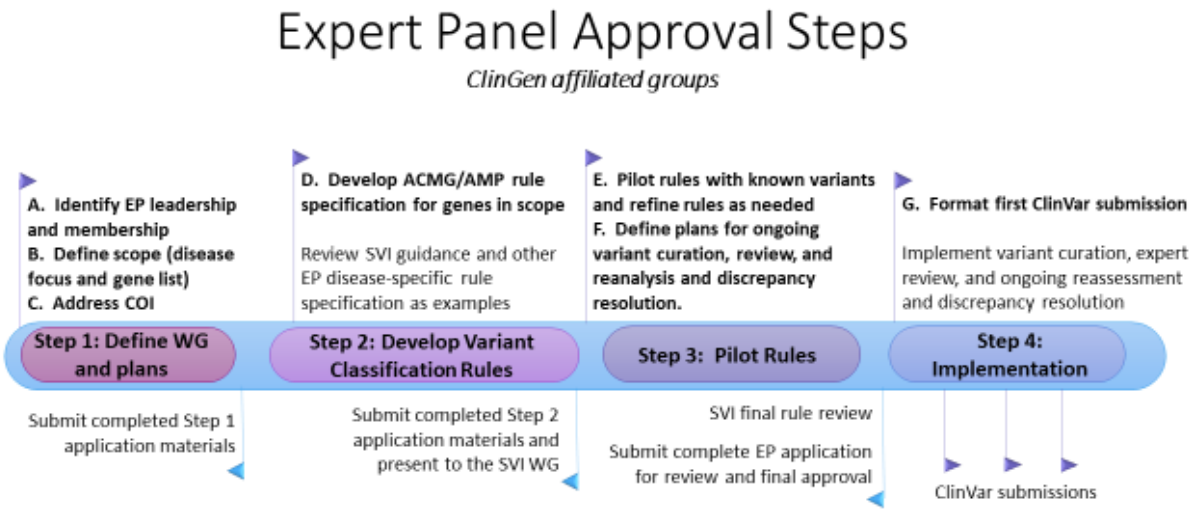
ClinGen Variant Curation Expert Panel Application

Submitter Information	
Full Base Name of Expert Panel: TP53 Variant Curation Expert Panel	
Short Base Name of Expert Panel (≤15 characters): TP53 VCEP	
Expert Panel Member responsible for ClinVar submission: Kristy Lee/Sharon Savage	
Email address: kristy_lee@med.unc.edu	**Phone**: 919-843-3158
Expert Panel Coordinator and email address: Kristy Lee (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
Sharon Savage, MD	National Cancer Institute Division of Cancer Epidemiology and Genetics	Medical oncologist/Clinic researcher with interest in molecular epidemiology	Chair
Maria Isabel Achatz, MD, PhD	National Cancer Institute Division of Cancer Epidemiology and Genetics	Molecular cancer epidemiology	Expert
Laura Attardi, PhD	Stanford University	Basic science/functional studies	Expert
Kelvin Andrade, MSc, PhD	NIH DCEG, clinical genetics branch/International Research Center, A.C. Camargo Cancer Center, Sao Paulo, SP Brazil	NCI Research fellow	Biocurator
Rebecca Bassett, MS, CGC	Kaiser Permanente	Clinical Genetic Counselor	Expert
Gareth Evans, MD, FCRP	St. Mary's Hospital, Manchester,UK, Department of Medical Genetics	Clinical Geneticist	Expert
Bingjian Feng, PhD	The University of Utah, Dermatology	Bioinformatics	Expert

Cristina Fortuno, PhD candidate	QIMR Berghofer Medical Research Institute, Brisbane, Queensland,Austrailia, Genetics and Computational Biology Department	Molecular Cancer Epidemiology	Expert
Megan Frone, MS, CGC	NIH DCEG, Clinical Genetics Branch	Genetic Counselor	Expert/Future coordinator
David Goldgar, PhD	University of Utah, Dermatology	Molecular Cancer Epidemiology	Expert
Robert Huether, PhD	Tempus Labs	Computational Biologist	Expert
Paul James, MBChB, DPhil, FRACP	University of Melbourne	Clinical Geneticist	Expert
Kristy Lee, MS, CGC	UNC Chapel Hill	Clinical genetic counselor/Coordinator	Coordinator
Phuong Mai, MD, MS	University of Pittsburgh	Medical oncologist	Expert
Kelly McGoldrick, PhD	Ambry Genetics	Variant Science Specialist	Expert/biocurator
Jessica Mester, MS, CGC	GeneDx	Laboratory Genetic Counselor	Expert
Magali Olivier, PhD	International Agency for Research on Cancer (IARC)	Research Scientist/functional studies	Expert
Tina Pesaran, MA, MS, CGC	Ambry Genetics	Laboratory Genetic Counselor	Expert
Sharon Plon, MD, PhD	Baylor College of Medicine/Texas Children's Hospital	Medical Geneticist	Expert
Deb Ritter, PhD	Baylor College of Medicine	Research Scientist	Baylor liaison

Thomas P. Slavin, MD	City of Hope	Clinical Geneticist	Expert
Amanda Spurdle, PhD	QIMR Berghofer, Medical Research Institute	Molecular Cancer Epidemiology	Expert
Leora Wikowski, PhD	McGill University	Clinical Molecular Geneticist	Biocurator
Liying Zhang, MD, PhD	Memorial Sloan Kettering Cancer Center	Diagnostic Molecular Genetics Laboratory Director	Expert

(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 *TP53* gene provides instructions for tumor protein p53 (or p53). This protein acts as a tumor suppressor, regulating cell division by preventing cells from proliferating in an uncontrolled way.

The *TP53* Variant 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.

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 Survey Monkey COI questionnaire will be circulated to all current members. 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:

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 refer to the following Google document:

https://docs.google.com/document/d/1RFgC8YRwGPcT0pvMj1tHC3QRJ9wYyqENNR-YCGS_EJI/

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 Submission:

E. Validation of ACMG guideline specifications

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

Expert members of the *TP53* VCEP submitted variants for rule pilot testing. Each variant was submitted with a variant assertion along with any clinical and functional data available to them. Biocurators were trained on the *TP53* rule specifications by the chair and coordinator. The dual curation system was used to test user interpretability of the specifications and to better ensure that all pertinent information was utilized. Their curation results were presented to expert panel members on conference calls, and final expert assertions were agreed upon.

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 pilot curation spreadsheet.

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:** monthly

- **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.

  X **Version 2: One curator performs biocuration and presents directly to the full EP for review and consensus classification. Dual curation will be used as a training tool for new curators.**

  □ **Other**

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.

- ✓ **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.**
- ✓ **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**
- ✓ **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.

- ✓ **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.

- ✓ **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: