

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

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<https://nih.webex.com/nih/onstage/g.php?MTID=e43f514247608b4c54f23641fb3d49cdd>

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Eunice Kennedy Shriver National Institute  
of Child Health and Human Development



# Agenda

## Pre-Application Webinar

- Objectives of the 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: NCI, NEI, NICHD, NIMH and NINDS.
- 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.

FDA has recognized ClinGen as the first public genetic variant database that can be used to validate genetic variant information in regulatory submissions.



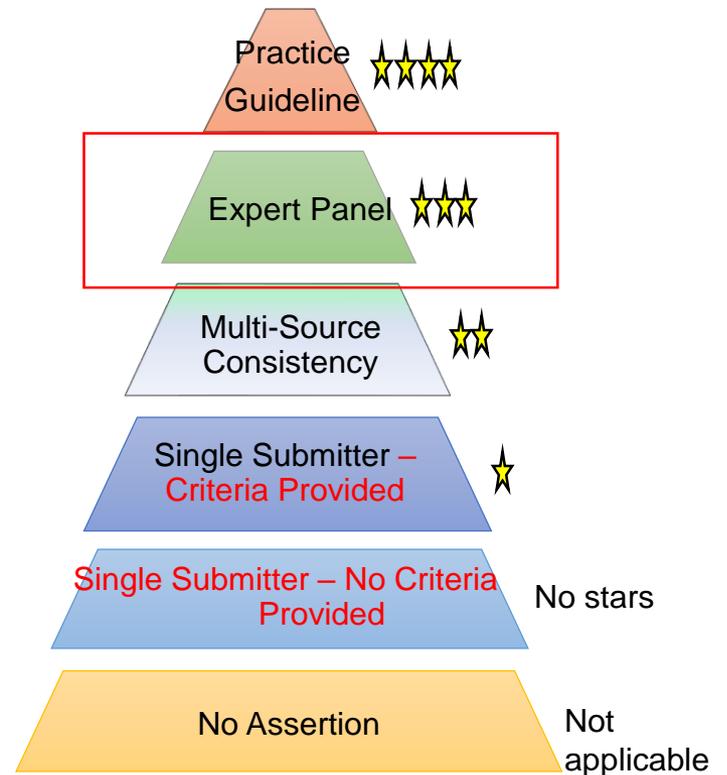
# Priority Areas

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

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

## 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 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.

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*

Improved Patient Care  
Through Genomic Medicine





# 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](http://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.



# 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.
- 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 some 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: Sharing Data. Building Knowledge. Improving Care.



# 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



# 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.

- **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

[[www.clinicalgenome.org](http://www.clinicalgenome.org)]

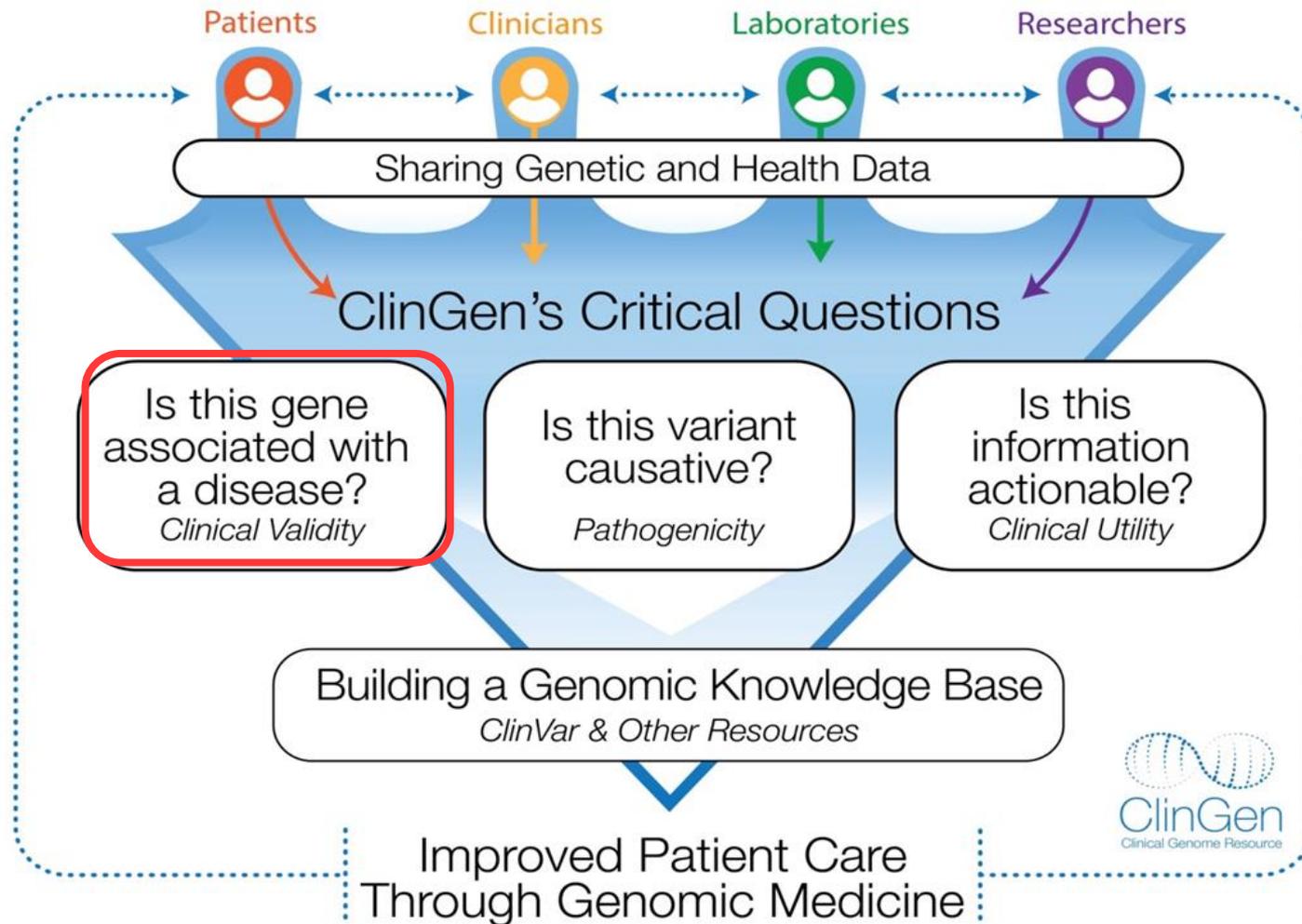
The screenshot shows the ClinGen website homepage. At the top, there is a navigation bar with the ClinGen logo, a search bar, and links for 'About ClinGen', 'Working Groups & Expert Panels', 'Resources & Tools', 'GenomeConnect', 'Share Your Data', and 'Curation Activities'. Below the navigation bar is a large blue banner with the text 'Defining the clinical relevance of genes & variants for precision medicine and research...'. The banner features three large numbers: '1590 ClinGen Curated Genes', '33 Expert Groups', and '10703 Expert Reviewed Variants in ClinVar'. Below the banner is a section titled 'Sharing Data. Building Knowledge. Improving Care.' with a sub-header 'ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Learn more about our organization and our ongoing efforts below.' This section contains six tiles: 'ClinGen-ClinVar Partnership', 'How to share genomic & health data', 'Learn about ClinGen curation activities', 'GenomeConnect Patient Registry', 'View ClinGen's Resources & Tools', and 'Get Involved'. At the bottom, there is a section titled 'ClinGen Receives Recognition Through New FDA Human Variant Database Program' with a 'Learn more >' link.

# 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](http://www.clinicalgenome.org)**



# 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

ARTICLE

## Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

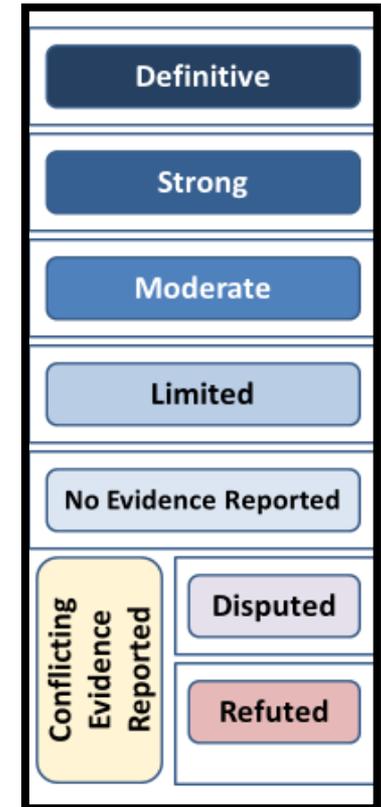
Natasha T. Strande,<sup>1,14</sup> Erin Rooney Riggs,<sup>2,14</sup> Adam H. Buchanan,<sup>3</sup> Ozge Ceyhan-Birsoy,<sup>4,5,6,7</sup> Marina DiStefano,<sup>4</sup> Selina S. Dwight,<sup>8</sup> Jenny Goldstein,<sup>1</sup> Rajarshi Ghosh,<sup>9</sup> Bryce A. Seifert,<sup>1</sup> Tam P. Sneddon,<sup>8</sup> Matt W. Wright,<sup>8</sup> Laura V. Milko,<sup>1</sup> J. Michael Cherry,<sup>8</sup> Monica A. Giovanni,<sup>3</sup> Michael F. Murray,<sup>3</sup> Julianne M. O'Daniel,<sup>1</sup> Erin M. Ramos,<sup>10</sup> Avni B. Santani,<sup>11,12</sup> Alan F. Scott,<sup>13</sup> Sharon E. Plon,<sup>9</sup> Heidi L. Rehm,<sup>4,5,6,7</sup> Christa L. Martin,<sup>2,3,\*</sup> and Jonathan S. Berg<sup>1,\*</sup>



**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

[www.clinicalgenome.org](http://www.clinicalgenome.org)

All approved Gene Curation Expert Panels listed with genes within scope

<b>Assertion criteria</b>	<b>Genetic Evidence (0-12 points)</b>	<b>Experimental Evidence (0-6 points)</b>	<b>Total Points (0-18)</b>	<b>Replication Over Time (Y/N)</b>
<b>Description</b>	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)
<b>Assigned Points</b>				
<b>CALCULATED CLASSIFICATION</b>		<b>LIMITED</b>	<b>1-6</b>	
		<b>MODERATE</b>	<b>7-11</b>	
		<b>STRONG</b>	<b>12-18</b>	
		<b>DEFINITIVE</b>	<b>12-18 AND replication over time</b>	
<b>Valid contradictory evidence? (Y/N)</b>	List PMIDs and describe evidence:			
<b>CURATOR CLASSIFICATION</b>				
<b>FINAL CLASSIFICATION</b>				

# Curation Interfaces - clinicalgenome.org

## Curation Activities



### Gene-Disease Validity

Can variation in this gene cause disease?

[Learn More](#)

[Browse Curations](#)



### Variant Pathogenicity

Which changes in the gene cause disease?

[Learn More](#)

[Browse Curations](#)



### Clinical Actionability

Are there actions that could be taken to improve outcomes for patients with this genetic risk?

[Learn More](#)

[Browse Curations](#)



### Dosage Sensitivity

Does loss or gain of a copy of this gene or genomic region result in disease?

[Learn More](#)

[Browse Curations](#)



### Somatic Variant

Somatic Cancer Working Group curates the clinical significance of genomic anomalies associated with different cancer types within the following diseases specific taskforces - pediatric cancers, pancreatic cancer, lung cancer and genitourinary cancers

[Learn More](#)

[Interface](#)

# 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](http://clinicalgenome.org)

Affiliation: Hearing Loss EP To change your affiliation, go to

## MSRB3 – nonsyndromic genetic deafness

*Autosomal recessive inheritance*

[Preview Evidence Summary](#)
[Classification Matrix](#)

<p><b>MSRB3</b> HGNC Symbol: <a href="#">MSRB3</a> NCBI Gene ID: <a href="#">253827</a></p>	<p><b>nonsyndromic genetic deafness</b> <a href="#">[View definition]</a> Disease ID: <a href="#">MONDO:0019497</a> OMIM ID: <a href="#">[Add]</a></p>	<p><b>Creator:</b> Sarah Hemphill (Hearing Loss EP) — 2017 Oct 24, 10:26 am <b>Contributors:</b> Sarah Hemphill, Rebecca Siegart <b>Last edited:</b> Rebecca Siegart (Hearing Loss EP) — 2018 Oct 04, 10:17 am</p>
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**All classifications for this record in the Gene Curation Interface (GCI)**

➤ My classification

Hearing Loss EP — Calculated: Strong; Modified: Moderate; Status: APPROVED PUBLISHED

### Gene-Disease Record Variants

Click a variant to View, Curate, or Edit it. The icon indicates curation by one or more curators.

NM\_001031679.2(MSRB3):c.55C>T (p.Arg19Ter)
NM\_198080.3(MSRB3):c.265T>G (p.Cys89Gly)
NC\_000012.12:g.65278788T>G (GRCh38)

#### Add New PMID

Ahmed ZM et al. Functional null mutations of MSRB3 encoding methionine sulfoxide reductase are associated with human deafness DFNB74. **2011** Jan 07;88(1):19-29.

PMID: [21185009](#)

Kim MA et al. Methionine Sulfoxide Reductase B3-Targeted In Utero Gene Therapy Rescues Hearing Function in a Mouse Model of Congenital Sensorineural Hearing Loss. **2016** Apr 10;24(11):590-602.

PMID: [26649646](#)

Kwon TJ et al. Methionine sulfoxide reductase B3

Ahmed ZM, Yousaf R, Lee BC, Khan SN, Lee S, Lee K, Husnain T, Rehman AU, Bonneux S, Ansar M, Ahmad W, Leal SM, Gladyshev VN, Belyantseva IA, Van Camp G, Riazuddin S, Friedman TB, Riazuddin S. Functional null mutations of MSRB3 encoding methionine sulfoxide reductase are associated with human deafness DFNB74. *American journal of human genetics.* **2011** Jan 07;88(1):19-29.

PubMed

PMID:21185009 added by Sarah Hemphill.

#### Abstract

The DFNB74 locus for autosomal-recessive, nonsyndromic deafness segregating in three families was previously mapped to a 5.36 Mb interval on chromosome 12q14.2-q15. Subsequently, we ascertained five additional consanguineous families in which deafness segregated with markers at this locus and refined the critical interval to 2.31 Mb. We then sequenced the protein-coding exons of 18 genes in this interval. The affected individuals of six apparently unrelated families were homozygous for the same transversion (c.265T>G) in MSRB3, which encodes a zinc-containing methionine sulfoxide reductase B3. c.265T>G results in a substitution of glycine for cysteine (p.Cys89Gly), and this substitution cosegregates with deafness in the six DFNB74 families. This cysteine residue of MSRB3 is conserved in orthologs from yeast to humans and is involved in binding structural zinc. In vitro, p.Cys89Gly abolished zinc binding and MSRB3 enzymatic activity, indicating that p.Cys89Gly is a loss-of-function allele. The affected individuals in two other families were homozygous for a transition mutation (c.55T>C), which results in a nonsense mutation (p.Arg19X) in alternatively spliced exon 3, encoding a mitochondrial localization signal. This finding suggests that DFNB74 deafness is due to a mitochondrial dysfunction. In a cohort of 1,040 individuals (aged 53-67 years) of European ancestry, we found no association between 17 tagSNPs for MSRB3 and age-related hearing loss. Mouse *Marb3* is expressed widely. In the inner ear, it is found in the sensory epithelium of the organ of Corti and vestibular end organs as well as in cells of the spiral ganglion. Taken together, MSRB3-catalyzed reduction of methionine sulfoxides to methionine is essential for hearing.

#### Evidence for PMID:21185009

**Genetic Evidence**

➤ Case Level

Group

Family

PKDF805  
Last edited by: Rebecca Siegart 2018 Oct 02, 11:39 am  
No associations  
Variants: [1](#)  
[View](#) | [Edit](#)  
[Add new Individual to this Family](#)

Individual

proband-PKDF805   
Last edited by: Rebecca Siegart 2018 Oct 02, 11:39 am  
Associations: PKDF805  
Variants: [1](#)  
[View/Score](#) | [Edit](#)

proband-4258   
Last edited by: Jimmy Zhen 2017 Oct 24, 12:30 pm  
No associations  
Variants: [1](#)  
[View/Score](#) | [Edit](#)

➤ Case-Control

Case-Control

**Experimental Evidence**

Experimental Data

mouse expression

# Gene Validity Classification Summary

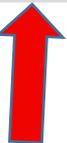
Gene/Disease Pair: **BLM : Bloom syndrome**

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**



	Evidence Type	Case Information Type	Guidelines				Points		PMIDs/Notes	
			Default	Range	Max	Count	Total	Counted		
Genetic Evidence	Variant Evidence	Variant is de novo	2	0-3	12					
		Autosomal Dominant or X-linked Disorder	Proband v predicted proven null v Proband v other varian with son evidence of impact							
		Autosomal Recessive Disease	Two varian trans and at one de novi predicted/p null varie Two variant: predicted/p null) with s evidence of impact in t							
		Segregation Evidence	Candidate Exome/ger sequenced Total Sum							
	Case-Level Data		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).						
Control Data	Case-Control Study Type	Case-Co Qualit Criteri								
	Single Variant Analysis	1. Variant Detection Methodology								

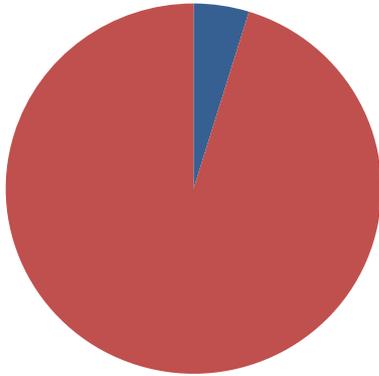
# Examples of Gene Curation Expert Panels

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



# Select Gene Curation Expert Panel Results

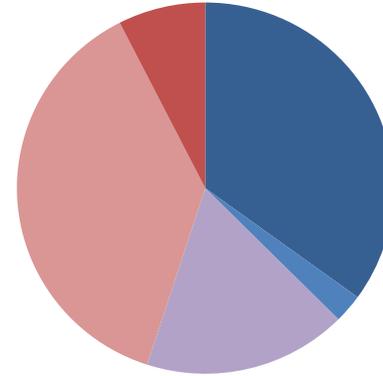
**Brugada Syndrome**  
21 gene-disease pairs



[Circulation 2018]

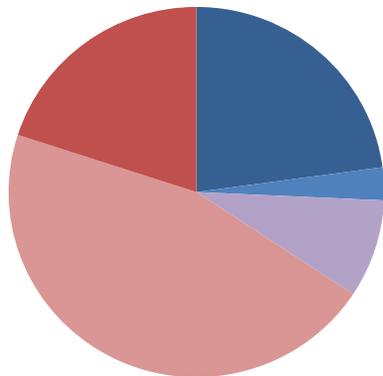
- Definitive
- Strong
- Moderate
- Limited
- Refuted or Disputed

**Colorectal Cancer**  
40 gene-disease pairs



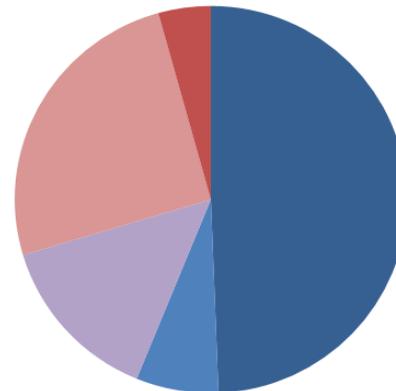
[Gen In Med 2018]

**Hypertrophic Cardiomyopathy**  
37 gene-disease pairs



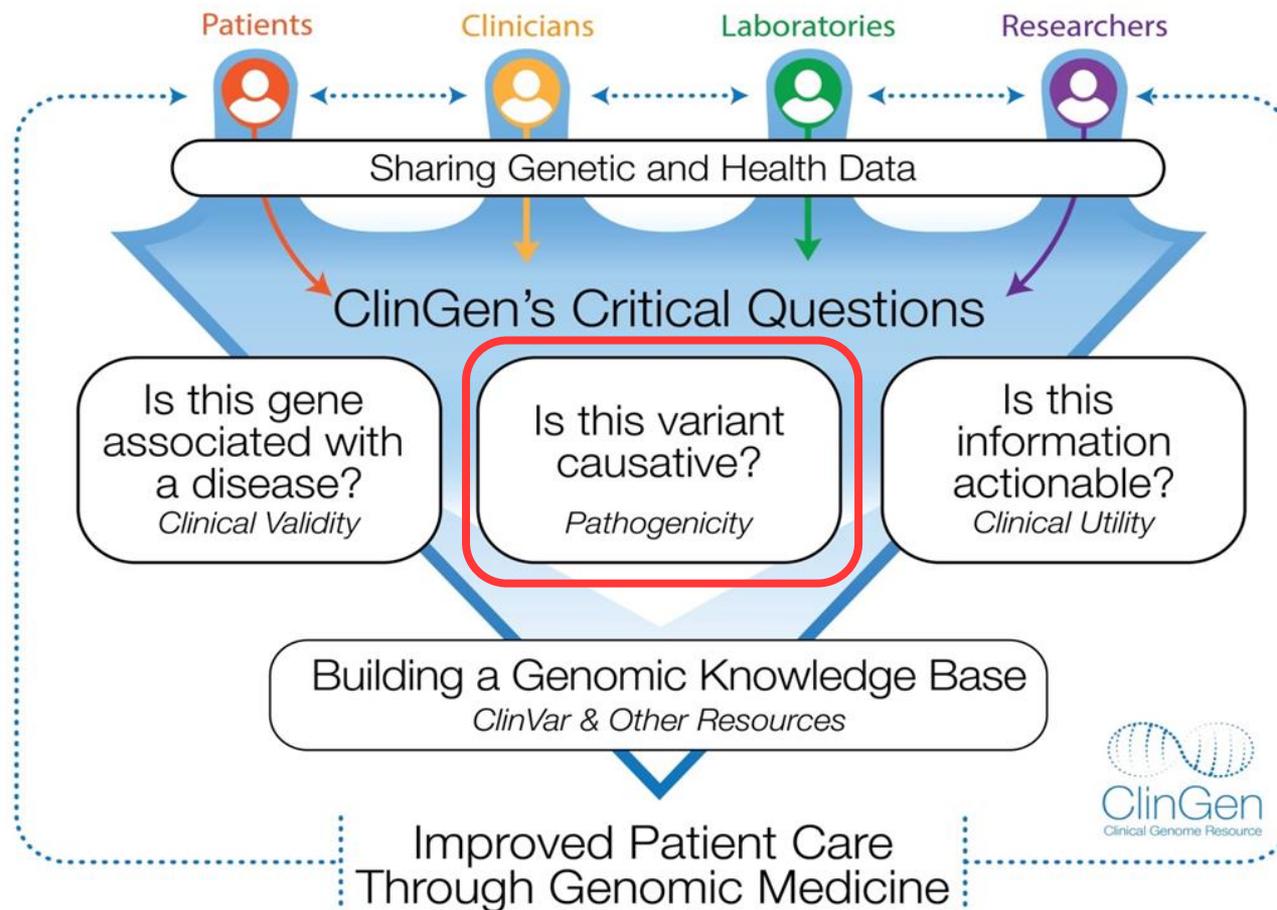
[Circulation Gen 2019]

**Hearing Loss**  
164 gene-disease pairs



[Hum Mutat 2018]

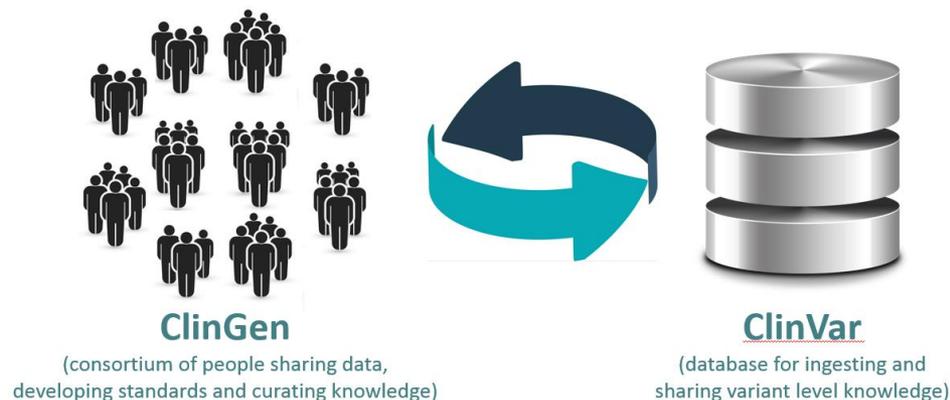
# Variant Pathogenicity through Variant Curation Expert Panels



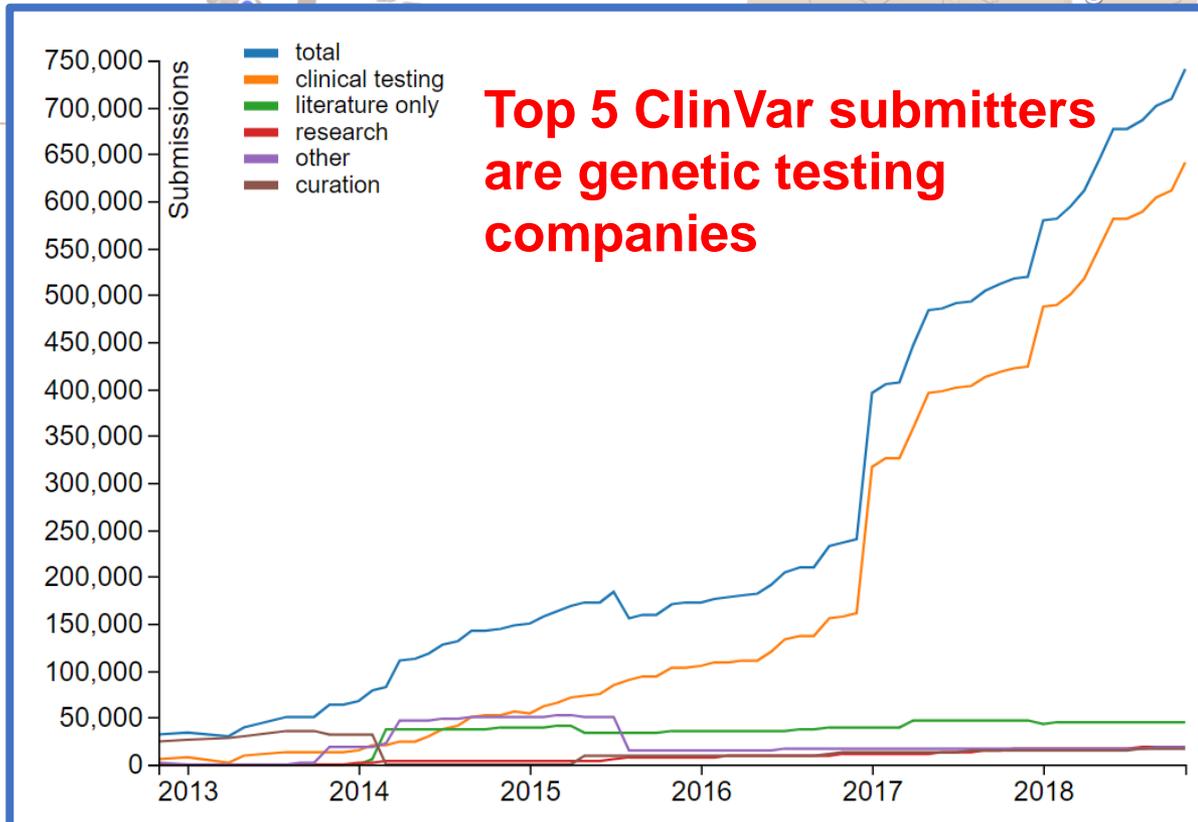


# Multi-pronged effort needed for variant curation and interpretation

- 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



**676868 unique variants with interpretations submitted to ClinVar (>1 million submissions) from 1,479 submitters across >67 countries**



[Created by Natalie Pino, NHGRI]



# Sequence Variant Interpretation Committee

- Refine the ACMG/AMP guidelines as they are deployed by the community

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

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
<b>Population Data</b>	MAF is too high for disorder <i>BA1/BS1</i> OR observation in control inconsistent with disease penetrance <i>BS2</i>			Absent in population databases <i>PM2</i>	Prevalence in affecteds statistically increased over controls <i>PS4</i>	
<b>Computational And Predictive Data</b>		Multiple lines of computational evidence suggest no impact <i>BP4</i> Missense when only truncating cause disease <i>BP1</i> Silent variant with non predicted splice impact <i>BP7</i> In-frame indels in repeat w/out known function <i>BP3</i>	Multiple lines of computational evidence support a deleterious effect on the gene / gene product <i>PP3</i>	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before <i>PM5</i> Protein length changing variant <i>PM4</i>	Same amino acid change as an established pathogenic variant <i>PS1</i>	Predicted null variant in a gene where LOF is a known mechanism of disease <i>PVS1</i>
<b>Functional Data</b>	Well-established functional studies show no deleterious effect <i>BS3</i>		Missense in gene with low rate of benign missense variants and path. missenses common <i>PP2</i>	Mutational hot spot or well-studied functional domain without benign variation <i>PM1</i>	Well-established functional studies show a deleterious effect <i>PS3</i>	
<b>Segregation Data</b>	Non-segregation with disease <i>BS4</i>		Co-segregation with disease in multiple affected family members <i>PP1</i>	Increased segregation data		
<b>De novo Data</b>				<i>De novo</i> (without paternity & maternity confirmed) <i>PM6</i>	<i>De novo</i> (paternity & maternity confirmed) <i>PS2</i>	
<b>Allelic Data</b>		Observed in <i>trans</i> with a dominant variant <i>BP2</i> Observed in <i>cis</i> with a pathogenic variant <i>BP2</i>		For recessive disorders, detected in <i>trans</i> with a pathogenic variant <i>PM3</i>		
<b>Other Database</b>		Reputable source w/out shared data = benign <i>BP6</i>	Reputable source = pathogenic <i>PP5</i>			
<b>Other Data</b>		Found in case with an alternate cause <i>BP5</i>	Patient's phenotype or FH highly specific for gene <i>PP4</i>			

**Human Mutation**  
Variation, Informatics, and Disease

OFFICIAL JOURNAL  
**HGV**  
HUMAN GENOME VARIATION SOCIETY

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

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SPECIAL ARTICLE | [Free Access](#)

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

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

### Evidence Codes Combined for Final Classification:

- Benign, Likely Benign,
- Uncertain Significance,
- Likely Pathogenic, Pathogenic

- Moving towards a more quantitative framework

Article | Published: 04 January 2018

**Genetics in Medicine**

### 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

- A. Identify EP membership
- B. Define scope
- C. Address COI

- D. Develop ACMG/AMP rule specifications for genes

- E. Pilot rules with known variants
- F. Define plans for ongoing variant curation

**APPROVAL**  
**G. ClinVar submission**  


**Step 1: Define WG and plans**

**Step 2: Develop Variant Classification Rules**

**Step 3: Pilot Rules**

**Step 4: Implementation**

Limb Girdle Muscular Dystrophy  
 Hemoglobinopathies  
*ABCD1*  
 Skeletal Dysplasia  
 Craniosynostoses  
 von Willebrand

Glaucoma  
*DICER1*  
 Cerebral Creatine Deficiencies  
 Coagulation Factor Deficiencies  
 HHT/Vascular  
 Breast, ovarian, pancreatic cancer  
 von Hippel-Lindau syndrome  
 Monogenic Diabetes  
 Mitochondrial Diseases  
 VLCAD deficiency

Rett-Angelman  
 Brain Malformations  
*KCNQ1/LQTS*  
*RYR1*/Malignant Hyperthermia  
*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)

The screenshot displays the ClinGen Variant Curation Interface (VCI) with several key components:

- ClinGen Curator Interfaces:** A sidebar on the left provides information about the VCI, including contact details and a link to explore a demo version.
- Evidence Panel:** Shows genomic information (NC\_000222.11g.19963748G>A (GRCh38)), overall ClinVar interpretation (reviewed by expert panel), and a table of interpretations submitted to ClinVar.
- Variant Interpretation Record:** The central panel displays the variant's status (Benign/Pathogenic), basic information (European (Finnish) population), and population criteria evaluation (BA1, PM2, BS1).
- Evaluation Summary:** A detailed table on the right lists criteria meeting an evaluation strength (B/P, Criteria, Criteria Descriptions, Modified, Evaluation Status, Evaluation Explanation) and criteria evaluated as "Not met".

- 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

Met                      Not Met                      Not Evaluated

BA1 BS1 BS2 BS3 BS4 BP1 BP2 BP3 BP4 BP5 BP6 BP7 PP1 PP2 PP3 PP4 PP5 PM1 PM2 PM3 PM4 PM5 PM6 PS1 PS2 PS3 PS4 PVS1

Mouse over a criterion code to see its description; click on it to go to its evaluation section.

## Variant Interpretation Record

Disease + Inheritance +

**Benign** Stand alone: 1 Supporting: 2      **Pathogenic** Moderate: 1      **Calculated Pathogenicity** Uncertain significance - conflicting evidence

Basic Information    Population    Variant Type    Experimental    Case/Segregation    Gene-centric

Missense    Loss of Function    Silent & Intron    In-frame Indel

### Null variant analysis

**PVS1:** Null variant (nonsense, frameshift, canonical +/- 1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease (has caveats) Disease-specific

Not Evaluated    Explanation:

[Sequence Variant Interpretation \(SVI\) Working Group guidance](#) Save

# 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

The screenshot shows the FDA website's navigation bar with the logo and 'U.S. FOOD & DRUG ADMINISTRATION'. Below the navigation bar, there are links for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The main content area is titled 'Medical Devices' and includes a breadcrumb trail: Home > Medical Devices > Products and Medical Procedures > In Vitro Diagnostics > Precision Medicine. The page title is 'FDA Recognition of Public Human Genetic Variant Databases'. Below the title, there are social media sharing options for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print. The main content is a table titled 'List of Recognized Databases'.

Database	Database Recognition Decision Summary	Scope of Recognition (if applicable)	Date Recognized
Clinical Genome Resource (ClinGen)	Decision Summary	Germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (such as high penetrance)	12/4/2018

## Data / People / Process

1

### Required

#### Variant Curation Standard Operating Procedure, Version 1

Detailed documentation outlining the variant curation process.

→ [Variant Curation Standard Operating Procedure, Version 1](#)

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

## 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 <b>FDA RECOGNIZED DATABASE</b> Accession: SCV000930120.1 Submitted: (Jul 23, 2019)	Evidence details Publications PubMed (3) Other databases <a href="https://erepo.clinicalgenome.o...">https://erepo.clinicalgenome.o...</a> 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 20785012, 20786350) (less)

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

# FDA program led to improvements in transparency and access

## ClinGen Evidence Repository

*NM\_000314.7(PTEN):c.1093G>A (p.Val365Ile)*

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

**Uncertain Significance**

**Met criteria codes** 3  
BS3 PP2 PM2

**Unmet criteria codes** 19  
BS1 BS4 BS2 PVS1 PS1  
PS3 PS4 PS2 BP7 BP5  
BP4 BP2 BA1 PP3 PP1  
PM4 PM5 PM1 PM6

**Expert Panel**  
PTEN VCEP

**Evidence Links** 2

Evidence submitted by expert panel

**PTEN VCEP**

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)

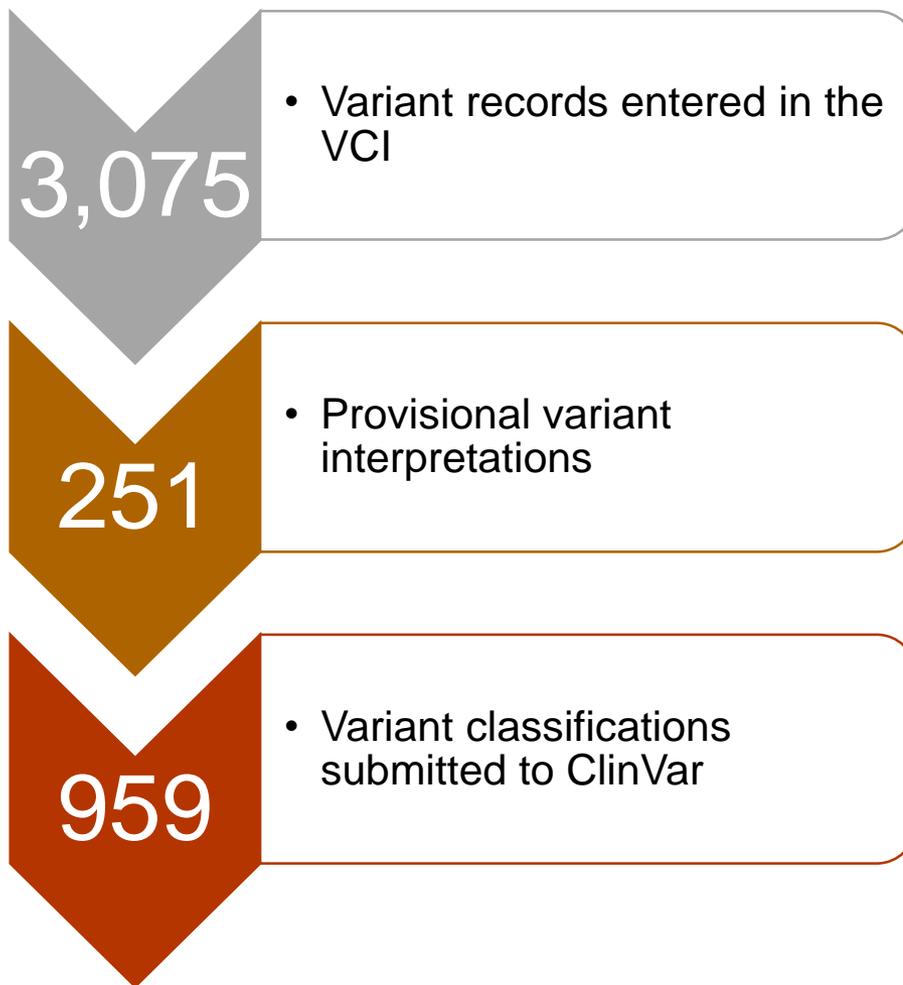
**Met criteria codes**

**BS3** KS: Matreyek results is WT-like (1.140914254). Mighell results is WT-like (-0.102592235). Suggest BS3\_Supporting. FH: BS3 -0.1 Mighell; wt-like abundance in Matreyek (1.14)  
[PubMed](#)  
[PubMed](#)

**PP2** I agree (FH)

# 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.



Gene-Disease Validity

Gene-Disease Validity The Process **Educational and Training Materials** Interface Results

The following documents and presentations are available to help people learn and understand the Gene Disease Validity curation process. For questions about existing materials or requests for new materials, contact us at [clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org).

-  **Standard Operating Procedures**  
Detailed documentation outlining the gene disease validity process.  
[Learn more »](#)
-  **Curation Spreadsheet Template version 5**  
An Excel spreadsheet to guide those groups not using the ClinGen Curation Interface in collecting and documenting evidence. This spreadsheet is for the most current framework (Version 5) that includes the changes in segregation scoring.  
[Learn more »](#)
-  **General Training Presentation**  
Updated February 2018. Focuses on how to use the curation spreadsheet, but also provides general instruction on gene disease validity process.  
[Learn more »](#)
-  **Interactive Training Modules**  
Interactive Powerpoint training modules walk users through basic gene-disease validity curation concepts.  
[Learn more »](#)



D. Azzariti, MS, CGC



E. Riggs, MS, CGC

# Engage and Train the Broader Community



American Board of Medical Genetics and Genomics

**Maintenance of Certification:  
Improvement in Medical Practice**

**ClinGen – Variant Interpretation  
Discrepancy Resolution Module**

Interested in volunteering for curation efforts,  
take our **survey!**

If you have any questions, please feel free to email us at [volunteer@clinicalgenome.org](mailto:volunteer@clinicalgenome.org)



Want to get involved in ClinGen activities?  
We look forward to collaborating with you!  
Here are some ways to participate:



**Sign up for our Mailing List**

Sign up to get ClinGen news and updates delivered to your inbox.

[Learn more »](#)



**Attend ClinGen Events**

Find when and where ClinGen is exhibiting and hosting events.

[Learn more »](#)



**Volunteer to Curate**

Interested in volunteering to curate for ClinGen? Please complete this brief survey.

[Learn more »](#)



**Join the ClinVar Community Call**

Join a monthly call bringing together Clinvar users to discuss topics related to ClinVar.

[Learn more »](#)

The screenshot shows the ClinGen YouTube channel interface. The 'VIDEOS' tab is selected, displaying a grid of video thumbnails with titles and view counts. The videos include:

- English - Clinical Broad Data Sharing Consent Video...** (1.2K views • 1 year ago)
- Introduction to Sequence Variant Nomenclature** (1K views • 11 months ago)
- Introduction to Genomic Variant Interpretation for...** (841 views • 3 years ago)
- ClinGen Dosage Sensitivity Map** (828 views • 3 years ago)
- Evaluating Sequence Variants** (377 views • 3 years ago)
- Evaluating the Clinical Significance of Cytogenomi...** (251 views • 3 years ago)
- GenomeConnect** (232 views • 3 years ago)
- Gene Disease Validity Classifications** (179 views • 1 year ago)
- Why Clinicians Should Learn About Variant Interpretation** (161 views • 11 months ago)
- ClinGen Gene-Disease Validity Scoring Overview** (141 views • 11 months ago)
- Introduction to Genome Builds and Transcripts** (147 views • 11 months ago)
- GenomeConnect: How to Upload Genetic Test Reports** (65 views • 1 year ago)

# Examples of Training Materials

## Variant Pathogenicity Training Materials

- Variant Pathogenicity
- Training Materials
- Documents
- Interface 
- Browse Curations 

Interested in Variant Curation? The following documents and presentations are available to help people learn and understand the variant curation process, as well as ClinGen's efforts to modify ACMG variant assessment criteria. In order to get involved with our Variant Curation activities, please fill out our volunteer survey: <http://bit.ly/clingenvolunteersurvey>. For questions about existing materials or requests for new materials, contact us at [clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org).

- ✓ Training Modules
-  Additional Supporting Materials

1

Required

### Variant Curation Standard Operating Procedure, Version 1

Detailed documentation outlining the variant curation process.

→ [Variant Curation Standard Operating Procedure, Version 1](#)

Start →

2

Required

### 2015 ACMG/AMP Sequence Variant Interpretation Guidelines

The guidelines are freely available through PubMed Commons.

→ [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.](#)

Start →

3

Required

### SVI General Recommendations for Using ACMG/AMP Criteria

SVI provides general recommendations for using the ACMG/AMP criteria to improve consistency in usage and transparency in classification rationale.

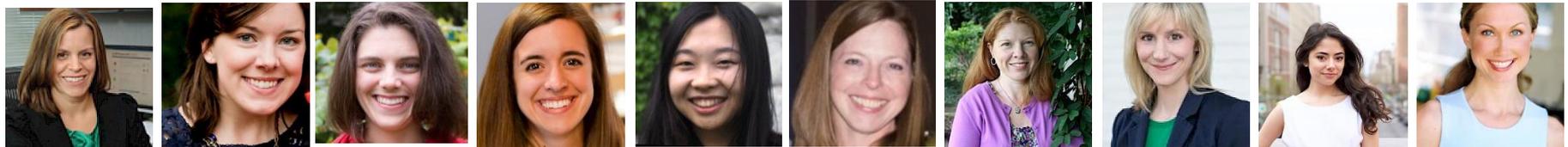
→ [Sequence Variant Interpretation](#)

Start →

# 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 Domain Working Group Oversight Committee reviews VCEP progress.
- Attend ClinGen/DECIPHER “Curating the Clinical Genome” open meeting

# ClinGen Leadership and Coordinators





# Final Considerations

# 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?

## PAR-20-101 Contact Information:

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

### Scientific Contacts:

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### ClinGen Contacts:

- General inquiries:  
[clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org)
- Curation Interface inquiries:  
[clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu)



## Questions?

Only written questions will be answered. Please write questions in the **Q&A bar** at the bottom right of the screen.

Frequently Asked Questions will be posted on:

<https://www.nichd.nih.gov/about/org/der/branches/iddb>

Under the Highlights Section