PAR-20-101: Genomic Variants Expert Curation Panels Pre-Application Informational Webinar

February 20, 2020

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

To access the Webinar

- Use the following WebEx meeting address and telephone numbers:
  - https://nih.webex.com/nih/onstage/g.php?MTID=e43f514247608b4c54f23641fb3d49cdd
  - Call the number below and enter the access code:
    - 1-650-479-3208 Call-in toll number (US/Canada)
    - Access code: 628 792 461

Pre-Application Webinar

- Agenda
  - Objectives of the Program Announcement (PAR)
  - 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
- You will be muted upon entry. If you have questions, please type into the Q&A tab on the bottom right part of the screen. Your questions will be addressed at the end of the presentation.

Objectives of the Genomic Expert Curation Panels (PAR-20-101)

- Establish expert panels to select genes and genomic variants associated with diseases or conditions of high priority to participating institutes.
- Utilizing ClinGen tools, systematically determine the clinical significance for diagnosis and treatment 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.

U.S. Food and Drug Administration (FDA) has recognized ClinGen as the first public genetic variant database that can be used to validate genetic variant information in regulatory submissions.

Priority Areas

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): gynecologic, andrologic, and reproductive health; poor pregnancy outcomes; high-risk newborn conditions; structural birth defects; intellectual and developmental disabilities; and susceptibility to infections
- National Cancer Institute (NCI): inherited susceptibility to cancer development and/or response or resistance to therapy
- 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

What is ClinVar?

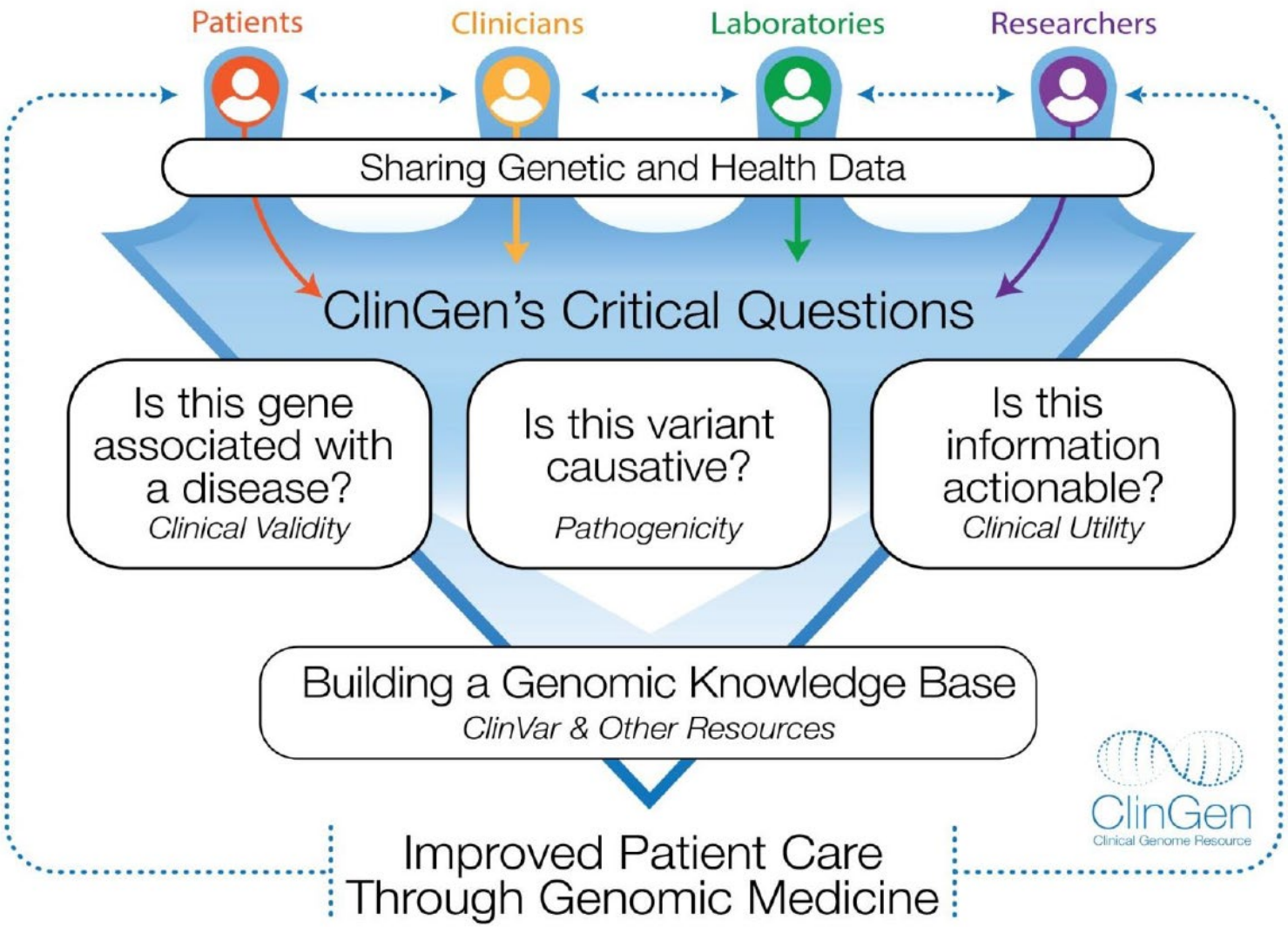
Levels for submission of Clinical Assertions about Genetic Variants in ClinVar; Rehm, HL, et. al. *NEJM* 2015; 372:2235-2242

- 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.
- Expert panels provide definitive assertions regarding clinical significance of genes/variants. To be recognized in ClinVar, panel must first apply to ClinGen.

What is ClinGen?

- National Human Genome Research Institute (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 has developed tools and frameworks to evaluate clinical validity of gene-disease associations and pathogenicity of genetic variants for use in clinical care.
- ClinGen tools enable quantification of evidence supporting a gene/variant disease association and clear and robust criteria to guide decisions regarding pathogenicity.
- Partners with ClinVar to approve Expert Curation Panels, which submit clinical validity assertions to ClinVar
- Final determinations together with supporting evidence are deposited in ClinGen and submitted to ClinVar with expert panel validity.
- ClinGen Variant Curation Expert Panels are recognized by the FDA as a source of valid scientific evidence to support clinical validity in regulatory submissions.

How does ClinGen work?



Structure of the Genomic 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, should 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.
- Adequate staffing is critical 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.
- ClinGen training tools and resources are available online and through participation in meetings.

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 based on ClinGen published methods (see clinicalgenome.org for most up-to-date versions).
- Describe the initial curation process and 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.

Funding and Eligibility

Eligibility and Funding

- Applications should be submitted from U.S. institutions. Inclusion of foreign members is encouraged to ensure broad expertise and international involvement.
- Funding is limited to $220,000/year in direct costs. As a PAR, no funds will be 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.
- The primary emphasis should be on funding a project coordinator, biocurator(s), and bioinformatics specialists who are critical to the success of the Panel's work.
- Funds can be used for meeting support and travel to face-to-face meetings including attending the annual Curating the Clinical Genome conference.
- Additional costs that may be associated with training on ClinGen tools, development of informatics interface, and integration with ClinGen should be included as consulting fees.
- Panel members can receive nominal consulting fees.

Interfacing with ClinGen and ClinVar

How will NIH-funded Expert Curation Panels Integrate with ClinGen and ClinVar?

- Collaborate with ClinGen by formally applying for ClinVar/ClinGen Expert Panel status and utilize 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

Sharon E. Plon, MD, PhD

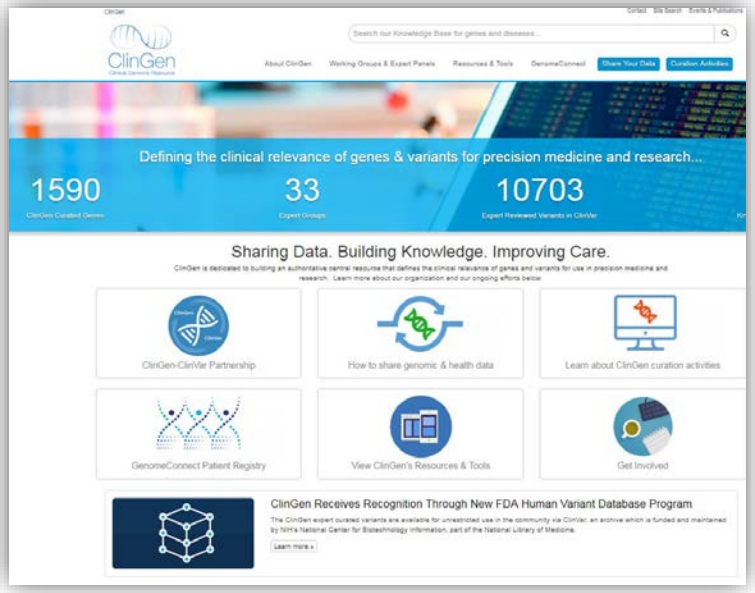
Chair, ClinGen Steering Committee
Baylor College of Medicine
February 20, 2020

ClinGen
Clinical Genome Resource

The ClinGen Program

Increase data sharing and build an authoritative resource to define the clinical relevance of genes and variants for use in medicine and research.

www.clinicalgenome.org

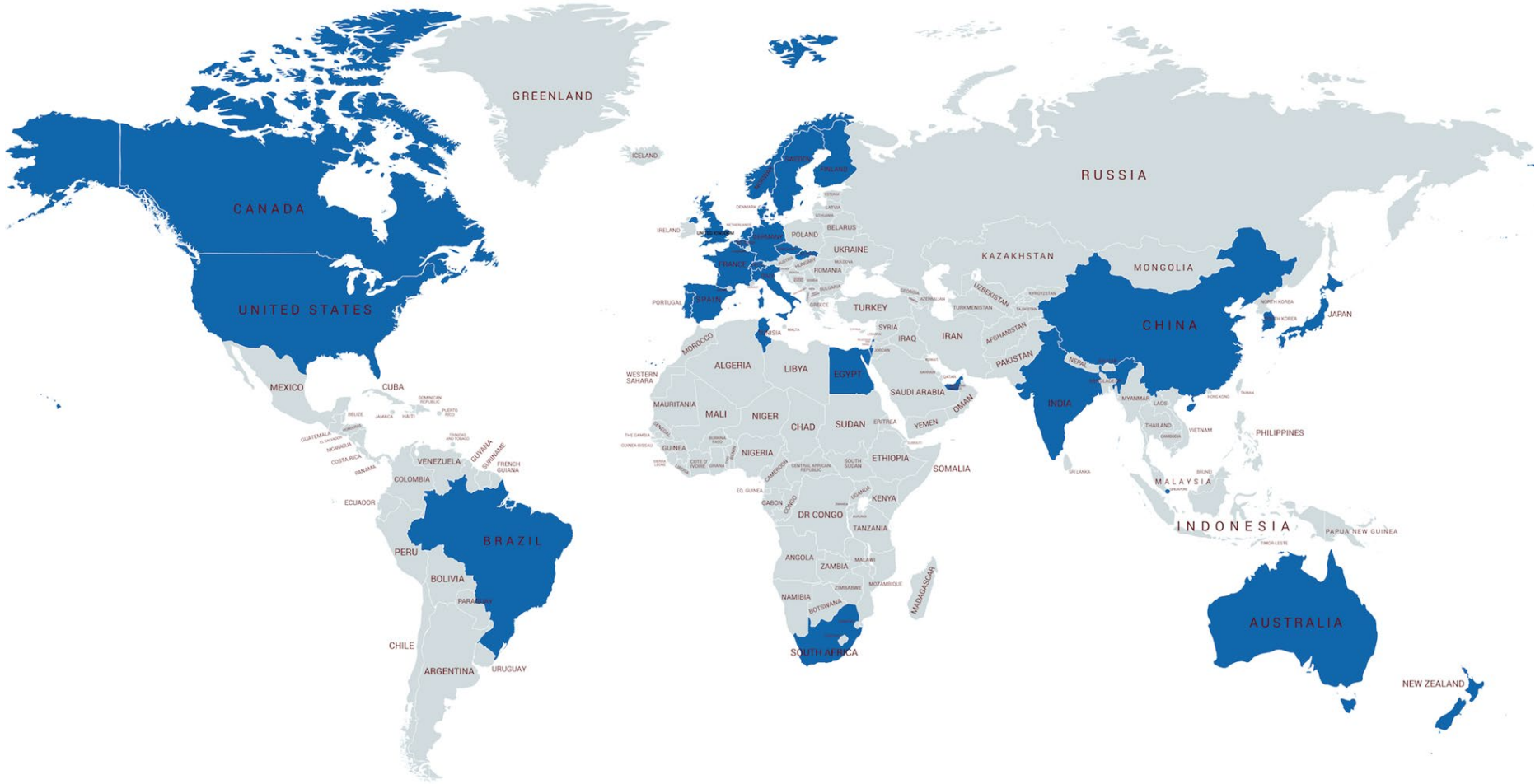


- **Launched: Sept 2013**
- **Phase II: Sept 2017 (3 U41 grants)**
  - **University of North Carolina – Chapel Hill, Geisinger, ACMG**
    - J. Berg, K. Goddard, M. Watson, M. Williams
  - **Brigham Women's Hospital, Geisinger**
    - H. Rehm, C. Martin, D. Ledbetter
  - **Stanford University, Baylor College of Medicine**
    - T. Montine, S. Plon

ClinGen Expert Curation Ecosystem Goals

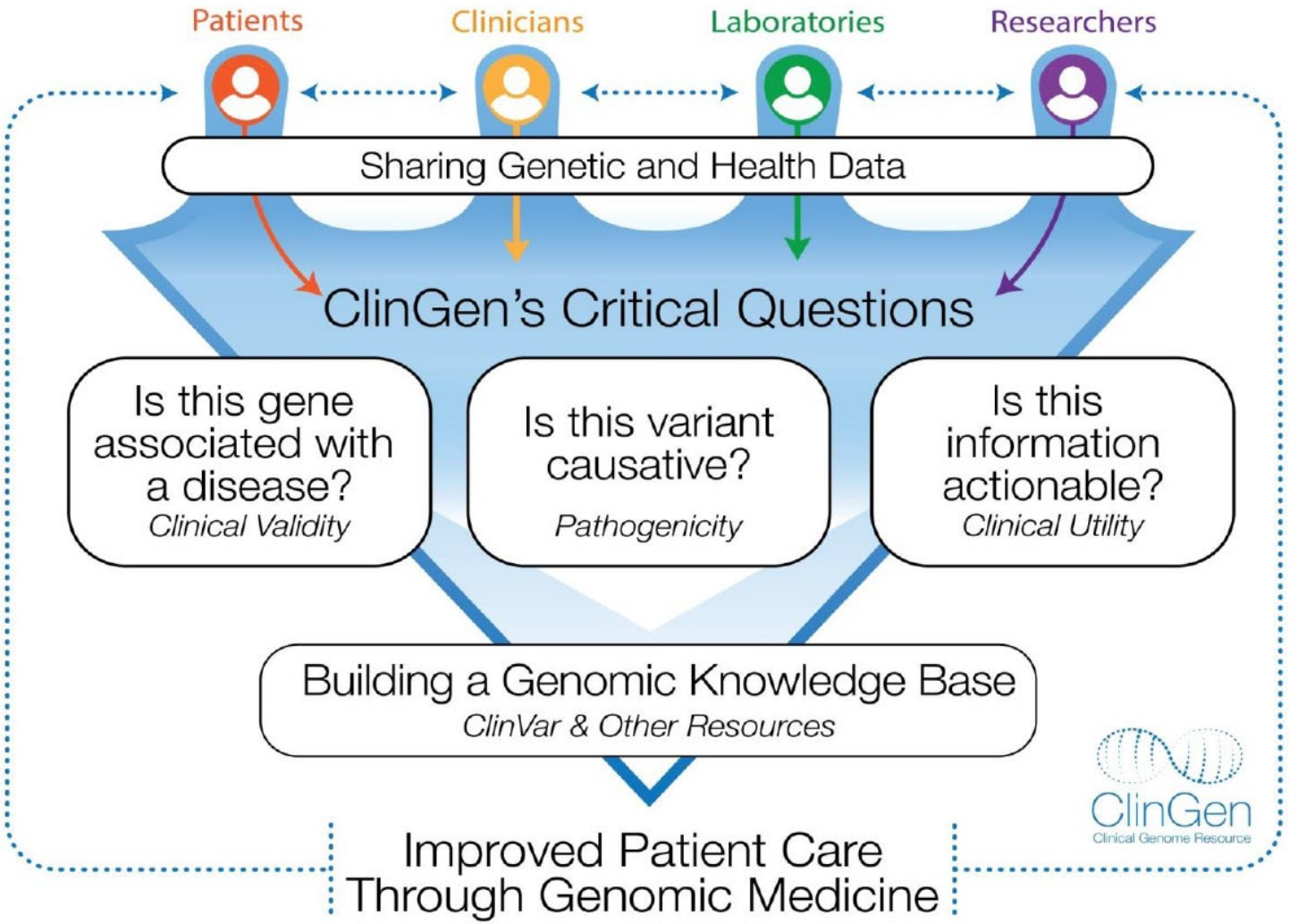
- Mobilize a broad community of experts
- Encourage submission of variant data by researchers/laboratories
- Identify existing expert curation efforts and coordinate/avoid duplication
- Prioritize efforts toward development of expert curation groups for gene-disease validity and variant pathogenicity
- Provide access to all ClinGen panels, working groups, educational materials and SOP on www.clinicalgenome.org

ClinGen WG and EP representation from 1125 investigators across 30 countries



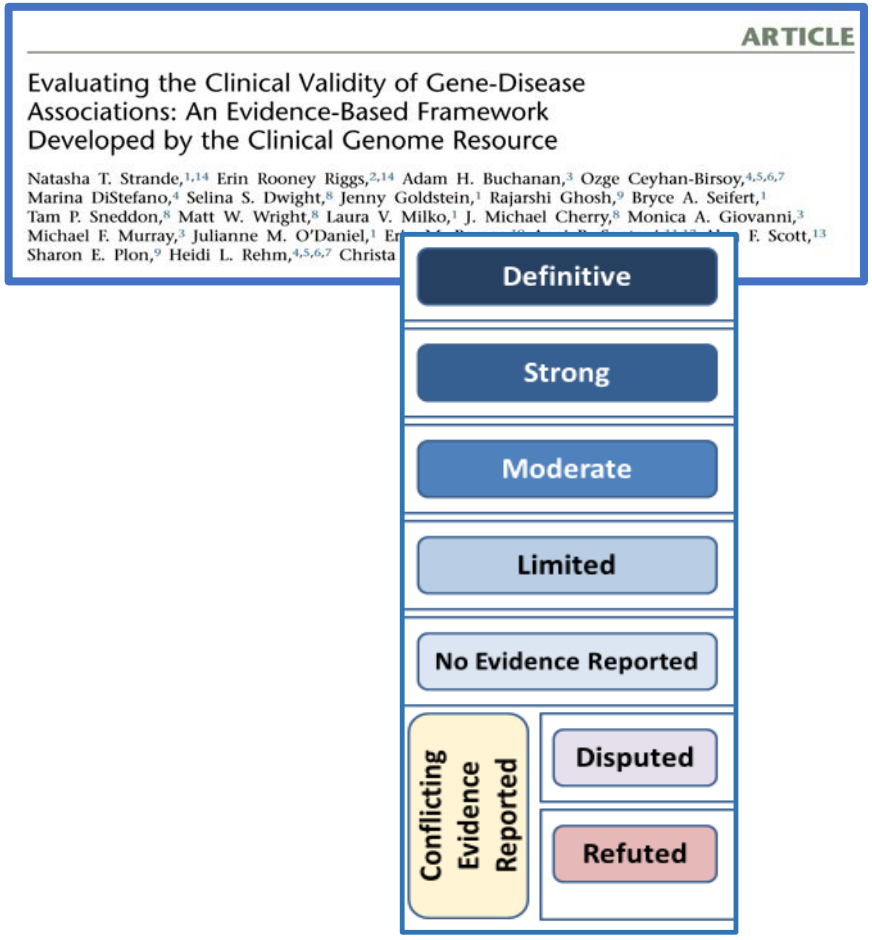
Updated October 2019 by Natalie Pino

Clinical Validity of Gene/Disease Association through ClinGen Gene Curation



ClinGen Developed Semi-quantitative Framework to Classify Strength of Evidence for the Role of Genes in Disease

- Genetic Evidence: Case-level, family segregation, or case-control data
- Experimental Evidence: Expression, model organism, rescue studies, etc.
- Most Updated Gene Curation SOP: VERSION 7
  - All approved Gene Curation Expert Panels listed with genes within scope



Assertion Criteria

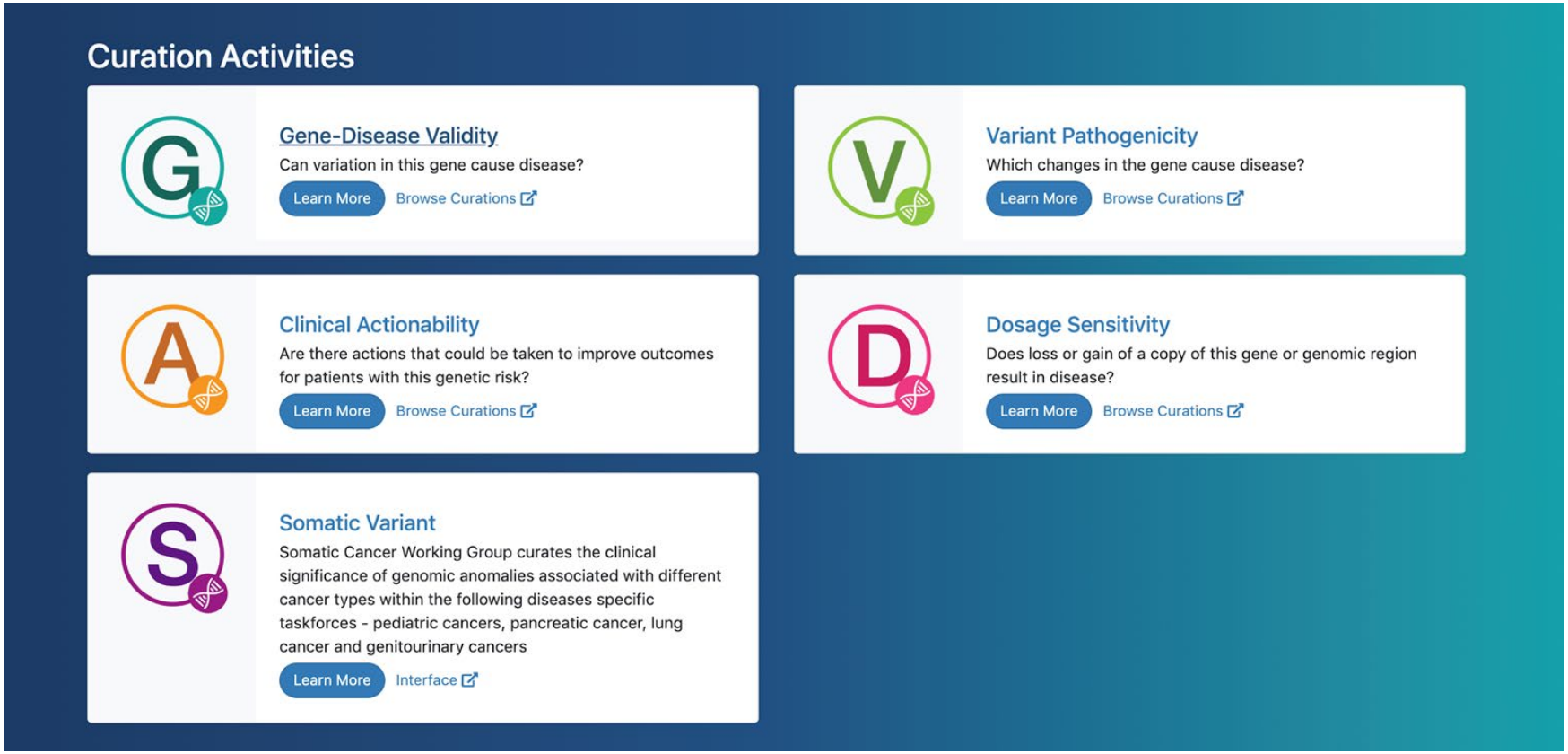
Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease 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	

Curation Interfaces



Gene Curation Interface

- Provides a web accessible workspace.
- Allows members of the GCEP to work together.
- Systematically characterize evidence from the literature to complete gene curation.
- Come to a final validity determination and “publish” on clinicalgenome.org

Gene Validity Classification Summary Listing

Gene Validity Classification Summary Screen

Gene Validity Classification Summary

Gene/Disease Pair: ***BLM* : Bloom syndrome**
HGNC:1058 | MONDO_0008876
Mode of Inheritance: **Autosomal recessive inheritance (HP:0000007)**
Expert Panel: **Hereditary Cancer**
SOP: **Gene Clinical Validity Standard Operating Procedures (SOP), Version 6**

Genetic Evidence				Evidence Type	Case Information Type	Guidelines Default	Guidelines Range	Guidelines Max	Guidelines Count	Points Total	Points Counted	PMIDs/Notes
Case-Level Data	Variant Evidence	Autosomal Dominant or X-linked Disorder			Variant is de novo	2	0-3	12				
					Proband with predicted or proven null variant	1.5	0-2	10				
					Proband with other variant type with some evidence of gene impact	0.5	0-1.5	7				
		Autosomal Recessive Disease			Two variants in trans and at least one de novo or a predicted/proven null variant	2	0-3	12	4	10	12	Ellis NA et al. 1995 Nov 17 (PMID:7585968); German J et al. 2007 Aug (PMID:17407155);
					Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0-1.5		2	2.5		Ellis NA et al. 1995 Nov 17 (PMID:7585968);
		Segregation Evidence					Summed LOD		Family Count			
					Candidate gene sequencing							
					Exome/genome or all genes sequenced in linkage region							
					Total Summed LOD Score							

Case-Control Data	Case-Control Study Type	Case-Control Quality Criteria	Guidelines Points/Study	Guidelines Max	Guidelines Count	Points Points	Points Counted	PMIDs/Notes
	Single Variant Analysis	1. Variant Detection Methodology 2. Power 3. Bias and confounding 4. Statistical Significance	0-6	12				
	Aggregate Variant Analysis		0-6					
				Total Genetic Evidence Points (Maximum 12)			12	

Send Feedback

Gene Validity Classification Summary Screen (Continued)

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	12	6	18	YES

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

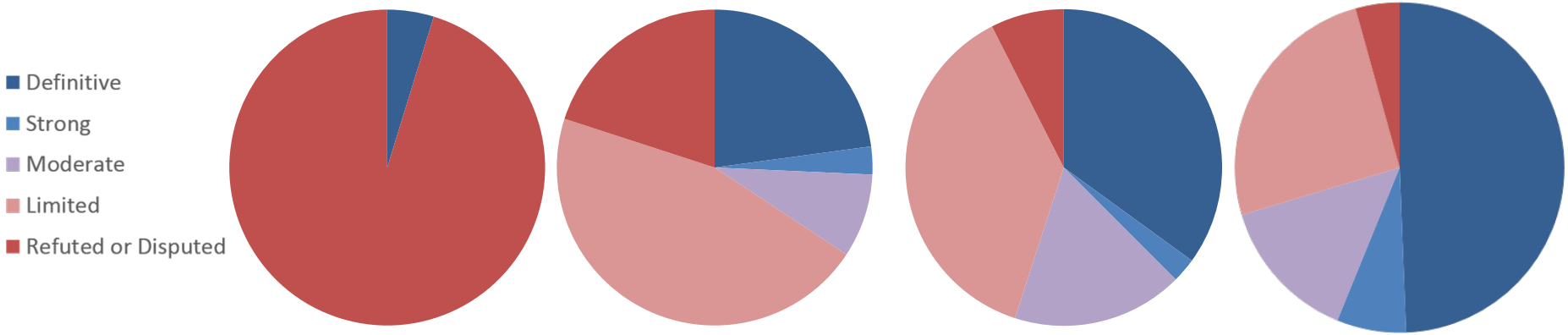
Valid contradictory evidence (Y/N)*	NO	
CALCULATED CLASSIFICATION (DATE)	Definitive	04/19/2019
EXPERT CURATION (DATE)	**Definitive**	04/19/2019
EVIDENCE SUMMARY	There has been substantial evidence published associating the BLM gene with Bloom syndrome since the gene-disease relationship was first proposed by Ellis et al. (1995). Multiple case level studies have been performed with BS patients that have variants in the BLM gene. WRN and RECQL4, another two RecQ DNA helicases, are associated with Werner and Rothmund–Thomson syndromes. All three are disorders of chromosomal instability and manifest growth retardation, and predisposition to malignancies. Northern blot analysis of mRNAs derived from selected Bloom's syndrome cell lines showed absent or abnormal BLM RNA. Multiple BLM deficient mouse models have been established to show consistent phenotypes with BS patients, especially increased rate of SCE and the development of a wide spectrum of cancer. All of these types of evidence combined are consistent with a definitive relationship between the BLM gene and Bloom Syndrome (BS).	

Examples of Gene Curation Expert Panels

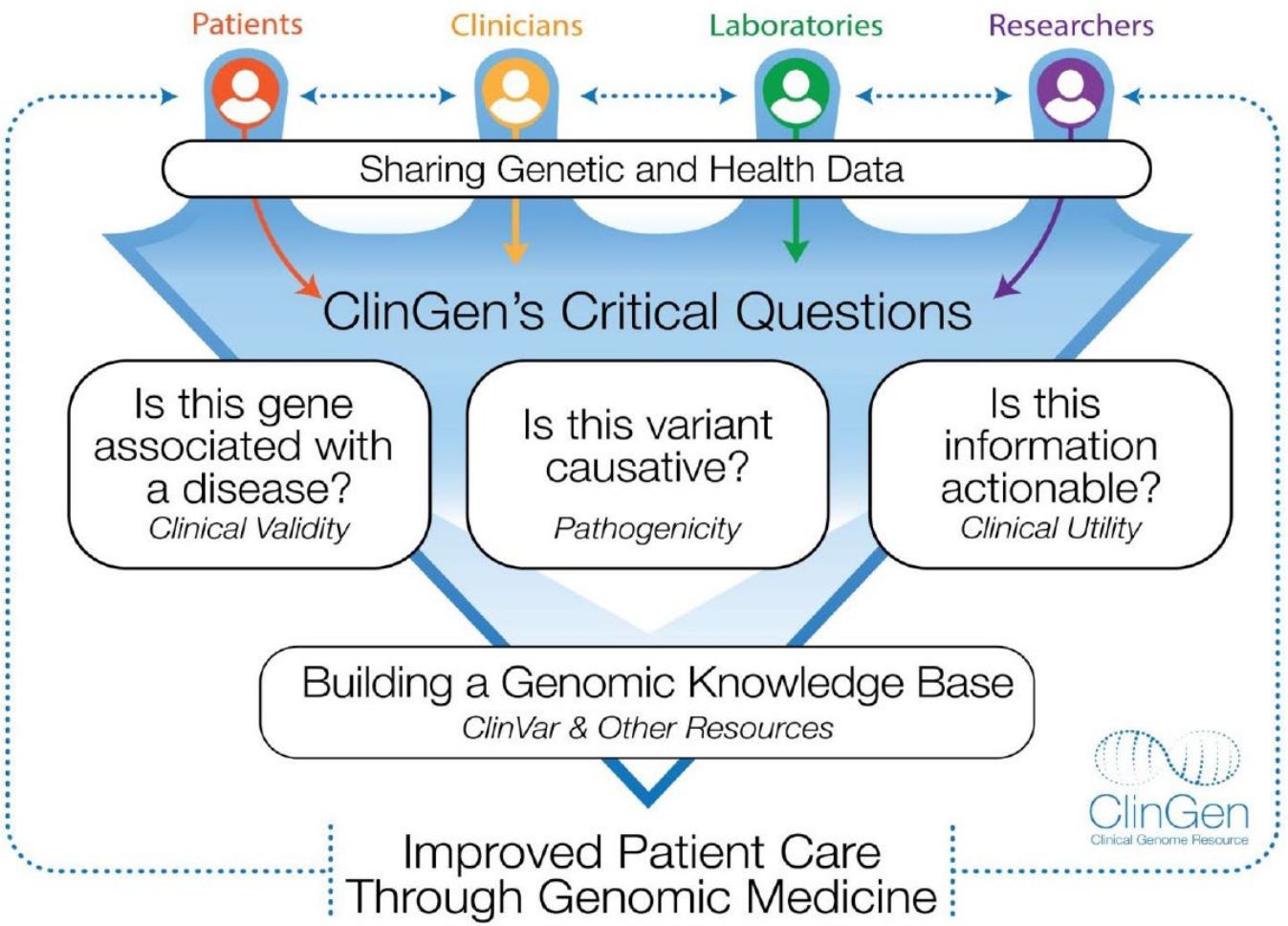
Clinical Domain Working Group (CDWG)	Gene Curation Expert Panel	# Genes Curated	Status
Cardiovascular	Aortopathy (FTAAD)	53	Renard, M. et al. 2018. *J Am Coll Cardiol.*
Cardiovascular	Arrhythmogenic Right Ventricular Cardiomyopathy	26	Manuscript in Progress
Cardiovascular	Brugada syndrome	21	Hosseini, SM et al. 2018. *Circulation*.
Cardiovascular	Hypertrophic cardiomyopathy	57	Ingles, J. et al. 2019 *Circ Genom Precis Med*
Cardiovascular	Long QT Syndrome	17	Adler, A. et al. 2020 *Circulation*
Cancer	Colorectal cancer/polyposis	42	Seifert, B. et al. 2018 *Genet Med*.
Cancer	Breast/ovarian cancer	63	Lee, K. et al. 2018 *Genet Med*.
Cancer	Hereditary cancer		In progress
Hearing Loss (Round 1)	Hereditary Hearing Loss	168	DiStefano and Hemphill et al. 2019 *Genet. Med.*
Inborn Errors of Metabolism	Fatty acid oxidation	28	McGlaughon, J. et al. 2019 *Mol Genet Metab.*
RASopathies (Round 1)	RASopathies	19	Grant, A. et al. 2018. *Hum Mut.*

Select Gene Curation Expert Panel Results

1. Brugada Syndrome
   - 21 gene-disease pairs
   - *Circulation* 2018
2. Hypertrophic Cardiomyopathy
   - 37 gene-disease pairs
   - *Circulation Gen* 2019
3. Colorectal Cancer
   - 40 gene-disease pairs
   - *Gen in Med* 2018
4. Hearing Loss
   - 164 gene-disease pairs
   - *Hum Mutat* 2018



Variant Pathogenicity through Variant Curation Expert Panels

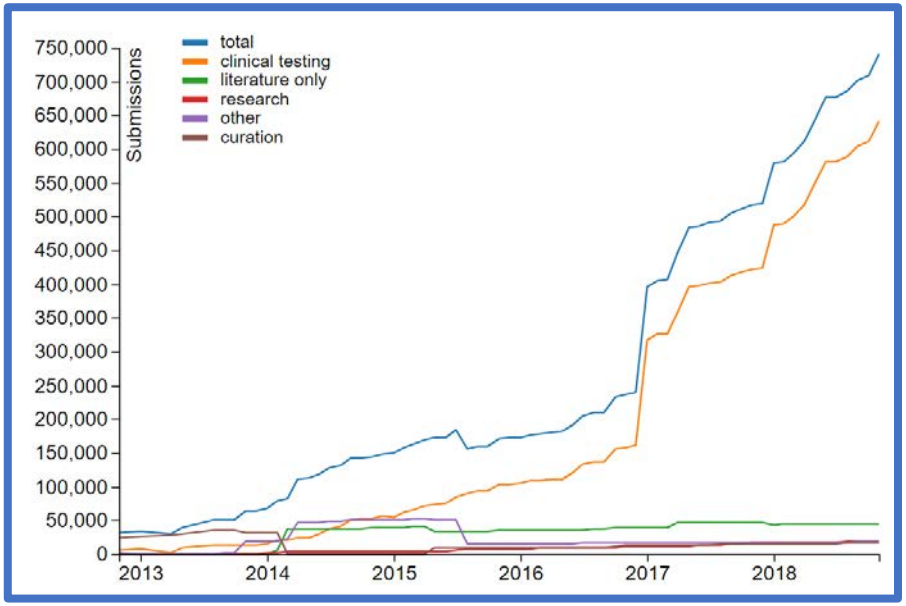


Multi-pronged effort needed for variant curation and interpretation

- Public sharing of existing variant interpretations via ClinVar
- Consistent use of ACMG/AMP Variant Classification with guidance from Sequence Variant Interpretation Committee
- Engaging experts in gene-specific expertise to provide systematic interpretation of variants (Variant Curation Expert Panels)
- Use of ClinGen Curation Interface and provide public access to evidence used for classification
- Submission of classified variants back to ClinVar

Current Statistics

- **676868 unique variants** with interpretations submitted to ClinVar (>1 million submissions) from 1,479 submitters across >67 countries
- Top 5 ClinVar submitters are genetic testing companies (62% of ClinVar variants with interpretations



Sequence Variant Interpretation Committee

- Refine the ACMG/AMP guidelines as they are deployed by the community
- Moving toward a more quantitative framework
- Evidence Codes Combined for Final Classification:
  - Benign, Likely Benign,
  - Uncertain Significance,
  - Likely Pathogenic, Pathogenic

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

Human Mutation
Variation, Informatics, and Disease

SPECIAL ARTICLE | Free Access

Updated recommendation for the benign stand-alone ACMG/AMP criterion

Rajarshi Ghosh, Steven M. Harrison, Heidi L. Rehm, Sharon E. Plon, Leslie G. Biesecker, on behalf of ClinGen Sequence Variant Interpretation Working Group

Human Mutation
Variation, Informatics, and Disease

SPECIAL ARTICLE | Free Access

Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion

Ahmad N. Abou Tayoun, Tina Pesaran, Marina T. DiStefano, Andrea Oza, Heidi L. Rehm, Leslie G. Biesecker, Steven M. Harrison, ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI)

Article | Published: 04 January 2018

Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework

Sean V Tavtigian phD, Marc S Greenblatt MD, phD, Steven M Harrison phD, Robert L Nussbaum MD, Snehit A Prabhu phD, Kenneth M Boucher phD, Leslie G Biesecker MD & on behalf of the ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI)

Genetics in Medicine **20**, 1054–1060 (2018) | Download Citation

ClinGen Variant Curation Expert Panels

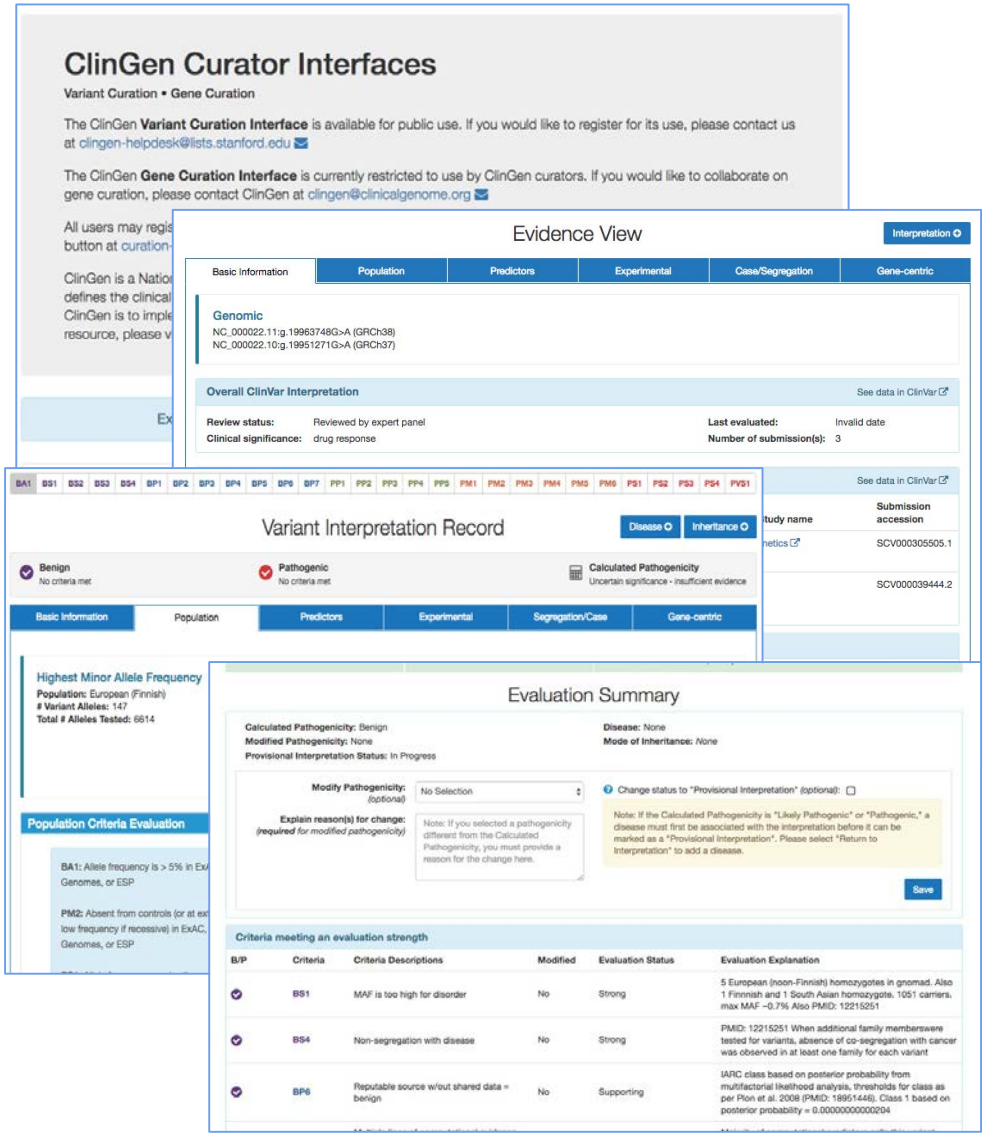
- Membership described on website and in the Program Announcement
- Four step process to final approval and “publishing” VCEP classified variants on ClinVar
- VCEP curation process recognized by FDA with detailed SOP describing each step.
- ClinGen has developed multiple online tools to support entire process.
- Multiple online training tools to support new VCEPs.

Stepwise Progress of Variant Curation Expert Panels

Step	1: Define WG and plans	2: Develop Variant Classification Rules	3: Pilot Rules	4: Implementation (At the 3-star level)
Substeps	-- Identify EP membership -- Define scope -- Address COI	Develop ACMG/AMP rule specifications for genes	-- Pilot rules with known variants -- Define plans for ongoing variant curation	**-- Approval** -- ClinVar submission
Panels Currently at This Step	Limb Girdle Muscular Dystrophy Hemoglobinopathies *ABCD1* Skeletal Dysplasia Craniosynostoses von Willebrand	Glaucoma *DICER1* Cerebral Creatine Deficiencies Coagulation Factor Deficiencies HHT/Vascular Breast, ovarian, pancreatic cancers von Hippel-Lindau syndrome Monogenic Diabetes Mitochondrial Diseases VLCAD deficiency	Rett-Angelman Brain Malformations *KCNQ1*/LQTS *RYR1*/Malignant Hyper-thermia *FBN1*/Marfan Syndrome Cardiomyopathy (Round 2) Familial Hypercholesterolemia Platelet Disorders	*MYH7*/Cardiomyopathy RASopathy *PAH*/PKU Hearing Loss *PTEN*/PHTS *CDH1*/Gastric Myeloid Malignancy *RUNX1* *TP53*/LFS *GAA*/Lysosomal Storage Diseases

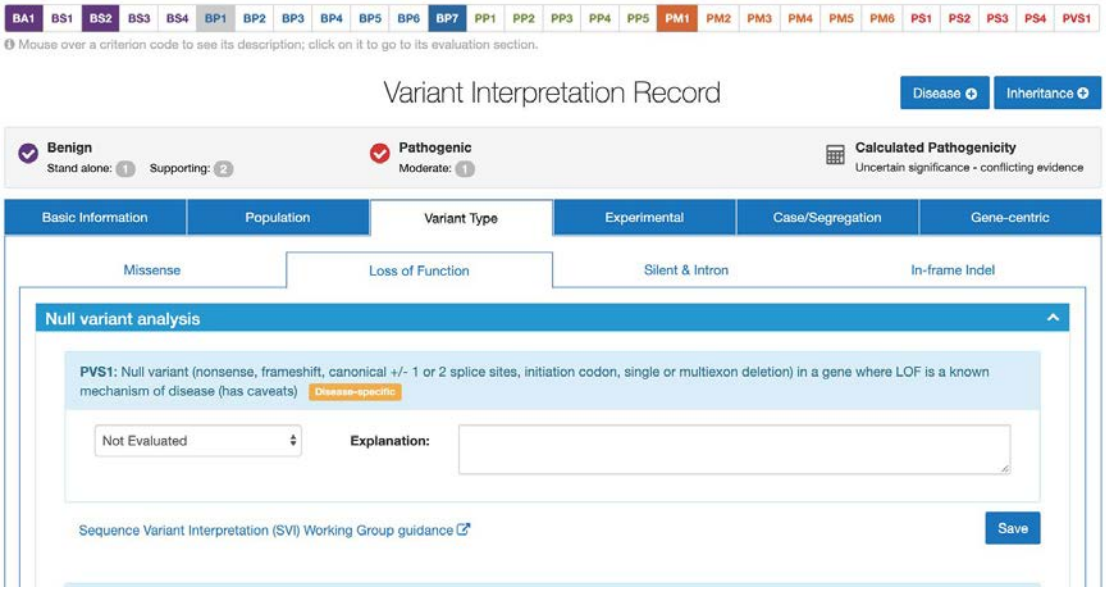
Variant Curation Interface (VCI)

1. Select ClinVar or ClinGen Allele Registry ID
2. View aggregated external and manually curated evidence
3. Evaluate evidence using ACMG/AMP guidelines
4. Review/approve interpretation and submit to the Evidence Repository and ClinVar



Different Variant View for Each Evidence Type Being Evaluated

- On the Variation Interpretation Record, screen PVS1 and PM6/PS2 criteria sections now have links added to Sequence Variant Interpretation (SVI) Working Group guidance and the top criterion bar links to the specific criteria.



FDA-Recognized Genetic Variant Database

- Data and assertions in the database are considered valid scientific evidence
- Genetic/genomic test developers can use these assertions to support clinical validity during FDA's regulatory review
- FDA hopes this program will:
  - Increase public sharing
  - Reduce regulatory burden on test developers
  - Advance the evaluation and implementation of precision medicine
- Data | People | Process: Variant Curation SOP Version 1 Required
- https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/PrecisionMedicine-MedicalDevices/ucm603675.htm

Final Classified Variant Appears in ClinVar with FDA-Recognized Tag and Summary

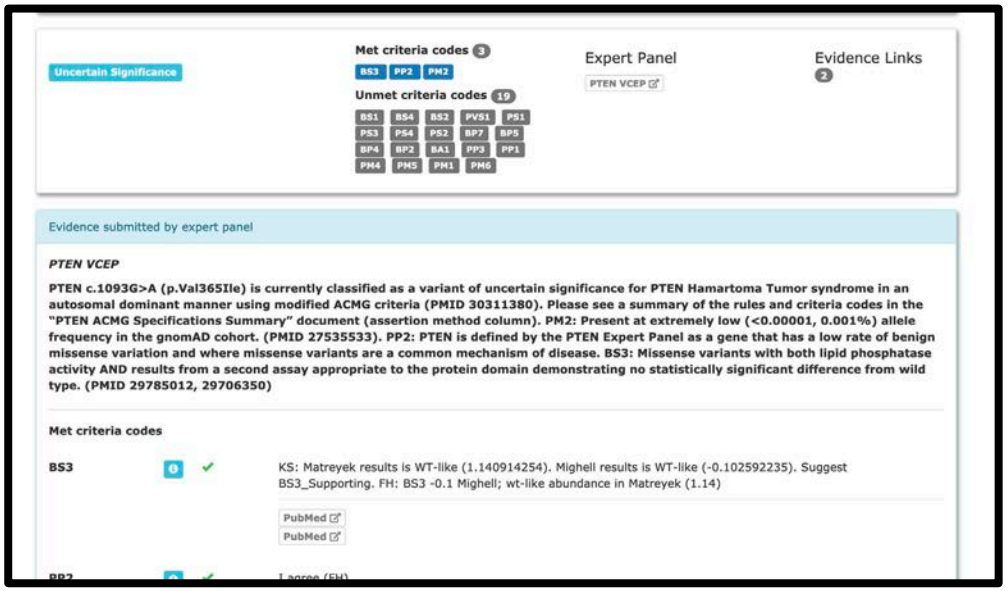
- All evidence used in VCEP Classification Directly Deposited into ClinGen Evidence Repository

Submitted interpretations and evidence

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Uncertain significance (Jun 25, 2019)	reviewed by expert panel (ClinGen PTEN ACMG Specifications v1) Method: curation	PTEN hamartoma tumor syndrome (Autosomal dominant inheritance) Allele origin: germline	ClinGen PTEN Variant Curation Expert Panel FDA RECOGNIZED DATABASE Accession: SCV000930120.1 Submitted: (Jul 23, 2019)	Evidence details Publications PubMed (3) Other databases https://erepo.clinicalgenome.o... Comment: PTEN c.1093G>A (p.Val365Ile) is currently classified as a variant of uncertain significance for PTEN Hamartoma Tumor syndrome in an autosomal dominant manner using modified ACMG criteria (PMID 30311380). Please see a summary of the rules and criteria codes in the "PTEN ACMG Specifications Summary" document (assertion method column). PM2: Present at extremely low (<0.00001, 0.001%) allele frequency in the gnomAD cohort. (PMID 27535533). PP2: PTEN is defined by the PTEN Expert Panel as a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease. BS3: Missense variants with both lipid phosphatase activity AND results from a second assay appropriate to the protein domain demonstrating no statistically significant difference from wild type. (PMID 29785012, 29706350) (less)

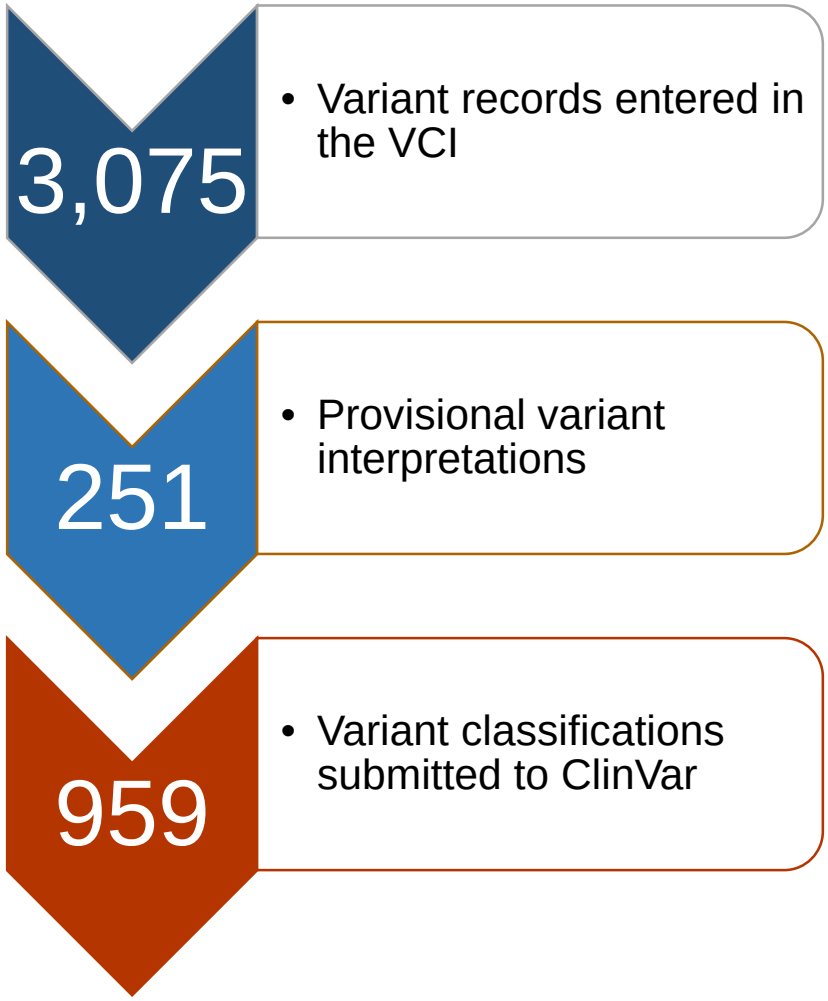
FDA program led to improvements in transparency and access

- Open API - Scientific Evidence and Provenance information Ontology (SEPIO) compliant JSON-LD

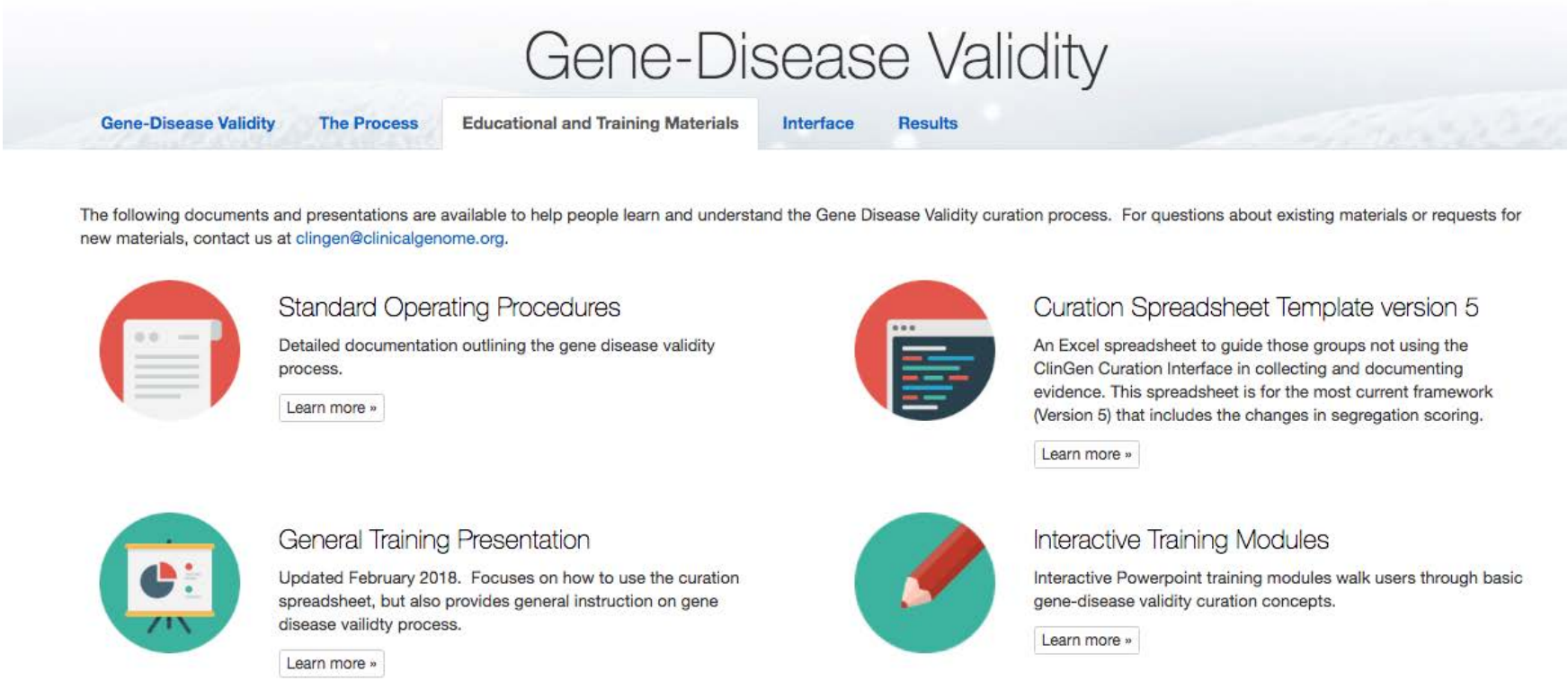


VCEP metrics (December 2019)

- 27 VCEPs
- 347 VCEP members
- 202 institutions
- 8+ publications



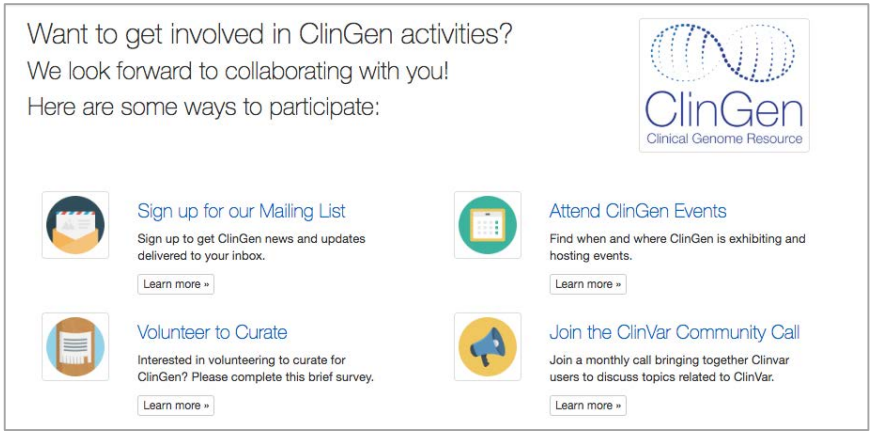
ClinGen's Education Working Group aims to foster community engagement through education, outreach, and resource development.

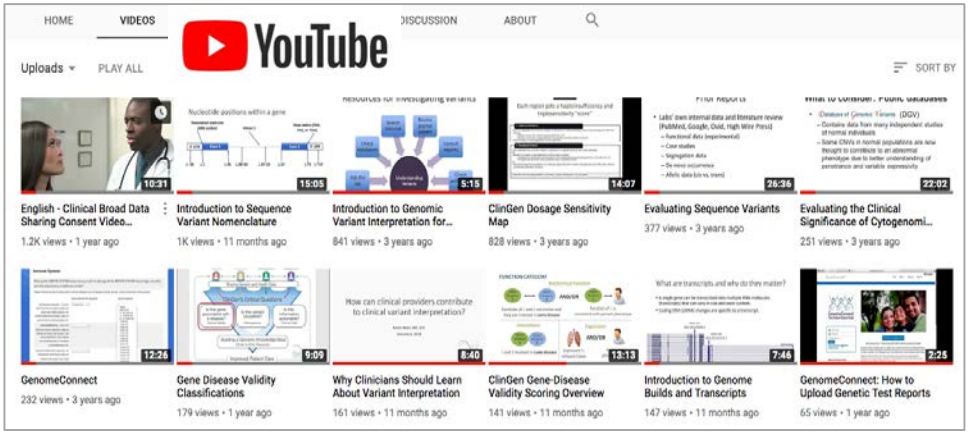


Engage and Train the Broader Community

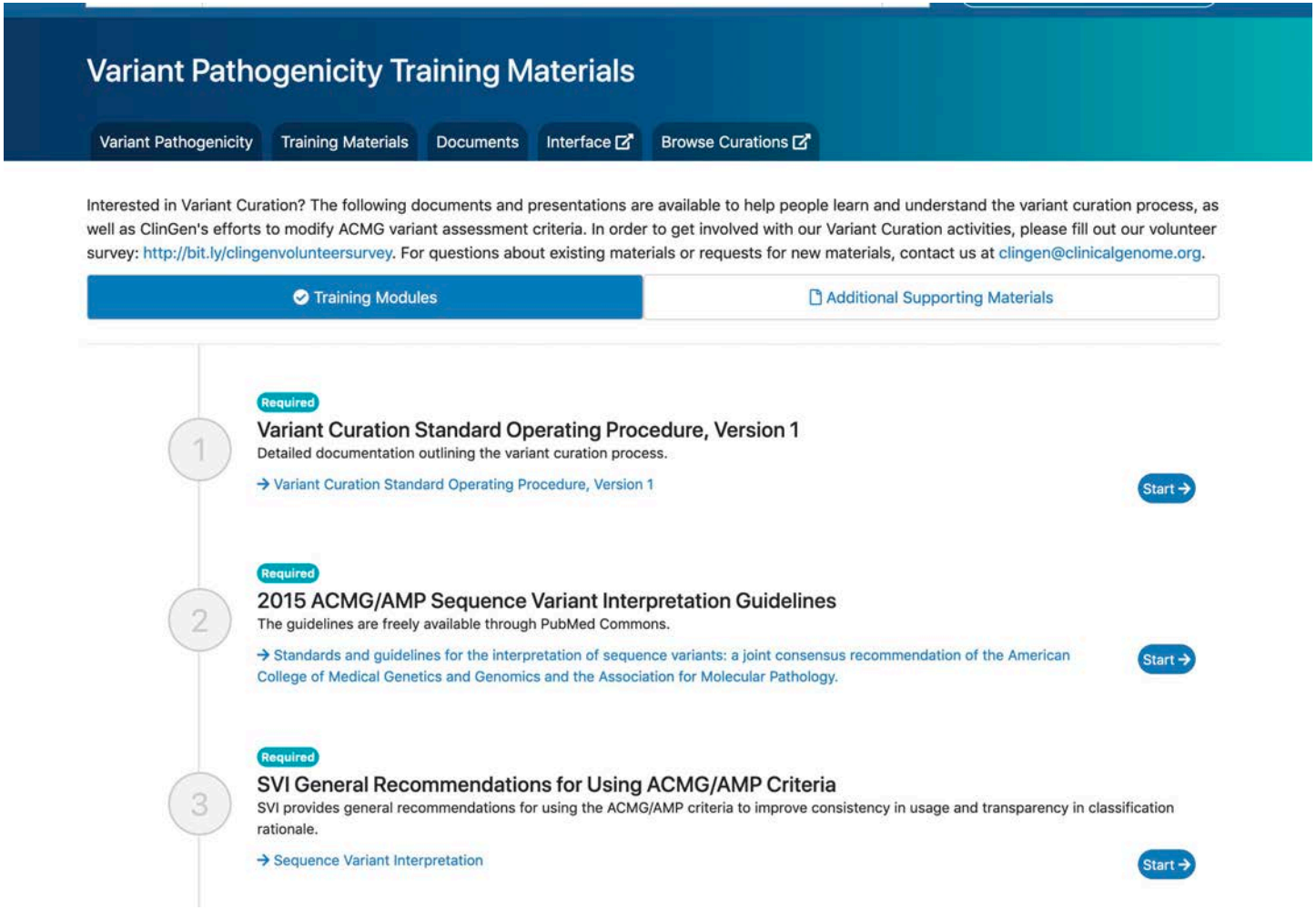
- Partnered with American Board of Medical Genetics and Genomics to Maintenance of Certification
- Incentivize members of the community to:
  - share and update data in ClinVar
  - resolve variant classification differences
  - participate in curation activities

- Interested in volunteering for curation efforts, take our **survey**!
  (If you have any questions, please feel free to email us at volunteer@clinicalgenome.org.)





Examples of Training Materials



Support and Training

- Materials on using ClinGen frameworks provided by Education WG including EP Toolkit
- Biocurator training by UNC Biocuration Core and participation in the Biocurators WG
- Training on the use of curation interfaces and tools by Stanford and Baylor
- Provided reports from ClinGen WGs on needed updating of curations over time.
- Clinical Doman Working Group Oversight Committee reviews VCEP progress.
- Attend ClinGen/DECIPHER “Curating the Clinical Genome” open meeting

ClinGen Leadership and Coordinators

In Summary

Final Considerations

- Are the genes/variants selected of high priority to the participating NIH ICs 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?

Contacts

https://grants.nih.gov/grants/guide/pa-files/PAR-20-101.html

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Questions?

Frequently Asked Questions will be posted on:
https://www.nichd.nih.gov/about/org/der/branches/iddb
Under the Highlights Section