NICHD Genomic Clinical Variant Expert Curation Panels Pre-Application Informational Webinar

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)
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NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Danuta Krotoski, Ph.D
Intellectual and Developmental Disabilities Branch

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 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.

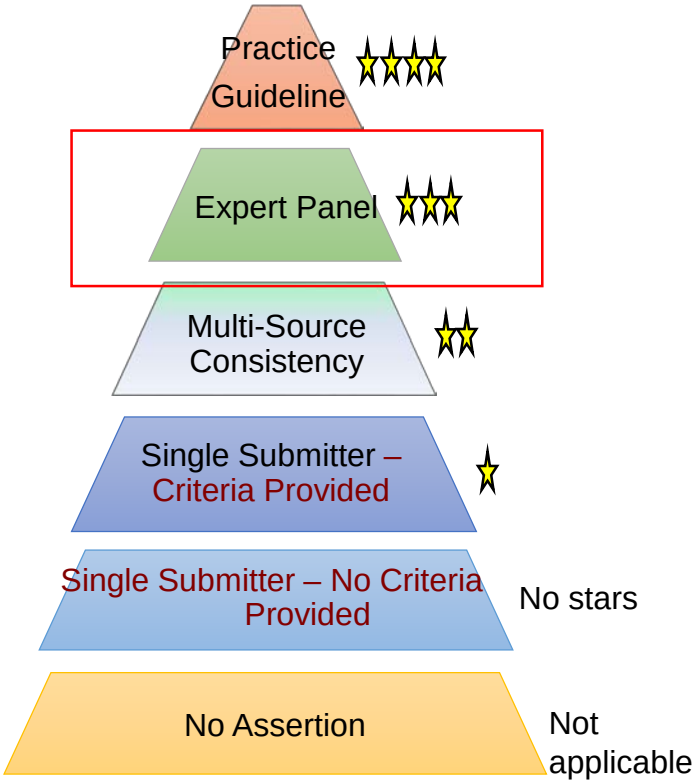
NICHD Priority Areas

- 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?

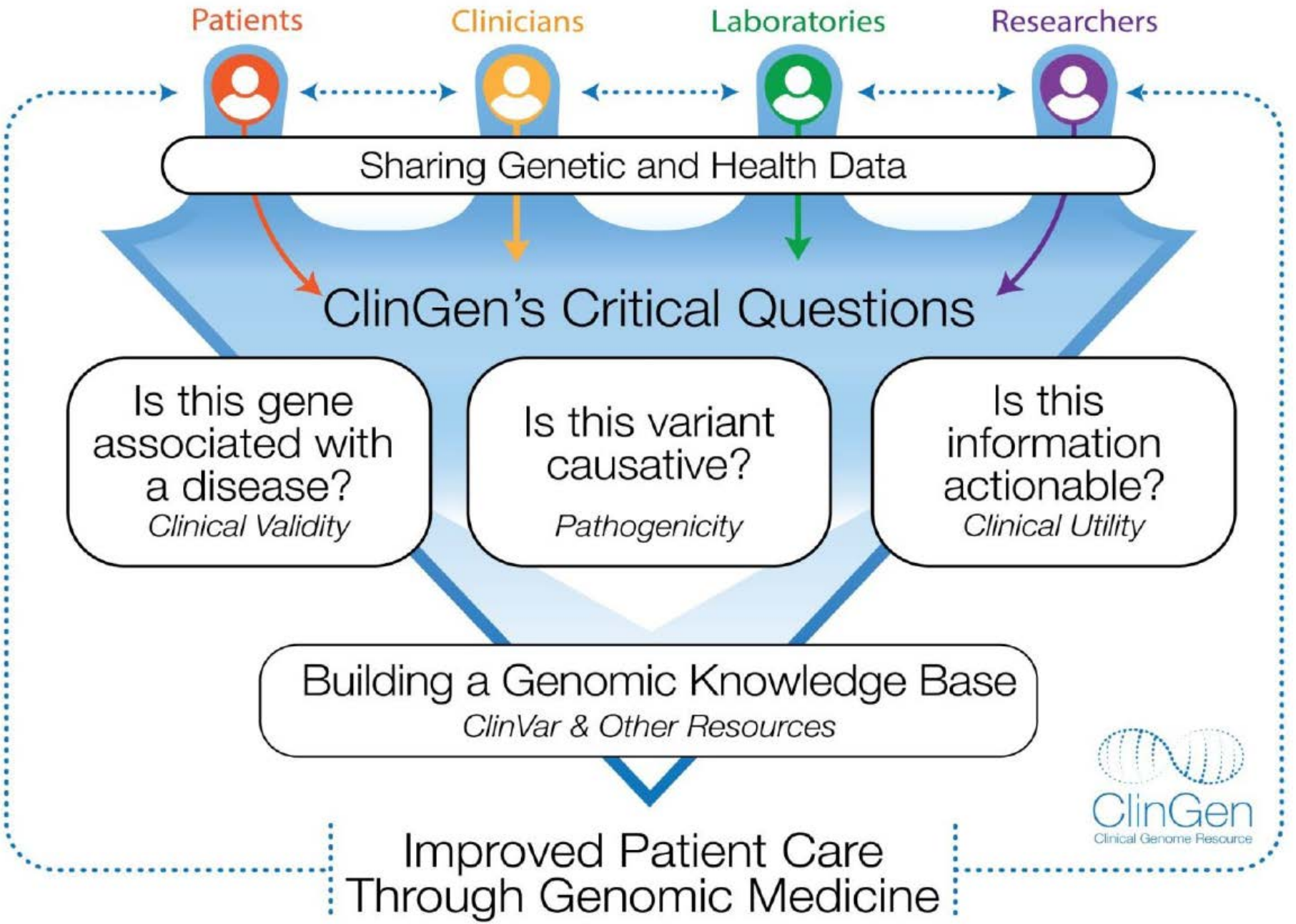
- NCBI Archival database that aggregates information about genomic variation and relationships to human health.
- Uses a rating system to help users assess the quality and consistency of submitted variant assertions.
- Assertions range from a single submitter, multiple submitters, through expert panel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

Levels for submission of Clinical Assertions about Genetic Variants in ClinVar



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.


Patients
Clinicians
Laboratories
Researchers
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
ClinGen
Clinical Genome Resource
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 must 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: Sharing Data. Building Knowledge. Improving Care.

ClinGen and ClinVar: an overview of the curation ecosystem

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

ClinGen
Clinical Genome Resource

PARTNERS HEALTHCARE

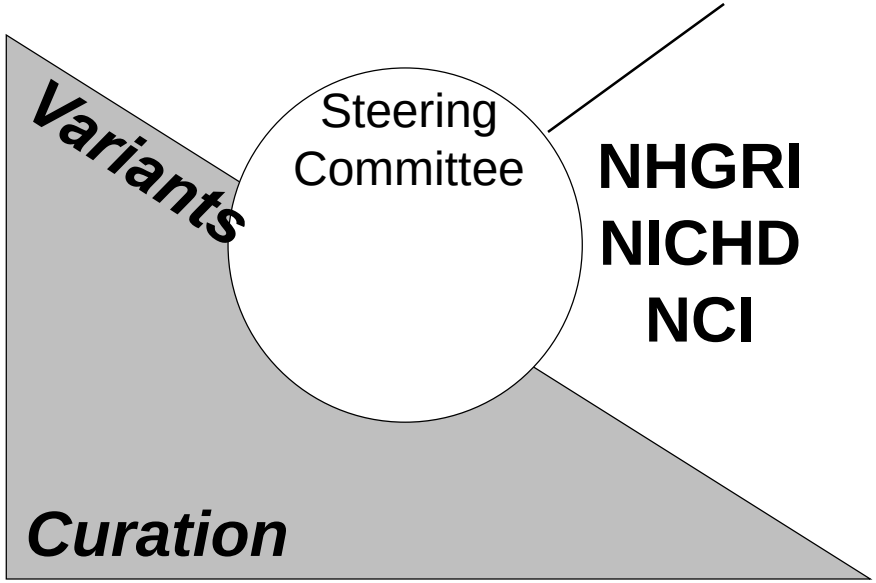
GEISINGER HEALTH SYSTEM

U41

ClinVar

National Center for Biotechnology Information

NCBI



NHGRI
NICHD
NCI

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

U01

U01

BCM Baylor College of Medicine

ACMG American College of Medical Genetics and Genomics
Translating Genes Into Health®

GEISINGER HEALTH SYSTEM

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

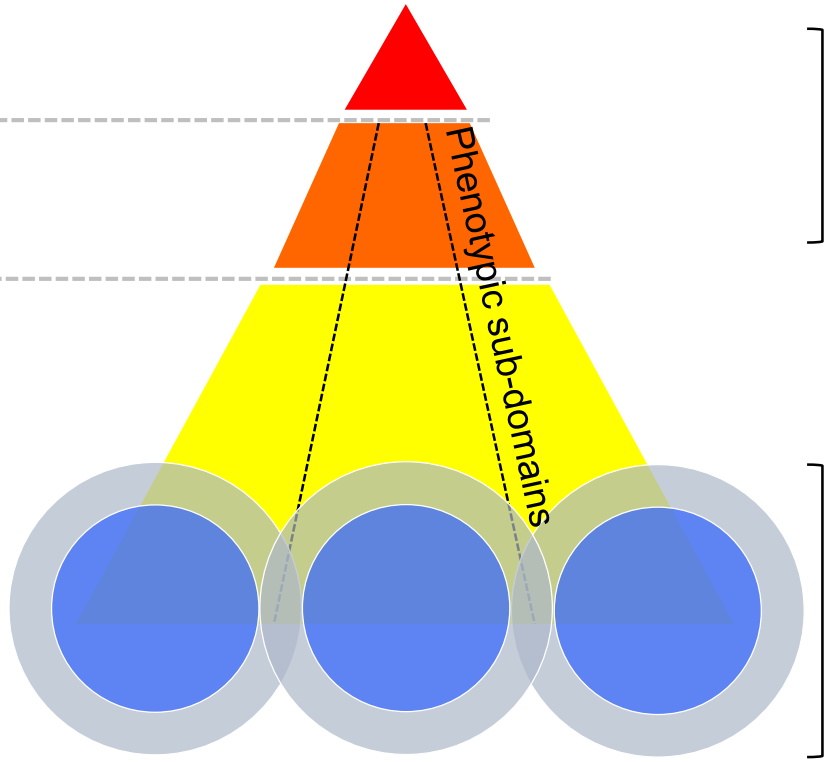
ClinGen Model for CDWG Organization

Communicating Chair

Co-Chairs / EP leaders

CDWG members

EP members
- Additional experts
- Community curators



ClinGen coordinator

ClinGen curators

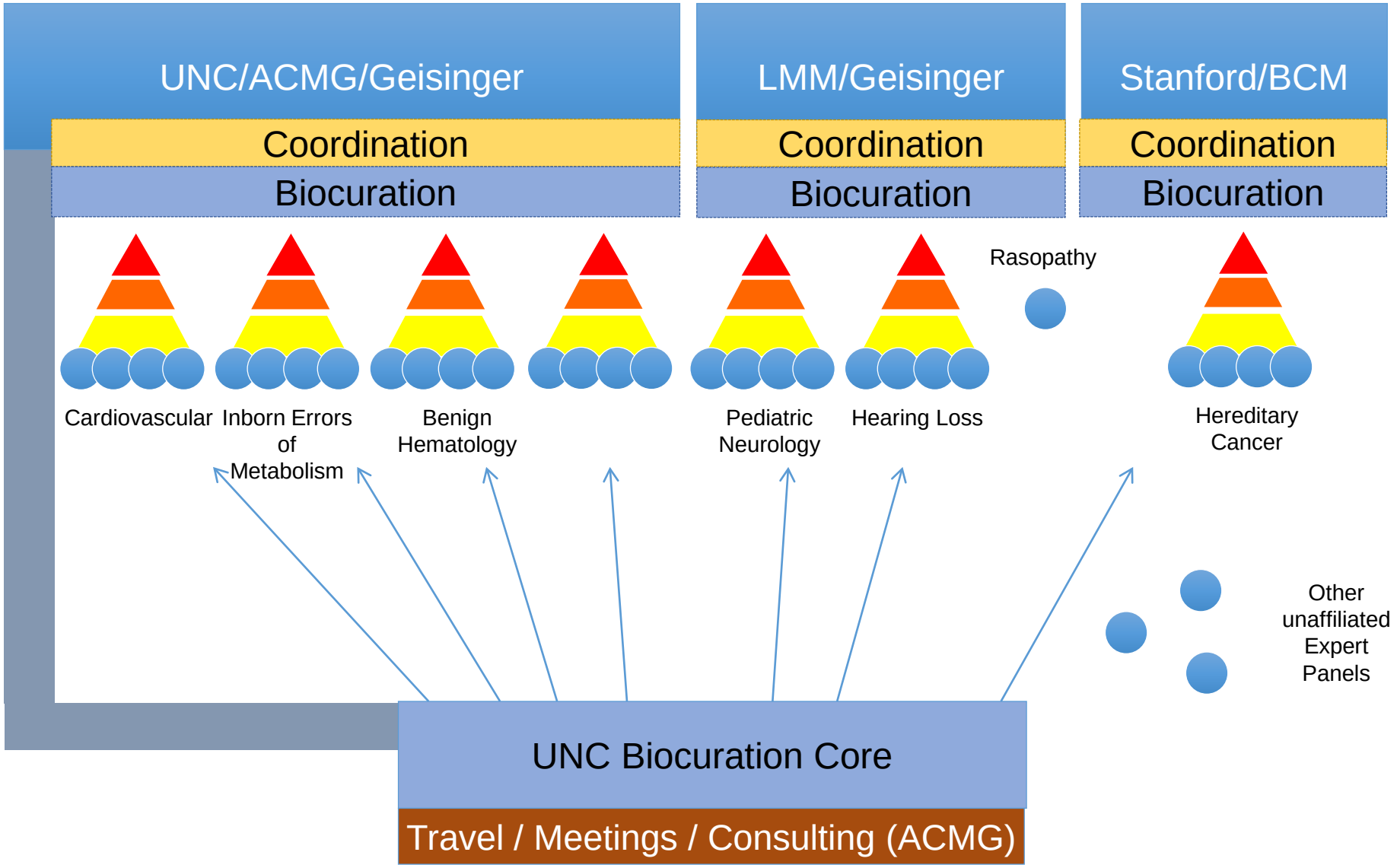
Executive Committee (with ClinGen PI liaison)

Expert curation groups (genes/variants)

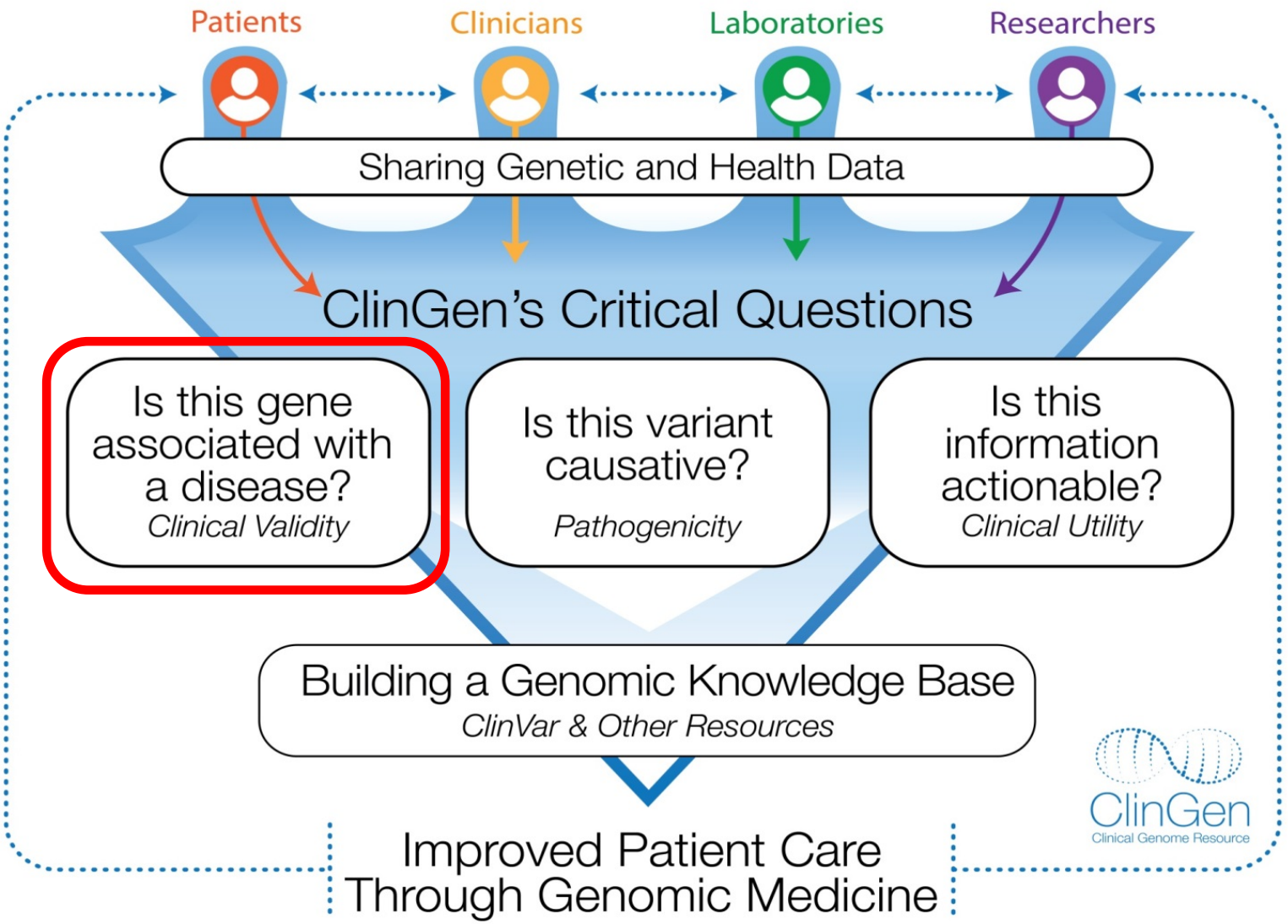
ClinGen Coordination and Curation Support

Summary of Expert Panels

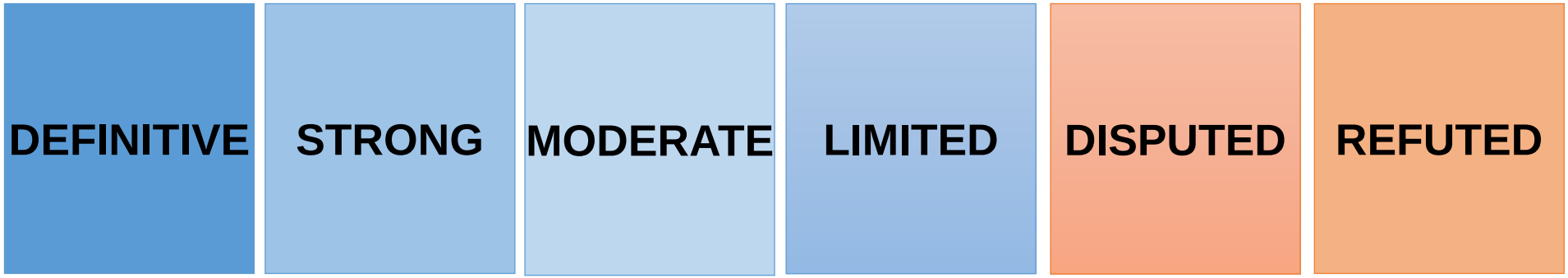
- Multi-institutional in nature
- Focus on a limited set of genes/diseases
- Multiple types of expertise contained within the committee (clinical/research/laboratory)
- Public access to the classification scheme and process
- Provide a sample ClinVar submission of variant classification
- Conflict of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


UNC/ACMG/Geisinger
LMM/Geisinger
Stanford/BCM
Coordination
Biocuration
Coordination
Biocuration
Coordination
Biocuration
Rasopathy
Cardiovascular
Inborn Errors of Metabolism
Benign Hematology
Pediatric Neurology
Hearing Loss
Hereditary Cancer
Other unaffiliated Expert Panels
UNC Biocuration Core
Travel / Meetings / Consulting (ACMG)

Building a genomic knowledge base to improve patient care



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/

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points				

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	

Genetic Evidence Scoring

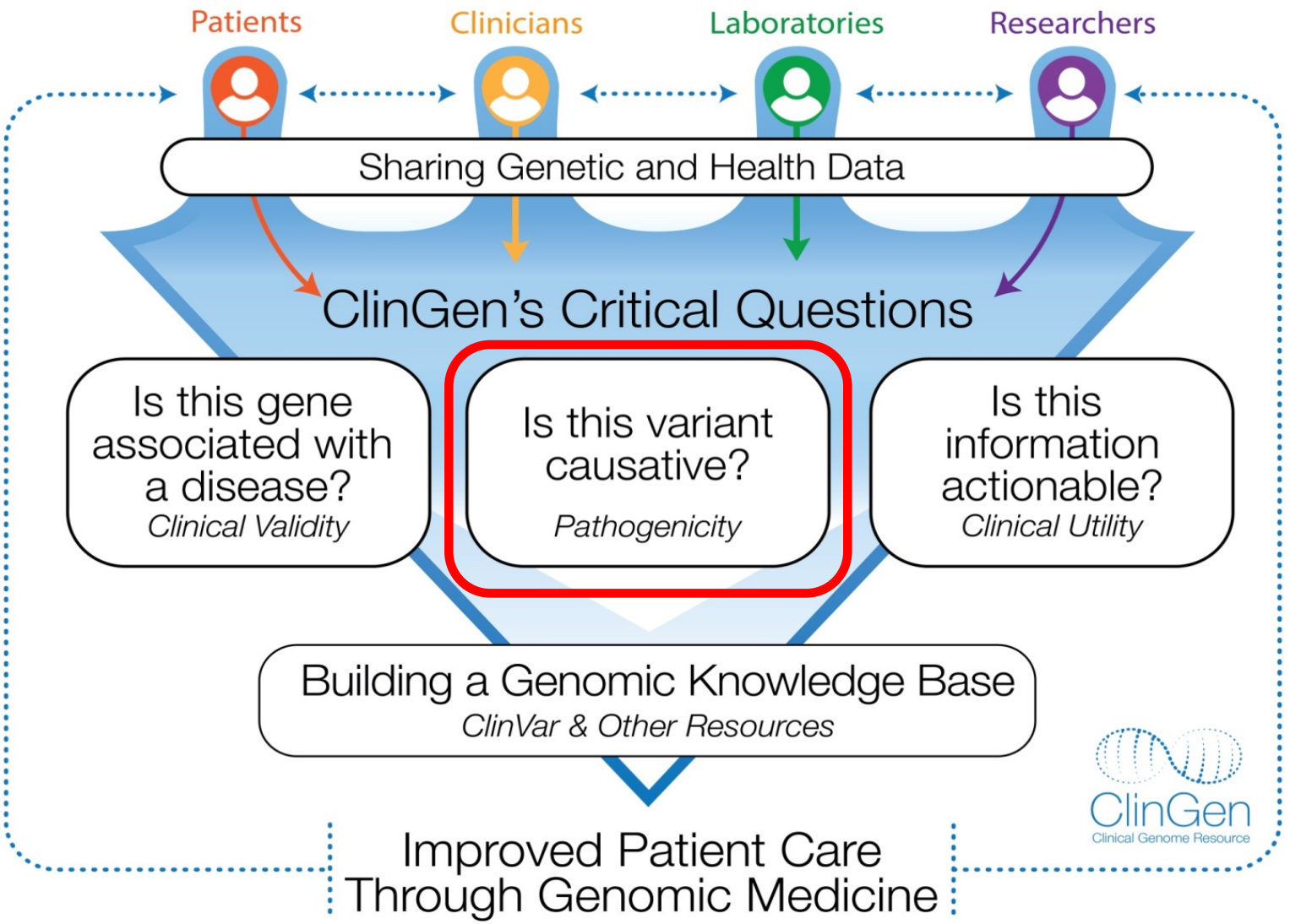
	Evidence Type		Case Information Type			Suggested points/case		Max Score
						Default	Range	
Case Level Data[1]	Variant Evidence	**Autosomal Dominant Disease**	Proband with non-LOF variant with some evidence of gene impact[2]			0.5	0-1.5	7
			Proband with LOF variant[3]			1.5	0.5-2	10
			Variant is *de novo*[4]			2	1-3	12
		Autosomal Recessive Disease	Two non-LOF variants[2] in *trans*			1	0.5-1.5	12
			Two variants in *trans* and at least one is LOF[3] or *de novo*[4]			2	1-3	
	Segregation Evidence		Evidence of segregation in one or more families[5]	LOD Score	3	5	0-7	7
					2	4		
					1.5	3		
					1	2		
					0.6	1		
Case Control Data[6]	**Case-Control Study Type[7]**		**Case-Control Quality Criteria[8]**			**Suggested points/study**		**Max Score**
	Single Variant Analysis[7a]		• Variant Detection Methodology[8a] • Power[8b] • Bias and Confounding[8c] • Statistical Significance[8d]			0-6		12
	Aggregate Variant Analysis[7b]					0-6		12

Experimental Evidence Scoring

Evidence Category	Evidence Type	Score Range	Recommended points/ evidence	Max Score
Function	Biochemical Function	½ - 2	½ point for each piece of evidence in any category	2
	Protein Interaction	½ - 2		
	Expression	½ - 2		
Functional Alteration	Patient cells	1 - 2	1 point	2
	Non-patient cells	½ - 1	½ point	
Models & Rescue	Animal model	1 - 4	2 points	4
	Cell culture model system	½ - 2	1 point	
	Rescue in animal model	1 - 4	2 points	
	Rescue in engineered equivalent	½ - 2	1 point	
			Total Final Score	**0 - 8**

ClinGen's Gene Curation Interface

Building a genomic knowledge base to improve patient care



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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, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		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 non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

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ACMG Rules

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ClinGen Expert Groups

- Cardio-myopathy
- Noonan Spectrum
- *PTEN*

Gene- or disease-specific modifications

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

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Computational And Predictive Data		Multiple lines of computational evidence suggest no impact *BP4* Missense when only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7* In-frame indels in repeat w/out known function *BP3*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
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Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

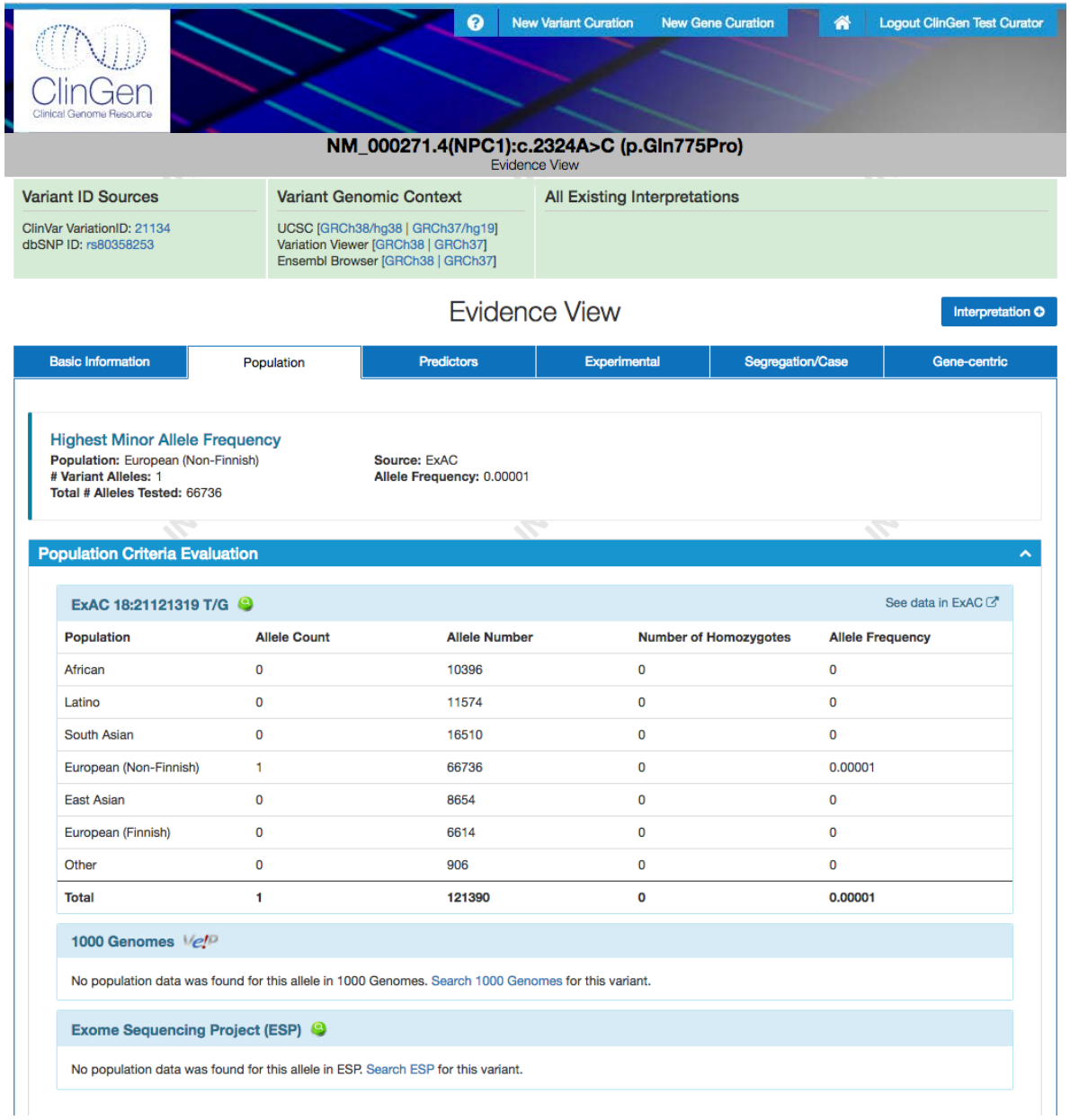
ClinGen Standards

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

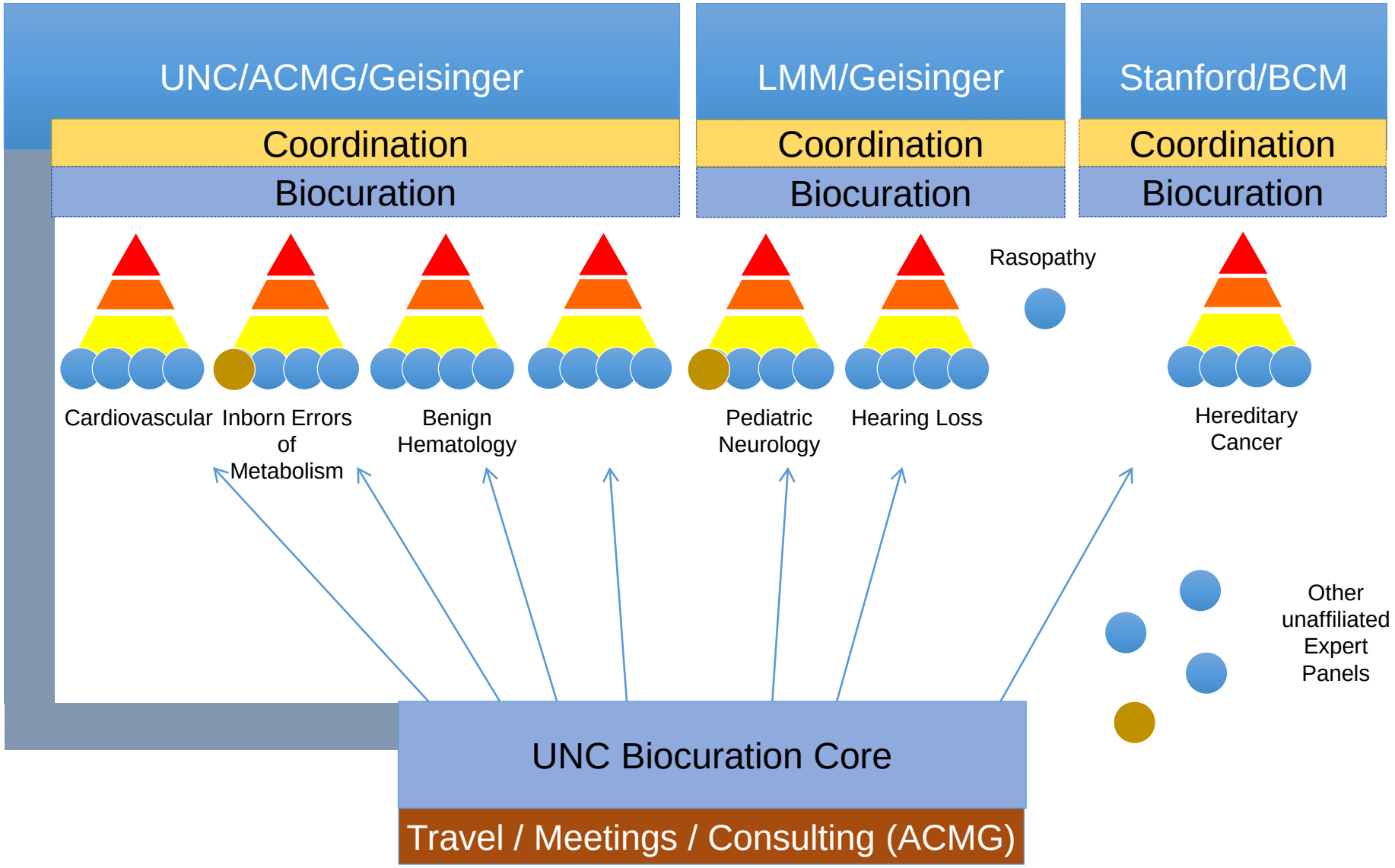
ClinGen's Variant Curation Interface



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
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Coordination
Biocuration
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Rasopathy
Cardiovascular
Inborn Errors of Metabolism
Benign Hematology
Pediatric Neurology
Hearing Loss
Hereditary Cancer
Other unaffiliated Expert Panels
UNC Biocuration Core
Travel / Meetings / Consulting (ACMG)

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
Lisa Brooks, NHGRI
Carlos Bustamante, Stanford
Mike Cherry, Stanford
James Evans, UNC
Andy Faucett, Geisinger
Andy Freedman, NCI

Katrina Goddard, Kaiser Permanente
Danuta Krotoski, NICHD
Melissa Landrum, NCBI
David Ledbetter, Geisinger
Christa Lese Martin, Geisinger
Aleks Milosavljevic, Baylor
Kelly Ormond, Stanford

Sharon Plon, Baylor
Erin Ramos, NHGRI
Heidi Rehm, Harvard
Steve Sherry, NCBI
Michael Watson, ACMG
Kirk Wilhelmsen, UNC
Marc Williams, Geisinger

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ClinGen Working Groups (WG) and WG Chairs

Clinical Domain WGs

Hereditary Cancer : Ken Offit, Sharon Plon

Cardiovascular: Birgit Funke, Ray Hershberger

Inborn Errors of Metabolism: Rong Mao, Robert Steiner, Bill Craigen

Pediatric Neurology: Michael Friez, Heather Mefford, Scott Myers

Pharmacogenomics: Teri Klein, Howard McLeod

Somatic Cancer: Shashi Kulkarni, Subha Madhavan

Data Model WG
Larry Babb, Chris Bizon

Informatics WG
Carlos Bustamante

Actionability WG
Jim Evans, Katrina Goddard

Phenotyping WG
David Miller

Education, Engagement, Access WG
Andy Faucett, Erin Riggs

Gene Curation WG
Jonathan Berg, Christa Martin

Genomic Variant WG
Christa Martin, Sharon Plon, Heidi Rehm

Electronic Health Record WG
Marc Williams

Consent and Disclosure Recommendations (CADRe) WG
Andy Faucett, Kelly Ormond

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

- RFA-HD-17-001: http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-17-001.html
- NICHD webpage: 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
- ClinGen Helpdesk and Webpages:
  - Curation interface helpdesk: clingen-helpdesk@lists.stanford.edu
  - https://clinicalgenome.org/about/clingen-curation-activities-overview/
  - https://clinicalgenome.org/events-news/clingen-in-the-news/announcing-nichd-funding-opportunity-and-demo-clingen-curation-tools/
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Questions?