



ClinGen Variant Curation Expert Panel Application

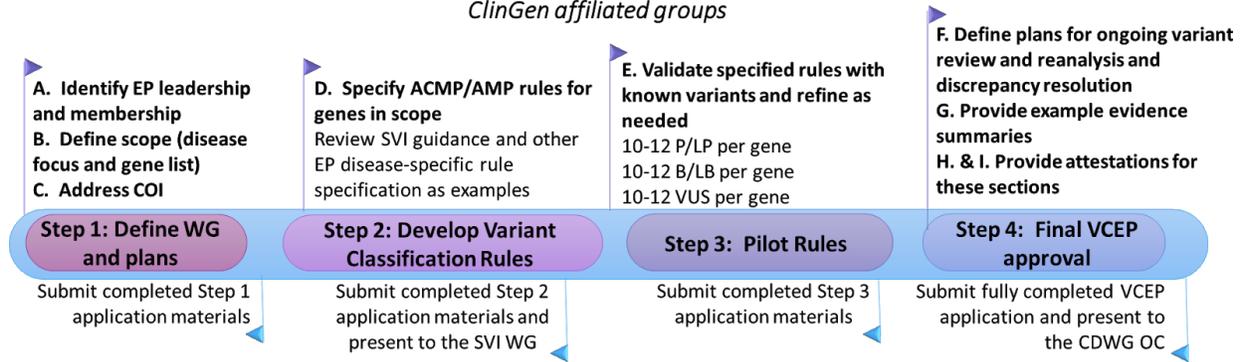
<u>Submitter Information</u>	
Full Base Name of Expert Panel: Familial Hypercholesterolemia Variant Curation Expert Panel	
Short Base Name of Expert Panel (≤15 characters): FH VCEP	
Expert Panel Coordinator: Brooke Palus, MS.	
Email address: brooke_palus@med.unc.edu	Phone: 267-804-1651
Expert Panel Member Responsible for ClinVar Submission: Brooke Palus	
Email address: brooke_palus@med.unc.edu	Phone: 267-804-1651

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. Refer to the ClinGen VCEP Protocol which can be found at https://clinicalgenome.org/site/assets/files/3263/vcep_protocol_v_8.pdf for detailed guidance on completing the ClinGen VCEP application and approval process. Additional pages may be added 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 in the field and should refer to Section 2.1 of the [VCEP Protocol](#) 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*
Mafalda Bourbon, PhD	Instituto Nacional de Saude, Portugal	Cardiovascular Disease Research/Laboratory Director	Chair	√
Alain Carrie, MD, PhD	Pitié-Salpêtrière Hospital	Laboratory Director	Expert	√
Tomas Freiburger, MD, PhD	Centre for Cardiovascular Surgery and	Laboratory Director	Expert	√

	Transplantation, Brno			
Robert Hegele, MD	Robarts Research Institute	Clinician	Expert	
Eric Sijbrands, MD, PhD	Erasmus University Rotterdam	Clinician	Expert	
Maggie Williams, DSc, FRCPath	NHS	Clinical Scientist	Expert	√
Heather Zimmermann, PhD	Ambry Genetics	Variant Assessment Specialist	Expert	√
Amanda Hooper, PhD	Royal Perth	Clinical Scientist	Expert	√
Margaret Chen, PhD, FACMG	Gene Dx	Laboratory Director	Expert	√
Sarah Leigh, PhD	Genomics England	Scientific Curator	Expert	√
Joana Chora, MSc	Instituto Nacional de Saude, Portugal	Researcher, PhD student	Biocurator trainer	<input type="checkbox"/>
Lukas Tichy, MSc	University Hospital Brno, Czech Republic	Molecular Geneticist	Biocurator trainer	<input type="checkbox"/>
Michael Iacocca, MS	The Hospital for Sick Kids, Canada	Clinical Genetics Laboratory Specialist	Biocurator trainer	<input type="checkbox"/>
Ana Margarida Medeiros, PhD	Instituto Nacional de Saude, Portugal	Researcher	Biocurator	
Olivier Bluteau, PhD	Pitié-Salpêtrière Hospital	Researcher	Biocurator	<input type="checkbox"/>
Jian Wang, MD	Robarts Research Institute	Researcher	Biocurator	<input type="checkbox"/>
Jessica Chonis, MGC, CGC	GeneDx	Lab Genetic Counselor	Biocurator	<input type="checkbox"/>
Alexandra Miller	Mayo Clinic	Researcher, PhD Student	Biocurator	<input type="checkbox"/>
Xiangqiang Shao, PhD	University of Wisconsin- Madison	Researcher	Biocurator	<input type="checkbox"/>

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.

Heather Zimmermann, PhD, is a variant scientist for Ambry Genetics and regularly curates variants using the ACMG guidelines. Margaret Chen, PhD FACMG, is a laboratory director at Gene Dx and regularly signs out variants. Sarah Leigh, PhD, is a senior biocurator with New England Genomics and regularly curates variants. Mafalda Bourbon PhD, Alain Carrie MD PhD, Tomas Freiburger MD PhD are all clinical laboratory directors and sign out clinical reports on a regular basis. Maggie Williams DSc, FRCPath, is the Deputy Head of Department at the Bristol Genetics Laboratory at North Bristol NHS Trust.

B. Scope of Work

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).

Refer to Section 2.1 of the VCEP Protocol for guidance and the established [VCEP webpages](#) on [clinicalgenome.org](#) for examples.

The ClinGen Familial Hypercholesterolemia Expert Panel (ClinGen FH EP) is specifying the ACMG/AMP guidelines for sequence variant interpretation for three main FH genes (*LDLR*, *APOB*, *PCK9*). All genes have been curated by a ClinGen GCEP and reached a definitive classification. The FH VCEP will first start with variant curation in *LDLR* before moving on to *APOB* and *PCK9*.

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.

Contact CDWG_OversightCommittee@clinicalgenome.org to create a COI SurveyMonkey for your EP and to access results before submission of the Step 1 application.

√ Check the box to attest that each member has completed a COI survey and an Excel file of results has been included with this 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

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 and present them to representatives from the [Sequence Variant Interpretation WG \(SVI\) 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:** The FH VCEP plans on meeting monthly.
- **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 -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 as described in Section 2.4 of the VCEP Protocol.

The NM_000527.5(LDLR):c.58G>A (p.Gly20Arg) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes (BS3, BS2, BS4 and PP1_Moderate) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (citation pending).

The supporting evidence is as follows:

BS3 - Level 1 assays: PMID 27175606. Heterologous cells (CHO), CLSM assays - result - normal cell surface LDLR, normal LDL-LDLR binding. Although not quantified, assume whole cycle is above 90% of wild-type, so BS3 is Met.

BS2 - variant identified in 5 individuals from Centre of Molecular Biology and Gene Therapy and 1 elderly heterozygous from the ABraOM database.

BS4 - Variant does not segregate with phenotype in 8 informative meioses from at least 3 families from different labs (Centre of Molecular Biology and Gene Therapy, University of British Columbia and Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge): 8 affected family members do not have the variant.

PP1_moderate - Variant segregates with phenotype in 5 informative meioses from Centre of Molecular Biology and Gene Therapy.

The NM_000527.5(LDLR):c.970G>A (p.Gly324Ser) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes (BA1, BS2, PP3 and PP1) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (citation pending).

The supporting evidence is as follows:

BA1 - FAF = 0.01263 (1.263%) in african genomes (accessed 4th June 2020). FAF is above 0.5%, so BA1 is Met;

BS2 - identified in 4 heterozygous non-affected family members from different labs (Robarts Research Institute and Laboratory of Genetics and Molecular Cardiology).

PP3 - REVEL = 0.815. It is above 0.75, so PP3 is Met;

PP1 - Variant segregates with phenotype in 2 informative meioses in 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 2 affected family members have the variant.

The NM_000527.5(LDLR):c.185C>T (p.Thr62Met) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PP4, PS4_Supporting and PP1) as defined by the ClinGen Familial

Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (citation pending).

The supporting evidence is as follows:

PM2 - FAF = 0.0001348 (0.013%) in latino exomes (accessed 1st June 2020). FAF is under 0.02%, so PM2 is Met;

PP4 - Variant meets PM2. Identified in at least 1 FH case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge who fulfills Simon-Broome criteria.

PS4_supporting - Variant meets PM2. Variant identified in at least 4 unrelated index cases with Simon-Broome criteria for FH from different labs (1 from Ambry Genetics, 2 from Laboratory of Genetics and Molecular Cardiology and 1 from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge).

PP1 - Variant segregates with phenotype in 3 informative meioses in 2 families from different labs (Laboratory of Genetics and Molecular Cardiology and Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge): 3 affected family members have the variant.

The NM_000527.4(LDLR):c.1061-?_1845+?del variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1 and PP1_Moderate) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (citation pending).

The supporting evidence is as follows:

PVS1 - Deletion of exons 8 through 12 predicted to lead to out-of frame consequence, so PVS1 is Met;

PP1_moderate - variant segregates with phenotype in 5 informative meioses in 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 4 affected family members have the variant, plus 1 unaffected family member does not have the variant.

The NM_000527.5(LDLR):c.718G>T (p.Glu240Ter) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PVS1, PM2 and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (citation pending).

The supporting evidence is as follows:

PVS1 - Stop in codon 240. It is upstream of amino acid 830, so PVS1 is Met.

PM2 - Not found in gnomAD (accessed 4th June 2020). FAF is under 0.02%, so PM2 is Met.

PP4 - Variant meets PM2. Identified in at least 1 FH case with clinical diagnosis of definite heterozygous hypercholesterolemia by DLCN score from PMID 16250003.

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:

Joana Chora, MSc; Lukas Tichy, MSc; Michael Iacocca, MSc; Olivier Bluteau, PhD; Jian Wang, MD; Jessica Chonis, MGC, CGC; Alexandra Miller; Xiang qiang Shao, PhD; and Ana Margarida Medeiros, PhD.

Biocurator Trainer(s) (*list below*)

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

Joana Chora, MSc, Lukas Tichy, MSc, and Michael Iacocca, MSc.

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.

Mafalda Bourbon PhD, Alain Carrie MD PhD, Tomas Freiburger MD PhD, Amanda Hooper PhD, Heather Zimmermann PhD, Sarah Leigh PhD, Maggie Williams Dsc, and Margaret Chen PhD FACMG,.

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 of the 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. It is expected that whenever possible, Expert Panel manuscripts will be submitted preprints to a preprint server (e.g. bioRxiv or medRxiv).

√ Check box to confirm plans to submit preprints or provide a written justification for not posting pre-print.

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.
