PAR-20-101 and NOT-HD-21-028 –Genomic Clinical Variant Expert Curation Panels (U24 Clinical Trial Not Allowed): Frequently Asked Questions (FAQs) and Answers

The following FAQs and answers are for PAR-20-101 and NOT-HD-21-028.

What is the objective of the Program Announcement (PAR)?

The objective of this Funding Opportunity Announcement (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 tosupport clinical practice.

What are the priority conditions or diseases for the NIH curationpanels?

For the purpose of this FOA, genes and variants should be associated with but notlimited to one or more of the following topic areas:

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): gynecologic, andrologic, and reproductive health; poorpregnancy outcomes; high-risk newborn conditions; structural birth defects; intellectual and developmental disabilities; and susceptibility to infections
- National Cancer Institute (NCI): genes and germline variants associated with inherited susceptibility to cancer development and/or response or resistance to therapy; somatic variants associated with cancer diagnosis and treatment
- National Eye Institute (NEI): diseases of the eye, central visual, and oculomotor pathways
- National Institute of Mental Health (NIMH): severe mental illnesses, e.g., autism and schizophrenia
- National Institute of Neurological Disorders and Stroke (NINDS): neurological, neuromuscular diseases and stroke

To the extent possible, applicants are encouraged to design curation efforts that emphasize the inclusion of data from underrepresented populations. While it is understood that there is limited availability of existing genomic data in understudied populations, especially for rare diseases, the research plan should nevertheless describe how the proposed curation activities will ensure that the genes analyzed reflect and include diverse populations (for gene curation expert panels) and/or that the data used to make variant assertions come from diverse populations (for germline variant curation expert panels or somatic cancer variant curation expert panels).

Please contact the individuals listed at the end of this document with any questions.

What genes or variants should be selected for curation?

Selection of genes or variants is at the discretion of the Principal Investigator (PI) and panel members. There is no minimum or maximum number of genes and/or variants required for a successful application. Applicants should justify their proposed scope of work in terms of the clinical importance of the disease area as a whole and the impact that their work is expected to have on clinical diagnosis and management of patients. Additionally, the proposed scope of clinical domain(s)/disorder(s) and the number of genes and/or variants to be curated should be feasible within a three-year project period. 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 to curate 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 strong 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 and will not be prioritized for funding consideration.

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-PI(s) of the grant). Members of the panel should include experts from at least three 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 PIs 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, if applicable, the co-chair(s).

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 breadth of expertise required to ascertain the clinical actionability of the genes and/or variants to be curated. 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, biocurator(s),and bioinformatics specialist(s).

Can all members of the expert panel be from the same institution?

No, in order to qualify for a ClinGen 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 (COI) 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. Please refer to ClinGen's Conflict of Interest Policy and COI reporting process outlined in the GCEP and VCEP applications.

How should expert panels organize their curation activities?

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 willfocus 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 may be paid nominal fees.

How should the expert panels be staffed?

The PI (and possibly co-PI(s)) 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 are 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 datasetswithin 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, if applicable, the co-chair(s), 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* (https://clinicalgenome.org/about/events/) 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 functional data is supported through this initiative.

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

Yes, renewal applications from 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. Past productivity of the existing Expert Panel should be provided, including metrics such as described here: https://search.clinicalgenome.org/kb/reports/stats.

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

Expert curation panels are expected to utilize the ClinGen/ClinVar framework and curation tools to assess current evidence supporting disease association for the chosengenes and/or variants (https://clinicalgenome.org/tools/). Expert panel curation staff are expected to receive training on ClinGen tools and resources through distance and/or in- person educational modules. The PI(s) 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 CDWGs 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 and/or variant curation and is an umbrella over a cluster of related expert panels. The following options exist for coordination of 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."

Because each expert panel is expected to utilize pre-defined ClinGen tools and procedures, the innovation in proposed expert panels arises from their capacity to make substantial and significant new contributions to publicly available knowledge and understanding of genomic variants.

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 strongly encouraged. Applicants should send letters of intent to Mollie Minear at mollie.minear@nih.gov.

Is a Letter of Support from ClinGen required?

No, a letter of support from ClinGen is not required, although applicants are strongly encouraged to include one with their application to clearly define the type and status of their curation panel:

- New Expert Panel that is not part of an existing CDWG
- New Expert Panel that is being initiated from within an existing CDWG
- Established Curation Expert Panel

To request a letter of support from ClinGen, please email clingen@clinicalgenome.org with the subject line: “Request for LOS for NIH GCEP/VCEP application, in response to PAR-20-101.”

Does the PI have to be U.S.-based even though the proposals are encouraged to be international?

Yes, because it is a U.S.-based initiative, the PI for any expert panel proposals needs to be based in the United States. 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, if applicable, co-PI(s). 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 panel’s curation activities.

What are the expectations for participating in working groups forfunded 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 ofthe 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 existingcuration expert panel apply for funding?

Both new groups and previously funded groups can apply; both must provide justification as to what work they will be undertaking, based on the requirements of the program announcements. For new expert panels that are not part of an existing CDWG, applicants should articulate plans to engage with the ClinGen consortium. For new expert panels that are being initiated from within an existing CDWG, applicants should describe the need for a new expert panel in their broad disease area. For established expert panels, applicants should describe how the funding from this mechanism will enable them to expand their scope or scale their curation efforts. We always recommend speaking to the relevant program director before applying because each institute has its own priorities.

Expert panels that are early in their lifespan will likely spend more time recruiting and training the biocurator and expert curation workforce, establishing their meeting schedule, and developing rule specifications. Once approved by the ClinGen consortium to proceed with curation activities, established expert panels will scale up their curation activities in order to address their scope of work. Mature expert panels that are engaged in ongoing curation within their original scope of work may seek to expand their scope of work (for example, an approved variant curation expert panel that proposes to establish a new set of rule specifications for an additional gene within their disease area).

How many genes and/or variants do expert panels typically tackle?

In general, gene curation expert panels tend to cover a larger number of genes, whereas variant curation expert panels typically focus on a smaller number of genes due to the need to establish variant classification guidelines and then curate hundreds or thousands of variants within each gene. Proposals that include both gene and variant curation activities should clearly describe the subdivision of these efforts within the grant period. For cancer-related curation of variants, applicants can propose to curate germline variants, somatic cancer variants, or both germline and somatic cancer variants.

ClinGen has a process to approve expert panels to ensure the numberof curators experienced with ACMG guidelines 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?

ClinGen approval is not required to submit an application to NIH for this PAR. Applications for ClinGen expert panel approval can be submitted after obtaining funding. However, applicants are strongly encouraged to clarify the ClinGen approval status of the proposed expert panel in their application, including:

- The type of expert panel (gene curation expert panel, variant curation expert panel, and/or somatic cancer variant curation expert panel);
- Whether the expert panel has a relationship to an existing ClinGen CDWG; and
- Whether they have already submitted an expert curation application to the ClinGen Clinical Domain Oversight Committee for approval and, if so, the status of their application and, if applicable, their approved curation activities.

Applicants can submit a proposal in response to this FOA to convene a curation expert panel that is anywhere along the continuum of curation activities for genes and/or variants, as long as the curation proposed is justified based on what is known about the disease(s) or condition(s) under study. Applicants are allowed to propose expert panels that will curate genes only, variants only (germline and/or somatic), or both genes and variants. If curation of both genes and variants is proposed, justification should be provided as to why both types of curation activities are needed and feasible.

Additional guidance can be found within ClinGen's Guidelines for Applying for Variant or Gene Curation Expert Panel Status at: https://www.clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/.

How can I contact ClinGen with questions?

For general inquiries, contact clingen@clinicalgenome.org or the NHGRI ClinGen team at: clingen@mail.nih.gov. For inquiries about the curation interface, contact clingen-helpdesk@lists.stanford.edu. For inquiries about the programmatic priorities of the NIH institutes participating in PAR-20-101, or for scientific questions, contact the NIH Contacts listed in the following table.

NIH Contacts:

Institute	Contact
NICHD	**Mollie Minear** Phone: 301-827-9442 Email: mollie.minear@nih.gov
NCI	**Melissa Rotunno** Phone: 240-276-7245 Email: rotunnom@mail.nih.gov
NEI	**Grace Shen** Phone: 301-451-2020 Email: sheng@nei.nih.gov
NIMH	**Alexander Arguello** Phone: 301-827-3547 Email: alexander.arguello@nih.gov
NINDS	**Vicky Whittemore** Phone: 301-496-1917 Email: vicky.whittemore@nih.gov