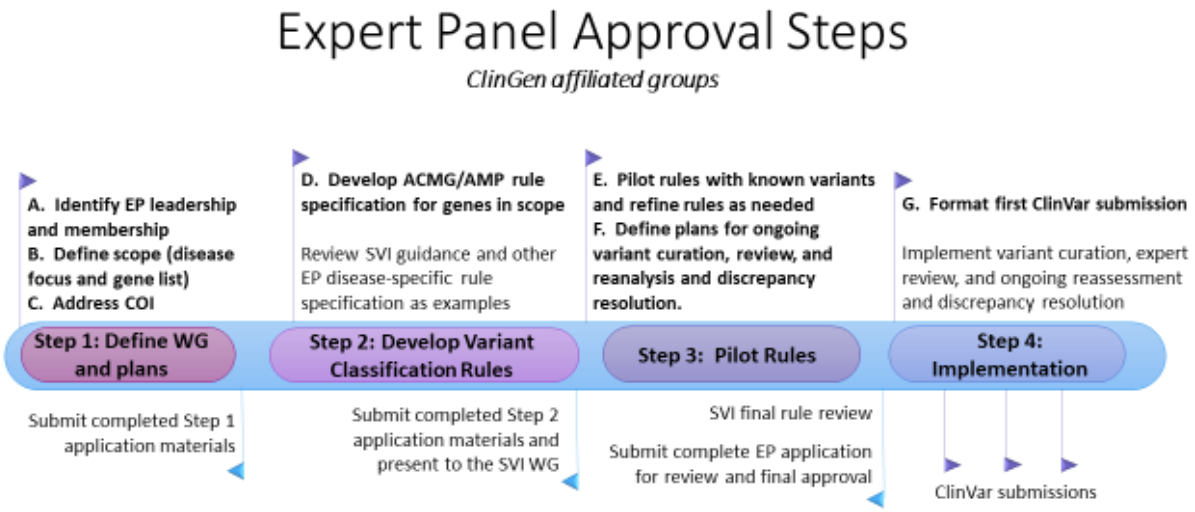
ClinGen Variant Curation Expert Panel Application

Submitter Information	
Full Base Name of Expert Panel: Platelet Disorders Variant Curation Expert Panel	
Short Base Name of Expert Panel (≤15 characters): Platelet Disorders VCEP	
Expert Panel Member responsible for ClinVar submission: Kristy Lee	
Email address: Kristy_lee@med.unc.edu	**Phone**: 919-843-3158
Expert Panel Coordinator and email address: kristy_lee@med.unc.edu	

ClinGen – affiliated groups should compose their Variant Curation Expert Panel (VCEP) application in accordance with the below timeline. ClinGen VCEPs are required to submit for Step 1 approval after completing items A-C. Similarly, after completing item D, ClinGen VCEPs are required to send their variant classification rules to the Rule Specification Review Committee of the Sequence Variant Interpretation (SVI) WG for feedback and approval. Finally, ClinGen VCEPs will pilot and refine rules, define a protocol for ongoing variant curation, review, and reanalysis and discrepancy resolution (complete items E-F) and submit for Step 3 (final) approval by ClinGen's Clinical Domain WG Oversight Committee. The Clinical Domain Working Group Oversight Committee will review your full and short base names as part of your GCEP/VCEP application, and may provide you with feedback to ensure that your name is clear and aligned with other ClinGen GCEP/VCEP names.

External VCEP applicants are also suggested to complete their VCEP application in a stepwise manner, in accordance to the timeline shown below. We encourage these groups to begin communication with the Clinical Domain WG Oversight Committee (after Step 1) and SVI (after Step 2) early in the application process. All VCEP applicants are required to submit for Step 3 (final) approval by ClinGen's Clinical Domain WG Oversight Committee.



Expert Panel Submission Details

A. Composition of the Expert Panel

Expert Panels are expected to represent the diversity of expertise in the field, including all major areas of expertise (clinical, diagnostic laboratory, and basic research). Membership should include representation from three or more institutions and will encompass disease/gene expert members as well as biocurators. Biocurators do not have to be gene/disease experts and will be primarily responsible for assembling the available evidence for subsequent expert member review. For area and type of expertise, please be as specific as possible (e.g. ABMGG laboratory diagnostician and type of lab; clinical geneticist with a focus on cancer genetics). For role in the Expert Panel, options include: primary biocurator, expert reviewer, coordinator or chair.

Member List

Name, credentials, and email	Institution	Area and Type of Expertise	Role
Jorge DiPaola, MD dipaolaj@wustl.edu	University of Colorado, School of Medicine, Hemophilia and Thrombosis Center	Clinician Researcher	Co-Chair
Wolfgang Bergmeier, PhD bergmeie@email.unc.edu	UNC Chapel Hill	Basic research science; functional data	Co-chair
Brian Branchford, MD Brian.Branchford@UCDenver.edu	University of Colorado Denver, School of Medicine, Department of Pediatrics	Pediatric Hematology/Oncology	Expert
Paul Bray, MD paul.bray@hsc.utah.edu	University of Utah, School of Medicine, Division of Hematology and Hematologic Malignancies	Clinical Hematologist	Expert
Stefanie Dugan, MS, CGC SDugan@Versiti.org	BloodCenter of Wisconsin	Clinical & Lab Genetic Counselor	Expert
Kathleen Freson, PhD kathleen.freson@kuleuven.be	University of Leuven	Basic Scientist with vast genomic experience	Expert
Andrew Johnson, PhD johnsonad2@nhlbi.nih.gov	NIH, Population Sciences Branch	Hemostasis and Platelet Research	Expert
Walter Kahr, MD, PhD walter.kahr@sickkids.ca	University of Toronto, The Hospital for Sick Children	Clinician scientist	Expert
Michele Lambert, MD lambertm@email.chop.edu	University of Pennsylvania	Pediatric clinician scientist	Expert
Kristy Lee, MS, CGC kristy_lee@med.unc.edu	UNC Chapel Hill	Clinical Genetic Counselor/Coordinator	Coordinator

Minjie Luo, PhD, FACMG LuoM@email.chop.edu	University of Pennsylvania/Children's Hospital of Philadelphia	Clinical Lab Director	Expert
Lori Luchtman-Jones, MD lori.luchtman-jones@cchmc.org	Cincinnati Children's Hospital/ University of Cincinnati	Pediatric Hematologist	Expert
Shruthi Mohan, PhD shruthi_mohan@med.unc.edu	UNC Chapel Hill	UNC Biocurator	Curator
Andrew Mumford, BSc, MB, ChB, PhD, FRCPath A.Mumford@bristol.ac.uk	University of Bristol and University Hospitals Bristol NHS Foundation Trust	Professor/Co-chair of Thrombogenomics	Expert
Juliana Perez Botero, MD JPerezBotero@Versiti.org	Associate Medical Director, BloodCenter of Wisconsin and Assistant Professor, Medical College of Wisconsin, US	Clinician scientist/Medical lab director	Expert
Matt Rondina, MD, MS matthew.rondina@hsc.utah.edu	University of Utah	Clinical Hematologist	Expert
Justyne Ross, PhD justyne@email.unc.edu	UNC Chapel Hill	UNC Biocurator	Curator
Gabriella Ryan, PhD, PMP gryan@hematology.org	American Society of Hematology	Senior Manager of Precision Medicine	ASH liaison
Sarah Westbury, BA, BMBch, PGCert MedEd sarah.westbury@bristol.ac.uk	University of Bristol and University Hospitals Bristol NHS Foundation Trust	Clinical hematologist	Expert
Bing "Melody" Zhang, PhD mbzhang@stanford.edu	Stanford University	Clinical Lab Director	Expert
Samya Chakravorty, PhD samya.chakravorty@emory.edu	Emory University	Molecular and Human Geneticist	Biocurator
Paula Heller, MD, PhD paulaheller@hotmail.com	Universidad de Buenos Aires	Clinician Scientist	Expert
Claire Lentaigne, PhD c.lentaigne@nhs.net	UK National Health Service	Hemostasis and Platelet Research	Expert
Jose Rivera, PhD jose.rivera@carm.es	Centro Regional de Hemodonación	Molecular Geneticist	Expert
Shannon McNulty, PhD shannon_mcnulty@med.unc.edu	UNC Chapel Hill	UNC Biocurator Core	Biocurator
Abul Kalam Azad, PhD	Montefiore Health System		Biocurator
Angela Hoang, MS ahoang18@students.kgi.edu	Keck Graduate Institute		Biocurator
Poornima Vijayan poornima.vijayan@mail.utoronto.ca	University of Toronto		Biocurator

Please describe the specific variant interpretation expertise and experience with the ACMG/AMP guidelines and variant curation within the EP membership.

This group is very well-versed in the ACMG/AMP guidelines. We have representation from three of the major clinical testing labs in the US: BloodCenter of Wisconsin, CHOP and Stanford University. They are US experts in molecular and biochemical testing for platelet disorders. Juliana Perez Botero is at the clinical director level at BloodCenter of Wisconsin. Stefanie Dugan, Shruthi Mohan, Justyne Ross and Kristy Lee have extensive experience with ACMG/AMG Guidelines and curate variants using these guidelines on a routine basis. Most other members have familiarity with the rules and have been great resources for specifying specific rule codes.

(Insert additional page if needed)

B. Scope of Work

Describe the scope of work of the Expert Panel (disease areas and gene(s) being addressed).

The Platelet Disorders Expert Panel will curate clinically relevant variants using the specified classification rules developed by the group. After interpreting variants using these specified guidelines, the group will make their final interpretations publicly available through ClinVar.

This VCEP plans to begin ACMG/AMP rule specification for genes associated with Glanzmann thrombasthenia (OMIM: 273800). These genes include *ITGA2B* and *ITGB3*. The group then plans to move to rule specifications for Bernard-Soulier syndrome (OMIM: 231200), including the *GP9*, *GP1BA* and *GP1BB* genes. These two platelet disorders are well studied and their biology is well understood, and these genes are commonly ordered for testing in hematology practices. We plan to submit for full EP status after completion of rule specifications for the genes associated with Glanzmann thrombasthenia, and then we will update our application once the Bernard-Soulier gene specifications are completed and approved by the SVI committee.

C. Conflict of Interest Management

Expert Panels are expected to represent the diversity of expertise in the field and should be composed of a sufficient number of eligible expert reviewers to address academic and financial conflicts of interest that may arise.

- *Academic COI: Authors of literature about relevant variants may serve on the Expert Panel 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.*
- *Financial COI: Commercial entities may participate on the Expert Panel, but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that entity.*
- *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.*
- *All conflicts will be declared publicly on the clinicalgenome.org website and reported in publications as appropriate.*

A COI survey was submitted to all expert panels members, and responses have been collected from the entire working group. The responses will be made available on the ClinGen public website.

Note to Submitters: After completing Step 1 (application items A-C), please submit your draft Expert Panel application to the ClinGen Clinical Domain WG Oversight Committee (CDWG_OversightCommittee@clinicalgenome.org) for review.

Date of Submission:

9/19/18

[redacted]

Expert Panels are encouraged to use the ACMG/AMP variant assessment criteria as their starting point for a framework to adjudicate Mendelian variants according to the five class criteria (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). The Expert Panel process typically entails reviewing the evidence types and making gene-specific specifications to the ACMG/AMP guidelines, including consultation with the Sequence Variant Interpretation WG in order to facilitate harmonization of approaches across different expert panels.

Provide the gene-optimized rules for variant classification designed by the Expert Panel as an appendix. Documentation will be made publicly available and could consist of an unpublished document, manuscript pre-print, or published manuscript. The following items must be included in the submitted material:

- **Please attach a description of the specified ACMG/AMP guidelines for the gene(s) of interest, including evidence and rationale to support the rule specifications.**

- **Describe combinations of rules and evidence sources that could be used to classify any categories of variants (e.g. Benign or Likely Benign) in a batch:**

Please see attached revised rule specifications set.

Note to Submitters: After completing Step 2 (application item D), please submit your draft Expert Panel application to the ClinGen Sequence Variant Interpretation Working Group (dazzarit@broadinstitute.org) for review.

Date of approval: 4/17/19

E. Validation of ACMG guideline specifications

Please provide a description of how your rules were validated with known variants.

35 variants for the *ITGA2B* gene and 30 variants for the *ITGB3* gene were curated by 1 of 2 senior biocurators from the UNC Biocuration Core. We planned to curate approximately 15 pathogenic/likely pathogenic variants, 5 VUS, and ~10 benign/likely benign variants for each gene. Variants were nominated by expert members, who also submitted clinical and laboratory phenotypic data and their variant assertion. In order to accrue enough variants in each assertion category, we used some variants listed in ClinVar. We also added variants to the pilot that were *in trans* with other variants in the study. Experts were sent results of variant curation results before calls. The results were reviewed on bimonthly conference calls with experts. Experts unanimously agreed on all variant assertions.

F. Model ClinVar submission

Expert Panels are encouraged to make submissions to ClinVar through the ClinGen Variant Curation Interface (VCI) in order to standardize the content across expert panels.

Please provide a sample list of classified variants curated in the VCI or attached in the ClinVar submission template. The submission template can be downloaded here: ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/submission_templates/

Please see spreadsheet with pilot study results.

G. Define plans for ongoing variant curation, review, and reanalysis and discrepancy resolution

Expert Panels are expected to develop work schedules, review and resolve differences in interpretation, and provide standard procedures for variant assessment.

Standard Operating Procedures:

- **Meeting/call frequency:** Once a month for the full VCEP and one monthly biocurator call

- **Curation/expert review/finalization process:**

  □ **Version 1: One curator performs and enters the data into the VCI for review and classification by one or more experts. Discussions with the full EP are triggered if:**

  a) the experts do not reach consensus,

  b) either expert raises concerns regarding any piece of evidence or criterion application,

  c) the expert would like to modify the final classification from the calculated category.

  □ **Version 2: One curator performs biocuration and presents directly to the full EP for review and consensus classification.**

  Version 3: One curator performs biocuration and enters the data into the VCI for review and classification by two experts. Curations will be presented directly to the full EP for review and consensus classification

  We plan to use the new streamlined variant curation process with the A) batched process (ex. BA1), B) streamlined voting process (a minimum of 5 experts will have to vote and agree on the classification, C) full discussion for variant requiring further discussion.

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.

X **Expert Panels 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.**

X **Expert Panels 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**

X **Expert Panels are expected to re-review any LB classifications when new evidence is available or when requested by the public via the ClinGen website.**

□ **If plans differ from the expectations above, please describe here:**

H. NHGRI Data Availability

Curated variant and genes are expected to be approved and posted for the community as soon as possible and should not wait for the publication of a manuscript.

X **Please 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.**

It is expected that whenever possible, Expert Panel manuscripts will be pre-published on bioRxiv. If the authors do not anticipate submitting their manuscript to bioRxiv they must provide a written justification.

X **Please check box to confirm plans to pre-publish on bioRxiv or provide justification for not posting pre-print.**

Note to Submitters: Please send your completed Expert Panel application to ClinVar (clinvar@ncbi.nlm.nih.gov) and to the ClinGen Clinical Domain WG Oversight Committee (CDWG_OversightCommittee@clinicalgenome.org) for review.

Date of Final Submission:

11/21/19

Updated 6/16/20