS from three or more labs that may be able to be reclassified by aggregating evidence, variants that can be classified at scale (predicted loss of function or those with high allele frequency), as well as those nominated by external parties.

3.2 Public Access and Inquiry

Public access to variant classifications and evidence via ClinVar submission provides a means for encouraging inquiries and public comments regarding the evidence and rationale for classifications. To support the receipt of comments and inquiries, the contact information for each specific VCEP is made public on the ClinVar Submitter

page. Users can quickly navigate to this contact information within ClinVar following embedded links from the variant assertion page.

Within ClinGen, each final, approved VCEP variant classification along with the curated variant-level evidence is available for external users to review via the Evidence Repository. The classifications are linked to the individual VCEP web pages within ClinGen to aid inquiry. In addition, a mechanism to receive public feedback is available via a comment box present throughout the ClinGen website.

3.3 Reanalysis and Discrepancy Resolution

VCEPs are expected to keep their variant interpretations up-to-date and to expedite the reassessment of variants that have a conflicting assertion submitted to ClinVar after the VCEP’s variant submission (see Table 1 below).

Expert Panel Interpretation Involving a Discrepancy with a ‘Single Submitter, Criteria Provided’ SCV after EP submission or within the year prior					
Scenario	Medically Significant Difference P/LP vs. VUS/LB/B		VUS vs. LB/B Confidence Difference		
Reanalysis	Contact other submitter within 3 months, update as needed within 6 months		Within 2 yr		
If a discrepancy is not reanalyzed in this time frame, the SCV may be dropped to “Single Submitter, Assertion criteria provided” status					
Expert Panel Interpretation, <u>No Discrepancy</u>					
Scenario	P	LP	VUS	LB	B
Reanalysis	Not required	2y	2y	*	Not required

*Review MAFs when new large population datasets are released

Table 1: VCEP discrepancy review and resolution process

Medically Significant Discrepancy

VCEPs should expedite the reassessment of variants that have a conflicting assertion submitted to ClinVar by groups with a “one-star” submitter level (addressing zero-star submissions are at the discretion of the VCEP). The one-star level in ClinVar corresponds to the submitter having provided some information with regard to variant classification criteria. For discrepancies involving a medically significant assertion (P/LP vs VUS/LB/B) made by a one star submitter or above, VCEPs are expected to contact the other submitter within 3 months of being notified about the conflict in their quarterly Variant Prioritization Report. The VCEP will first contact the submitter of the discrepant classification based on the submitter details available in ClinVar. If

the contact information is not correct in ClinVar, a reasonable effort will be made to contact the submitter.

If the external submitter does provide criteria and evidence in support of the discrepant classification, then the VCEP will review any new evidence or the submitter's rationale for differentially interpreting existing evidence and update their classification in ClinVar either confirming the original assertion or a new one.

If the submitter cannot be contacted or is non-responsive to contact efforts after 1 month, VCEPs should document this. VCEPs should then review their classification with available evidence and update their submission and document via their meeting notes in the Variant Prioritization Report.

If a VCEP variant classification is revised from the original, the VCEP will make every attempt to approve and expedite a ClinVar submission as soon as possible, but no later than 6 months from the original discrepancy notification unless communication with the submitter and obtainment of evidence is delayed.

Routine Variant Classification Reassessment

VCEPs are expected to support inquiries from ClinVar users to clarify evidence and rationale for classification as well as consideration of new evidence. Further, a mechanism to receive public feedback is available via a comment box present on every page of the ClinGen website.

VCEPs are expected to reassess all their LP and VUS classifications at least every 2 years and LB classifications when new large population datasets are released to see if new evidence has emerged to re-classify the variants.

If the VCEP does not maintain their interpretations in this timeframe, they may lose ClinGen Variant Curation Expert Panel status.

Review of Specified ACMG/AMP Criteria

The VCEP will conduct a review of their specified ACMG/AMP criteria every 2 years or as appropriate based on new gene-specific knowledge or SVI criteria guidance. This process will include consideration of any new guidance put forth by the SVI as well as updates to membership and scope, and in scientific and clinical knowledge about the characteristics of the particular disease/gene(s) group.

If the VCEP believes that a change/revision to the current approved specified ACMG/AMP criteria is needed, the change and the justification for the change must first be communicated to the SVI VCEP Review Committee. Communication can occur via email but the VCEP may be asked to present at a regular SVI VCEP Review Committee meeting or via an ad hoc meeting called for that purpose. The SVI VCEP Review Committee will provide guidance on whether to proceed with the proposed specification changes during that meeting.

Any criteria change must be validated based on an appropriate test set of variants. The results of this change validation should be communicated to the SVI VCEP Review Committee for approval.

- If the criteria change would lead to a variant moving from a more certain state to a less certain state (e.g. LP to VUS or LB to VUS) then all previously curated variants would be queried to determine if they are impacted by the criteria change. All variants that are impacted would be re-curated based on the criteria change and assessed for possible change in classification.
- If the rule change would lead to movement to a more certain state (VUS to LP or LB), then these changes may await routine re-evaluation as described in Table 1.

Recurated and re-assessed variants will be resubmitted to ClinVar as an update. VCEPs are encouraged to resubmit the re-assessed variant classifications to ClinVar within 1 month of the re-evaluation or as soon as reasonably possible based on the number of impacted variants from approval of the criteria change.

Revised specifications will be published on the VCEP webpage on the ClinGen website as well as on the VCEP submitter page on ClinVar. Such changes would be announced as appropriate at professional conferences to aid in communication to relevant audiences.