Join WebEx meeting
Meeting number (access code): 627 266 470
Meeting password: RFA-HD-17-001

Join by phone
1-877-668-4493 Call-in toll-free number (US/Canada)
1-650-479-3208 Call-in toll number (US/Canada)
Agenda
Pre-Application Webinar

• Objectives of the RFA
• Structure of the Expert Curation Panels
• Eligibility and funding
• Interfacing with ClinGen and ClinVar
• ClinGen and ClinVar: an overview of the curation ecosystem
• Final considerations
• Questions

Please mute your phone if you are not speaking
Objectives of the NICHD Genomic Clinical Variant Expert Curation Panels FOA

- Establish expert panels to select genes and genomic variants associated with diseases or conditions of high priority to NICHD.
- Systematically determine their clinical significance and utility for their diagnosis and treatment.
- Utilize the Clinical Genomics Resource (ClinGen) and the ClinVar tools and informatics infrastructure to determine the strength of evidence supporting the clinical significance of the selected genes and variants.
- Deposit final assertions of clinical pathogenicity of gene-disease associations and pathogenicity of variants together with the supporting evidence into ClinVar.
NICHD Priority Areas

• Include but are not limited to:
  • Reproductive and gynecological health
  • Poor pregnancy outcomes
  • High-risk newborn conditions
  • Structural birth defects
  • Intellectual and developmental disabilities
  • Susceptibility to infections

• Candidate genes/variants selected should have potential for high impact on clinical disease or practice.
What is ClinVar?

- NCBI Archival database that aggregates information about genomic variation and relationships to human health.
- Uses a rating system to help users assess the quality and consistency of submitted variant assertions.
- Assertions range from a single submitter, multiple submitters, through expert panel deliberation and finally clinical guidelines.
What is ClinGen?

- NHGRI funded program to create an authoritative resource that defines the clinical relevance of genes and variants for use in precision medicine and research.
- ClinGen is developing the tools and framework for evaluating the clinical validity of gene-disease associations and pathogenicity of genetic variants for use in clinical care.
- Enables quantification of the evidence for supporting a gene/variant disease association to develop clear and robust criteria to guide decisions regarding pathogenicity.
- Established expert curation panels to assess the clinical validity of the selected gene-disease associations or genetic variant pathogenicity.
- Final determinations together with supporting evidence are deposited in ClinGen and submitted to ClinVar with expert panel validity.
Sharing Genetic and Health Data

ClinGen’s Critical Questions

- Is this gene associated with a disease? (Clinical Validity)
- Is this variant causative? (Pathogenicity)
- Is this information actionable? (Clinical Utility)

Building a Genomic Knowledge Base (ClinVar & Other Resources)

Improved Patient Care Through Genomic Medicine
Structure of the NICHD Expert Panels
Expert Panel Membership

- Members should reflect the breadth of expertise required to ascertain the clinical actionability of genes identified.
- Include medical professionals, medical geneticists, clinical laboratory diagnosticians and/or molecular pathologists, researchers and statisticians.
- To ensure comprehensive curation, include multiple institutions, e.g. academic institutions and commercial laboratories, and encouraged to be international in scope.
- There is no predefined number of members
- Conflicts of interest must be reported and managed.
Expert Panel Structure

• Structure of the Expert Panel will depend on the number of genes or variants identified for curation.

• If needed, individual working group(s) may be formed to review the evidence available for a subset of the genes/variants and report to the Expert Panel.

• Ensure that there is adequate staffing to support each panel’s/working group’s function.

• Panel meetings can occur remotely, though at least one annual face-to-face meeting is recommended.
Staffing of Expert Panels

- Chair and Co-Chair
- Domain and condition experts.
- Biocuration staff who will assist the curation process through data collection and primary analysis of selected genes or variants. These may be genetic counselors, clinical fellows or researchers in the field, as well as bioinformatics specialists.
- A project coordinator.
- Biocurators and bioinformatics specialists are expected to utilize the ClinGen framework for variant and gene curation.
- ClinGen will provide training on its tools and resources.
Expert Panel Curation Activities

- Describe the prioritization process for selecting genes/variants to be curated.
- Describe the standard operating procedures for gene-disease/gene variant assessments.
- Describe the curation summaries/reports prepared by curators utilizing the ClinGen framework and tools.
- Describe the process by which the summaries are reviewed by the expert panels and process for decision making.
Eligibility and Funding
Eligibility and Funding

• Applications should be submitted from US institutions. Inclusion of foreign members is encouraged to ensure broad expertise and international involvement.

• Up to 3 Expert Curation Panels will be funded limited to $220,000/year in direct costs. $1,000,000 in total costs has been set aside for this initiative.

• Duration: up to 3 years

• Funded under a Cooperative Agreement mechanism in which substantial NIH programmatic involvement is anticipated during the performance of the activities.
Allowable costs

• Support for Expert Panel chair and under exceptional circumstances the co-chair.
• Panel members can receive nominal consulting fees.
• A primary emphasis should be on supporting a project coordinator, biocurator(s) and bioinformatics specialists.
• Funds can be used for meeting support and travel to face to face meetings including attending the ClinGen/Decipher meeting.
• Additional costs that may be associated with training on ClinGen tools, development informatics interface and integration with ClinGen should be included as consulting fees.
Interfacing with ClinGen and ClinVar
How will NICHD Expert Curation Panels Integrate with ClinGen and ClinVar?

• Collaborate with ClinGen by utilizing the ClinGen framework and curation tools to assess current evidence supporting disease association with chosen genes/variants.

• Receive training on ClinGen tools and resources through distance and in person modules.

• Participate on ClinGen working groups.

• Deposit final determinations and supporting evidence into ClinGen and ClinVar databases.
ClinGen and ClinVar: an overview of the curation ecosystem

Jonathan S. Berg, MD, PhD
Department of Genetics, UNC Chapel Hill
December 7, 2016
Expert Curation Ecosystem Goals

- Mobilize a broad community of experts
- Encourage submission of variant data by researchers/laboratories
- Identify existing expert curation efforts and coordinate/avoid duplication
- Prioritize efforts toward development of expert curation groups for gene-disease validity and variant pathogenicity
Clinical Expertise

- ClinGen is assembling Clinical Domain Working Groups (CDWGs) to curate the clinical genome
  - Cardiology
  - Hereditary Cancer
  - Inborn Errors of Metabolism
  - Pediatric Neurology
  - Hearing Loss
  - Hematology
  - More on the way!
  - Somatic Cancer
  - Pharmacogenomics
ClinGen Clinical Domain Working Groups

• Identify existing/nascent curation efforts
  • Review ClinVar EP requests
  • Encourage development of external EPs or integrate those efforts within ClinGen

• Facilitate ClinVar submissions
  • Laboratories that perform testing in the domain
  • Researchers with private datasets

• Foster internal ClinGen curation groups
  • Gene/Disease validity (Gene/Disease Curation Teams)
  • Variant pathogenicity (Expert Panels)

• Serve as ambassadors to their clinical field
ClinGen Model for CDWG Organization

Communicating Chair

Co-Chairs / EP leaders

CDWG members

EP members
- Additional experts
- Community curators

ClinGen coordinator

ClinGen curators

Executive Committee (with ClinGen PI liaison)

Expert curation groups (genes/variants)

ClinGen Coordination and Curation Support
Summary of Expert Panels

- Multi-institutional in nature
- Focus on a limited set of genes/diseases
- Multiple types of expertise contained within the committee (clinical/research/laboratory)
- Public access to the classification scheme and process
- Provide a sample ClinVar submission of variant classification
- Conflict of interest management
Building a genomic knowledge base to improve patient care

ClinGen’s Critical Questions

- Is this gene associated with a disease? Clinical Validity
- Is this variant causative? Pathogenicity
- Is this information actionable? Clinical Utility

Building a Genomic Knowledge Base
ClinVar & Other Resources

Improved Patient Care Through Genomic Medicine
ClinGen clinical validity framework includes six categories of gene-disease assertions

Assertions are based on five key parameters

1. Strength of genetic evidence
2. Strength of functional evidence
3. Replication
4. Test of time
5. Strength of refuting evidence, if any

https://www.clinicalgenome.org/working-groups/gene-curation/projects-initiatives/clinical-validity-classifications/
<table>
<thead>
<tr>
<th>Assertion criteria</th>
<th>Genetic Evidence (0-12 points)</th>
<th>Experimental Evidence (0-6 points)</th>
<th>Total Points (0-18)</th>
<th>Replication Over Time (Y/N)</th>
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</thead>
<tbody>
<tr>
<td>Description</td>
<td>Case-level, family segregation, or case-control data that support the gene-disease association</td>
<td>Gene-level experimental evidence that support the gene-disease association</td>
<td>Sum of Genetic &amp; Experimental Evidence</td>
<td>&gt; 2 pubs w/ convincing evidence over time (&gt;3 yrs)</td>
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<tr>
<td>Assigned Points</td>
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</table>

**CALCULATED CLASSIFICATION**

- LIMITED 1-6
- MODERATE 7-11
- STRONG 12-18
- DEFINITIVE 12-18 AND replication over time

**Valid contradictory evidence? (Y/N)**

List PMIDs and describe evidence:

**CURATOR CLASSIFICATION**

**FINAL CLASSIFICATION**
<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Case Information Type</th>
<th>Suggested points/case</th>
<th>Max Score</th>
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<tbody>
<tr>
<td><strong>Variant Evidence</strong></td>
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<tr>
<td><strong>Autosomal Dominant Disease</strong></td>
<td>Proband with non-LOF variant with some evidence of gene impact</td>
<td>0.5</td>
<td>7</td>
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<tr>
<td></td>
<td>Proband with LOF variant</td>
<td>1.5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Variant is \textit{de novo}</td>
<td>2</td>
<td>12</td>
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<tr>
<td><strong>Autosomal Recessive Disease</strong></td>
<td>Two non-LOF variants in \textit{trans}</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Two variants in \textit{trans} and at least one is LOF or \textit{de novo}</td>
<td>2</td>
<td>12</td>
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<tr>
<td><strong>Segregation Evidence</strong></td>
<td>Evidence of segregation in one or more families</td>
<td>LOD Score</td>
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<td></td>
<td></td>
<td>3</td>
<td>5</td>
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<td><strong>Case Control Study Type</strong></td>
<td>Case-Control Quality Criteria</td>
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<td>Variant Detection Methodology</td>
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<tr>
<td></td>
<td>Power</td>
<td>0-6</td>
<td></td>
</tr>
<tr>
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<td>Bias and Confounding</td>
<td>0-6</td>
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<tr>
<td><strong>Aggregate Variant Analysis</strong></td>
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<td>12</td>
</tr>
<tr>
<td></td>
<td>Statistical Significance</td>
<td>0-6</td>
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## Experimental Evidence Scoring

<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Evidence Type</th>
<th>Score Range</th>
<th>Recommended points/ evidence</th>
<th>Max Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Biochemical Function</td>
<td>½ - 2</td>
<td>½ point for each piece of evidence in any category</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Protein Interaction</td>
<td>½ - 2</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Expression</td>
<td>½ - 2</td>
<td></td>
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<tr>
<td>Functional Alteration</td>
<td>Patient cells</td>
<td>1 - 2</td>
<td>1 point</td>
<td>2</td>
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<tr>
<td></td>
<td>Non-patient cells</td>
<td>½ - 1</td>
<td>½ point</td>
<td></td>
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<tr>
<td>Models &amp; Rescue</td>
<td>Animal model</td>
<td>1 - 4</td>
<td>2 points</td>
<td>4</td>
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<tr>
<td></td>
<td>Cell culture model system</td>
<td>½ - 2</td>
<td>1 point</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rescue in animal model</td>
<td>1 - 4</td>
<td>2 points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rescue in engineered equivalent</td>
<td>½ - 2</td>
<td>1 point</td>
<td></td>
</tr>
</tbody>
</table>

**Total Final Score**: 0 - 8
ClinGen’s Gene Curation Interface

NHP2 – Dyskeratosis congenita
Autosomal recessive inheritance

Status: In progress
Creator: Erin Riggs — 2015 Dec 14, 11:49 am
Participants: Erin Riggs
Last edited: Erin Riggs — 2015 Dec 14, 11:50 am

Gene-Disease Record Variants
Click a variant to View, Curate, or Edit it. The icon indicates curation by one or more curators.

NHP2
HGNCSymbol: NHP2
NCBI Gene ID: 55651

Dyskeratosis congenita
Orphanet ID: ORPHA1775
OMIM ID: [Add]

Evidence for PMID: 11074001

Abstract
The H/ACA small nucleolar RNAs ( snoRNAs) are involved in pseudouridylination of pre-rRNAs. In the yeast Saccharomyces cerevisiae, four common proteins are associated with H/ACA snoRNAs: Gar1p, Cbf5p, Nhp2p, and Nop10p. In vitro reconstitution studies showed that four proteins also specifically interact with H/ACA snoRNAs in mammalian cell extracts. Two mammalian proteins, NAP57/dyskerin (the ortholog of Cbf5p) and hGAR1, have been characterized. In this work we describe properties of hNop10 and hNhp2, human orthologs of yeast Nop10p and Nhp2p, respectively, and further characterize hGAR1, hNop10 and hNhp2 complement yeast cells depleted of Nhp2p and Nop10p, respectively. Immunoprecipitation experiments with extracts from transfected HeLa cells indicated that epitope-tagged hNop10 and hNhp2 specifically associate with hGAR1 and H/ACA RNAs; they also interact with the RNA subunit of telomerase, which contains an H/ACA-like domain in its 3’ moiety. Immunofluorescence microscopy showed that hGAR1, hNop10, and hNhp2 are localized in the dense fibrillar component of the nucleolus and in Cajal (coiled) bodies. Deletion analysis

Add New PMID


PMID: 11074001


PMID: 20008900

Vulliamy T et al. Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis

PubMed

Currently, only the curator who adds a paper to a Gene-Disease record can associate evidence with that paper.

PMID: 11074001 added by Erin Riggs.

Genetic Evidence
Group
Family
Individual
Case-Control

Experimental Evidence
Experimental Data

Pogacic 2000 Biochemical Function

Erin Riggs
2015 Dec 14, 8:22 pm
View/Assess

Associated Variants
Building a genomic knowledge base to improve patient care

ClinGen’s Critical Questions

- Is this gene associated with a disease? (Clinical Validity)
- Is this variant causative? (Pathogenicity)
- Is this information actionable? (Clinical Utility)

Building a Genomic Knowledge Base (ClinVar & Other Resources)

Improved Patient Care Through Genomic Medicine
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD¹, Nazneen Aziz, PhD²,³, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD⁶,⁷, Wayne W. Grody, MD, PhD⁸,⁹,¹⁰,¹¹, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵; on behalf of the ACMG Laboratory Quality Assurance Committee

<table>
<thead>
<tr>
<th>Population data</th>
<th>Computational and predictive data</th>
<th>Functional data</th>
<th>Segregation data</th>
<th>De novo data</th>
<th>Allelic data</th>
<th>Other database</th>
<th>Other data</th>
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</thead>
<tbody>
<tr>
<td>MAF is too high for disorder BA1/351 OR observation in controls inconsistent with disease penetrance BS2</td>
<td>Multiple lines of computational evidence suggest no impact on gene (gene product BP4) Missense in gene where only truncating cause disease BP1 Silent variant with no predicted splice impact BP7 In-frame indels in repeat without known function BP3</td>
<td>Well-established functional studies show no deleterious effect BS9</td>
<td>Non-segregation with disease BS4</td>
<td>Observed in trans with a dominant variant BP2 Observed in cis with a pathogenic variant BP2</td>
<td>Observed in trans with a pathogenic variant BP2</td>
<td>Reputable source w/out shared data = benign BP5</td>
<td>Found in case with an alternate cause BP5</td>
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<tr>
<td>Supporting</td>
<td>Supporting</td>
<td>Moderate</td>
<td>Strong</td>
<td>Very strong</td>
<td>Absent in population databases PP2</td>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PP5</td>
<td>Missense in gene with low rate of benign missense variants and path missenses common PP9</td>
</tr>
<tr>
<td>Prevalence in affected statistically increased over controls PP4</td>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PP5</td>
<td>Protein length changing variant PM4</td>
<td>Simple amino acid change as an established pathogenic variant PS1</td>
<td>Predicted null variant in a gene where LQF is a known mechanism of disease PV11</td>
<td>Missense in gene with low rate of benign missense variants and path missenses common PP9</td>
<td>Mutational hot spot or well-studied functional domain without benign variant PM1</td>
<td>Missense in gene with low rate of benign missense variants and path missenses common PP9</td>
</tr>
</tbody>
</table>

ACMG STANDARDS AND GUIDELINES

Genetics in Medicine
ACMG Rules

- Minor allele frequency rules appropriate to the condition
- Relevant variant types (truncating versus missense)
- Reliable functional assays
- Use of *in silico* prediction tools
ACMG Rules

ClinGen Standards

Sequence Variant Interpretation Task Team

Consortium practices and procedures

- Review and harmonize specifications from expert panels
- Develop quantitative approaches to enhance use of ACMG guidelines
Possible Models for Integration of NICHD-funded Expert Panels

Based on NICHD/NHGRI and ClinGen review three models for collaboration and integration are proposed:

• Placement within an existing CDWG if appropriate
• Formation of a new CDWG if appropriate
• Or support as a standalone “Expert Panel”
UNC/ACMG/Geisinger

Coordination

Biocuration

Cardiovascular Inborn Errors of Metabolism

Benign Hematology

Pediatric Neurology Hearing Loss

Rasopathy

Hereditary Cancer

LMM/Geisinger

Coordination

Biocuration

Stanford/BCM

Coordination

Biocuration

UNC Biocuration Core

Travel / Meetings / Consulting (ACMG)

Other unaffiliated Expert Panels
Support and Training

- Consultation with the CDWG Oversight committee for leaders of groups
- Expert Panel Toolkit materials
- Participation in ClinGen CDWG and EP chairs teleconferences
- Invitation to in-person Steering Committee meetings and ClinGen/DECIPHER “Curating the Clinical Genome” open meeting
Support and Training

- Materials on using ClinGen frameworks provided by Education WG
- Biocurator training by UNC Biocuration Core
- Participation in the Biocurators WG
- Training on the use of curation interfaces by Stanford
- Participation in ClinVar community calls and ClinGen informatics working group calls
## ClinGen Acknowledgements

### ClinGen Steering Committee

| Jonathan Berg, UNC | Katrina Goddard, Kaiser Permanente | Sharon Plon, Baylor |
| Lisa Brooks, NHGRI | Danuta Krotoski, NICHD | Erin Ramos, NHGRI |
| Carlos Bustamante, Stanford | Melissa Landrum, NCBI | Heidi Rehm, Harvard |
| Mike Cherry, Stanford | David Ledbetter, Geisinger | Steve Sherry, NCBI |
| James Evans, UNC | Christa Lese Martin, Geisinger | Michael Watson, ACMG |
| Andy Faucett, Geisinger | Aleks Milosavljevic, Baylor | Kirk Wilhelmson, UNC |
| Andy Freedman, NCI | Kelly Ormond, Stanford | Marc Williams, Geisinger |

### Program Coordinators:
Danielle Azzariti, Miranda Hallquist, Brianne Kirkpatrick, Jules Koenig, Kristy Lee, Laura Milko, Annie Niehaus, Erin Riggs, Andy Rivera, Cody Sam, Meredith Weaver, Kira Wong

### ClinGen Working Groups (WG) and WG Chairs

#### Clinical Domain WGs

<table>
<thead>
<tr>
<th>Hereditary Cancer</th>
<th>Data Model WG</th>
<th>Education, Engagement, Access WG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ken Offit, Sharon Plon</td>
<td>Larry Babb, Chris Bizon</td>
<td>Andy Faucett, Erin Riggs</td>
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<tr>
<td>Cardiovascular</td>
<td>Informatics WG</td>
<td>Gene Curation WG</td>
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<tr>
<td>Birgit Funke, Ray Hershberger</td>
<td>Carlos Bustamante</td>
<td>Jonathan Berg, Christa Martin</td>
</tr>
<tr>
<td>Inborn Errors of Metabolism</td>
<td>Actionability WG</td>
<td>Genomic Variant WG</td>
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<tr>
<td>Rong Mao, Robert Steiner, Bill Craigen</td>
<td>Jim Evans, Katrina Goddard</td>
<td>Christa Martin, Sharon Plon, Heidi Rehm</td>
</tr>
<tr>
<td>Pediatric Neurology</td>
<td>Phenotyping WG</td>
<td>Electronic Health Record WG</td>
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<tr>
<td>Michael Friez, Heather Mefford, Scott Myers</td>
<td>David Miller</td>
<td>Marc Williams</td>
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<tr>
<td>Pharmacogenomics</td>
<td>Consent and Disclosure Recommendations (CADRe) WG</td>
<td>Andy Faucett, Kelly Ormond</td>
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<td>Teri Klein, Howard McLeod</td>
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<td>Somatic Cancer</td>
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<td>Shashi Kulkarni, Subha Madhavan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Final Considerations
Final Considerations

• Are the genes/variants selected of high priority to NICHD and will they support improvement in clinical practice?
• Do they duplicate other efforts?
• Have the appropriate experts been assembled for the curation panels?
• Is there adequate supporting staff to ensure completion of the proposed work in 3 years?
• How well will the Expert Curation Panels interface with the ClinGen/ClinVar curation resources in their determination of significance?
Thank You

- **NICHD webpage**: [https://www.nichd.nih.gov/grants-funding/opportunities-mechanisms/active-foa/Pages/default.aspx](https://www.nichd.nih.gov/grants-funding/opportunities-mechanisms/active-foa/Pages/default.aspx)
- **NICHD Branch Priorities**: [https://www.nichd.nih.gov/about/org/der/branches/pages/index.aspx](https://www.nichd.nih.gov/about/org/der/branches/pages/index.aspx)
- **ClinGen Helpdesk and Webpages**:  
  - Curation interface helpdesk: clingen-helpdesk@lists.stanford.edu  
  - [https://clinicalgenome.org/about/clingen-curation-activities-overview/](https://clinicalgenome.org/about/clingen-curation-activities-overview/)  
- **For further information please contact:**  
  Danuta Krotoski, Ph.D.  
  krotoskd@mail.nih.gov; 301 496 5576
Questions?