

Frequently Asked Questions for the NICHD Genomic Clinical Variant Expert Curation Panels Program Announcement (PAR-20-101)

What is the objective of the PAR?

The objective of this FOA is to establish expert curation panels that will select candidate genes and genomic variants associated with diseases or conditions of high priority to the participating NIH Institutes and that will have a high impact on clinical practice. The Expert Curation Panels will analyze all relevant data utilizing the ClinGen (<https://www.clinicalgenome.org/>) resource tools and based on this analysis, establish the clinical relevance of these genes and/or variants to support clinical practice.

What are the priority conditions or diseases for the NIH curation panels?

For the purpose of this FOA, genes and variants should be associated with but not limited to one or more of the following topic areas:

- NICHD: gynecologic, andrologic, and reproductive health; poor pregnancy outcomes; high-risk newborn conditions; structural birth defects; intellectual and developmental disabilities; and susceptibility to infections
- NCI: inherited susceptibility to cancer development and/or response or resistance to therapy
- NEI: diseases of the eye, central visual, and oculomotor pathways
- NIMH: severe mental illnesses, e.g., autism and schizophrenia
- NINDS: neurological, neuromuscular diseases and stroke

Please contact the individuals listed at the end of the Q&A document for any questions regarding

What genes or variants should be selected for curation?

Selection of genes or variants is at the discretion of the PI and panel members. There is no set number of genes. With only three years of funding, consideration should be taken of the scope of clinical domain/disorder and the number of genes or variants to be curated. The panel should identify those genes/variants that are most likely to impact clinical practice and for which evidence is available. The justification for selecting the genes/variants that have been identified should be based on this principle rather than a sample of convenience.

What if other groups/panels are evaluating the same domain or group of genes?

PIs are encouraged to work with the other groups to establish a single working group rather than duplicating effort. If this cannot be accomplished, a justification must be provided as to why the work of this panel will be unique, and any area of overlap must be described. As the goal of the PAR is to provide expert panel evaluation of gene-disease or variant pathogenicity assessments to support variant curation, having two groups duplicate efforts is not an efficient use of resources.

How should the Genomic Expert Panel be structured?

The panel should be led by a chair or co-chairs (who should serve as the PI or co-PIs of the grant). Members of the panel should include experts from at least 3 different institutions.

Expert panels should include supporting personnel that include a Project Coordinator, biocurators who will provide the panel members with primary curation and documentation of the selected genes/variants, and bioinformatics specialists.

Are multiple PI's allowed?

Multiple PIs are allowed. Funds are available to support partial salary of the PI who serves as the expert panel chair of the working group and under some circumstances, a co-chair.

What experts should be included on the expert panel ?

For the purpose of this FOA, membership of the expert panel should include domain and condition experts reflecting the breath of expertise required to ascertain the clinical actionability of the genes identified. The panels should include medical professionals, medical geneticists, clinical laboratory diagnosticians and/or molecular pathologists, researchers and statisticians. Since the goal of the PAR is to assess the clinical validity of the selected gene-disease associations or genetic variant pathogenicity based on current knowledge that could support guidelines for clinical practice, multiple institutions and organizations must be represented and international participation is strongly encouraged.

Critical to the success of gene/variant curation are a project coordinator, biocurators and bioinformatics specialist(s).

Can all members of the Expert Panel be from the same institution?

No, in order to qualify for a ClinVar expert panel, members are expected to be from multiple institutions, and foreign members are encouraged. Formation of Expert Panel guidance can be found at <https://www.clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/>.

How should conflicts of interest be managed?

Conflicts of interest should be identified for each member of the working group and managed by the Curation Panel PI and the PI's institution. These should be kept up-to-date and reported to ClinGen.

How should expert panels be organized?

Depending on the number of genes or variants, either a single panel could meet regularly to review individual genes/variants or subpanels could be established that will focus on specific subsets of genes/variants. These subpanels/working groups could then report to the entire expert panel to determine final assertions. The investigators should build on the experience of ClinGen Clinical Domain Working Groups (CDWG) and curation panels in organizing the work of the expert panel. Examples of ClinGen curation working groups can be found at <https://clinicalgenome.org/affiliation/>.

How should expert panel members be listed in the application?

Each member of the expert panel should be listed under personnel as consultants with a biosketch attached. Consultants do not require an E-commons name and are paid nominal fees.

How should the expert panels be staffed?

The PI (and possibly co-PI) will be responsible for leading the panels. However, experience has shown that the availability of a project coordinator, biocurator, and bioinformatician are critical to the success of the curation panel. The biocuration staff is expected to perform data collection and primary analyses for genes and variants. Biocurators may be genetic counselors, clinical fellows or researchers in the field. In addition, bioinformatics specialists should be engaged, to help analyze existing datasets within the framework of the tools available through ClinGen. Both the biocurators and bioinformatics specialists are expected to utilize the ClinGen tools and to participate on appropriate ClinGen working groups.

What are the allowable costs?

Partial salary support for expert panel chair and under some circumstances, the co-chair, is allowed. The primary emphasis should be on supporting a project coordinator, biocurators and bioinformatics specialists. Both domestic and international expert panel members can receive nominal consulting fees. Funds can also be used for meeting support and travel to face-to-face meetings and the annual Curating the Clinical Genome Conference by the PI and other appropriate members. There may be additional costs associated with training on ClinGen tools. Regarding budgeting for consultants, if they will not be conducting a substantive portion of the research, their fees will not be considered to be a sub-award, and therefore, no indirect costs would be involved. If they are conducting a substantive portion of the research, a sub-contract will be required. All costs, including indirect costs, come from the parent award.

Are functional studies to support curation calls allowed?

No, only evaluation of existing data is supported through this initiative.

Are renewal applications allowed, or can existing expert panels apply through this PAR?

Yes, existing expert panels can apply through this PAR. However, there needs to be adequate justification regarding the work that the panel proposes to do, and the scope needs to be sufficiently new to justify continued support.

How will NIH-funded expert curation panels interface with ClinGen and ClinVar?

Expert curation panels are expected to utilize the ClinGen/ClinVar framework and curation tools to assess current evidence supporting disease association for the chosen genes and variants (<https://clinicalgenome.org/tools/>). Expert panel curation staff are expected to receive training on ClinGen tools and resources through distance and in-person educational modules. The PI and curation staff are expected to participate on appropriate ClinGen working groups and to deposit final determinations and supporting evidence into ClinGen and ClinVar databases. Applicants are encouraged to review ClinGen curation and education tools at <https://clinicalgenome.org/curation-activities/>.

ClinGen's Clinical Domain Working Groups (CDWG) serve a strategic and organizational function for horizon scanning and fostering the expert curation groups. Each CDWG coordinates one or more expert panel groups undertaking gene or variant curation and is an umbrella over a cluster of related expert panels. ClinGen has proposed the following options for coordination with NIH expert curation panels

with ClinGen activities: placement within an existing ClinGen CDWG if appropriate; formation of a new CDWG if appropriate; or support of a standalone “expert panel.”

What ClinGen and ClinVar resources are available to guide and facilitate the curation process?

ClinGen has posted guidelines for obtaining ClinVar expert panel status for gene and or variant curation (<https://clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/>). This includes the process of curation and criteria for the levels of clinical assertions as well as an expert panel toolkit: <https://www.clinicalgenome.org/expert-groups/>. In addition, ClinGen has provided Demonstration Curation interfaces. For further information about these interfaces please contact the ClinGen help desk at: clingen-helpdesk@lists.stanford.edu.

Is a Letter of Intent required?

No, a Letter of Intent is not required, but is encouraged.

Does the PI have to be USA based even though the proposals are encouraged to be international?

Yes, because it is a US based initiative, the PI for any expert panel proposals needs to be based in the US. However, we encourage foreign collaborators.

Is a single expert panel or multiple expert panels allowable or preferred for submission when an expert panel already exists?

The intent of the PAR is to support individual expert panels, as the awarded funds are expected to support a coordinator, curators, the PI, and potentially, a co-PI. As stated in the PAR, if there are questions regarding overlap with existing expert panels, that needs to be clarified in the application. Applicants are encouraged to reach out to existing expert panels that can be found on the ClinGen website (<https://clinicalgenome.org/affiliation/>) and determine whether there is scientific overlap; if so, the applicant should provide supporting evidence that the scope of the application will not overlap with an existing activity.

What are the expectations for participating in working groups for funded expert panels?

Expert Panel members are expected to participate in monthly ClinGen meetings. In addition, coordinators and curators are expected to participate in regularly scheduled monthly calls involving their peers. This is required in the PAR.

Will non-priority conditions be considered?

If you are not sure whether your condition(s) would be considered for funding by one of the sponsoring Institutes, we strongly recommend that you reach out to the most appropriate program contact listed at the end of this FAQ and/or in the PAR.

Is funding restricted to new curation groups, or could an existing varied curation expert panel in step one or two apply for funding?

Both new groups and groups that have been funded before can apply; both must provide justification as to what work they will be undertaking, based on the requirements of the program announcements. We

always recommend speaking to the relevant program director before applying because each institute has its own priorities.

How many genes do expert panels typically tackle?

The number of genes expert panels tackle is highly variable; it has ranged from 1 to 50 and even more.

Is this funding only available to specific areas of interests, and not cardiovascular genes?

NHLBI is not participating in this PAR, but the application may fall within the interests of another institute such as NICHD if it addresses structural heart defects or newborn screening-related cardiac conditions. Reach out to Melissa Parisi for more information.

ClinGen has a process to approve expert panels to ensure the number of curators experienced with ACMG are present. Will the groups submitting to this PAR need to first be approved by ClinGen, the step 1 approval, or would these be external to ClinGen?

To be a ClinVar-approved Expert Panel, you must be approved by ClinGen. However, ClinGen approval is not required to submit an application to NIH for this PAR. Application for ClinVar Expert Panel approval can be submitted after funding.

How best to contact ClinGen?

For general inquiries, contact clingen@clinicalgenome.org. For the curation interface, contact clingen-helpdesk@lists.stanford.edu

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