

# Creating Global Resources to Support Variant Classification



*Heidi L. Rehm, PhD, FACMG*

*Chief Genomics Officer, Center for Genomic Medicine and Department of Medicine, MGH*

*Medical Director, Broad Institute Clinical Research Sequencing Platform*

*Professor of Pathology, MGH, BWH and HMS*

 [@HeidiRehm](https://twitter.com/HeidiRehm)



HARVARD  
MEDICAL SCHOOL



*By Amy Dockser Marcus  
Wall Street Journal*

# The Unfulfilled Promise of DNA Testing

Rapid advances in genetic testing are whipsawing families' diagnoses and treatment

# Esmé Savoie

2011 (birth) – hypotonic, FTT; frequent seizures; cardiac arrest 3.5 mo

- Cytogenomic microarray negative
- 36 epilepsy gene panel > **PCDH19 variant** - early infantile epileptic encephalopathy-9 (EIEE9) – not a perfect phenotype match but family grabbed onto it
- Family found an online support group started by parents of children with PCDH19 gene; started a foundation and raised money for PCDH19 research. Highly engaged for 2 years but noticed her daughter was not like other PCDH19 kids

2015 – variant reclassified and ruled out

- Exome testing - **SCN8A VUS** – new finding associated with EIEE
- The foundation she set up stopped funding future PCDH19 projects and started fundraising for SCN8A research.

2016 – exome reinterpreted – SCN8A still VUS but now also found two other gene variants, labeled “likely pathogenic” and “pathogenic”



Over 6 years ago, my lab detected a PTPN11 variant in a **fetus with increased nuchal translucency** seen on fetal ultrasound

It had been observed in an Ashkenazi Jewish patient with Noonan syndrome and was **reported as pathogenic** by a well-respected lab.

I had tried to get access to a **research dataset of Ashkenazi Jewish individuals** to determine the allele frequency and was **denied**.

We reported it as Likely Pathogenic and the couple **terminated the pregnancy**.

Later we found out that the variant had a high frequency in the AJ population and was **benign**

The Atlantic Popular Latest Sections Magazine More Subscribe

SCIENCE

## Clinical Genetics Has a Big Problem That's Affecting People's Lives

Unreliable research can lead families to make health decisions they might regret.

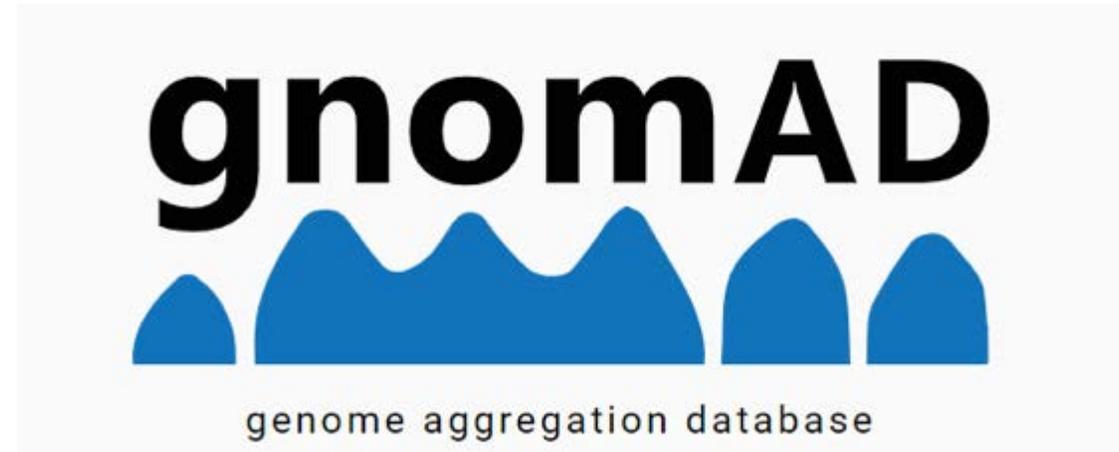
ED YONG DEC 16, 2015



CHERYL RAVELO / REUTERS

The image shows a hand holding a fetal ultrasound printout in a clinical setting. In the background, a pregnant woman is lying on a gynecological exam table. The printout shows several ultrasound images of a fetus. In the bottom right corner, there is a small inset video of a woman with glasses speaking.

6 years later we now have:



July 2017 – Prenatal genetic testing, prompted by increased NT, revealed a VUS (BRAF Ile208Val)  
 Concerned about their pregnancy, a couple contacted me based on our ClinVar entry

Clinical assertions	Summary evidence	Supporting observations					
Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Accession
Uncertain significance (Jul 18, 2013)	criteria provided, single submitter • <a href="#">LMM Criteria</a>	clinical testing	not specified <a href="#">[MedGen]</a>	germline	• <a href="#">PubMed (1)</a> <a href="#">[See all records that cite this PMID]</a>	<a href="#">Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine</a>	SCV000205449.3
Uncertain significance (Sep 28, 2016)	criteria provided, single submitter • <a href="#">GeneDx Variant</a>	clinical testing	not specified <a href="#">[MedGen]</a>	germline		<a href="#">GeneDx</a>	SCV000329576.3

Full description for Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine

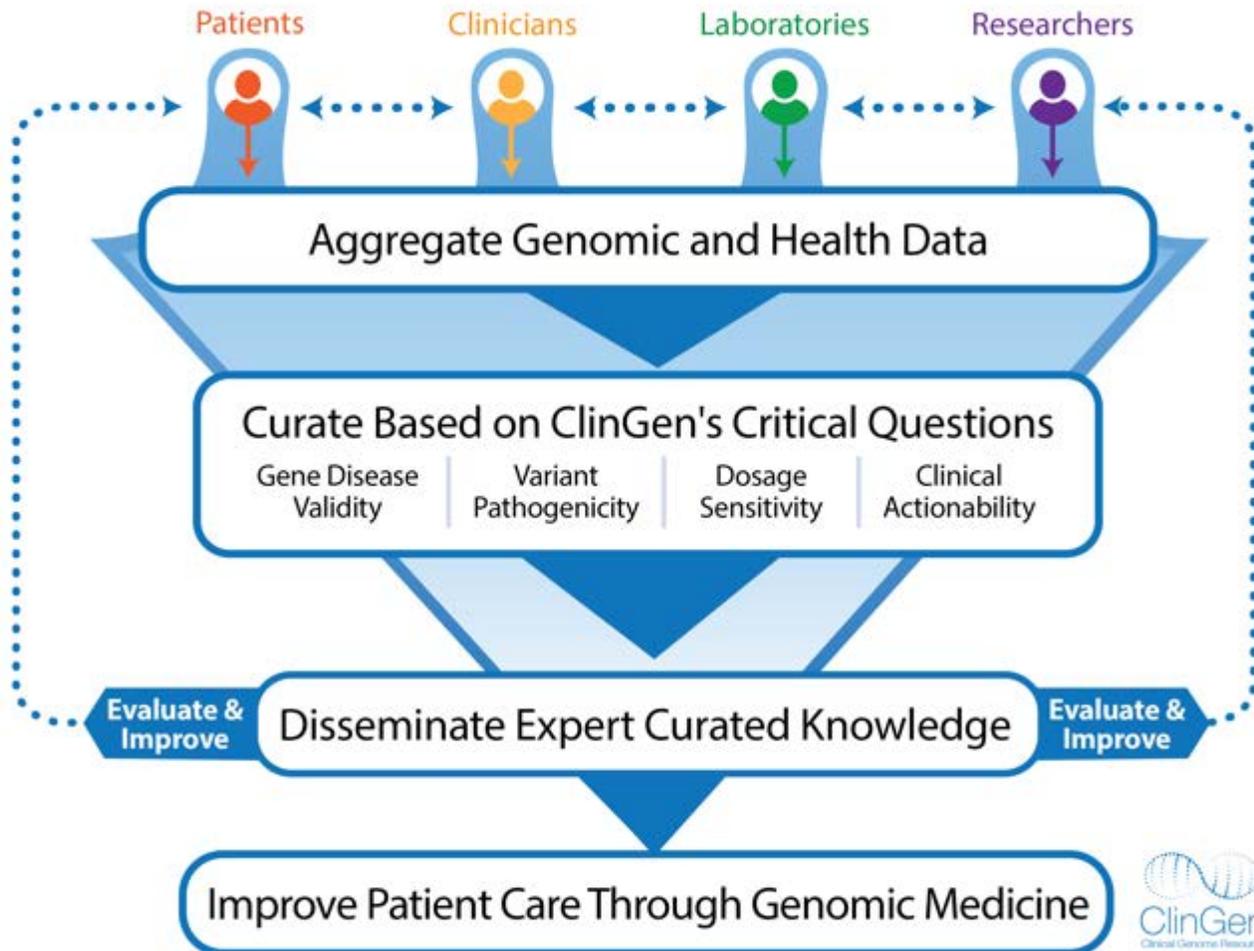
Germline

The Ile208Val variant in BRAF has previously been observed in one individual with clinical features of Noonan spectrum disorder and one reportedly unaffected individual tested by our laboratory. This variant has not been identified in large population studies. Ile208Val has been reported in a melanoma cell line which also carried Val600Glu, a well-characterized activating mutation (Ikediobi 2006). Computational analyses (biochemical amino acid properties, conservation, AlignGVGD, PolyPhen2, and SIFT) do not provide strong support for or against an impact to the normal function of the protein. In summary, additional information is needed to fully assess the clinical significance of the Ile208Val variant.

**New interpretation in ClinVar:** We observed the Ile208Val variant in BRAF in one individual with middle aortic syndrome, low nasal bridge, hypertension, facial coarseness, short stature, learning disabilities/mental retardation, wide-spaced nipples and webbed neck and her reportedly unaffected parent, both tested by our laboratory. **The variant was also found in a fetus with increased nuchal translucency and her unaffected father (personal communication with the mother via our ClinVar entry) and in three tested families from GeneDx without clinical features of a RASopathy.** This variant has also been population at a frequency of 3/276842 alleles (gnomAD, rs727504571). Ile208Val has been reported in a which also carried Val600Glu, a well-characterized activating mutation (Ikediobi 2006). Computational amino acid properties, conservation, AlignGVGD, PolyPhen2, and SIFT) do not provide strong support for to the normal function of the protein. In summary, based upon the 3 observations in the general population observations in unaffected parents this variant is **likely benign**.



# The Clinical Genome Resource



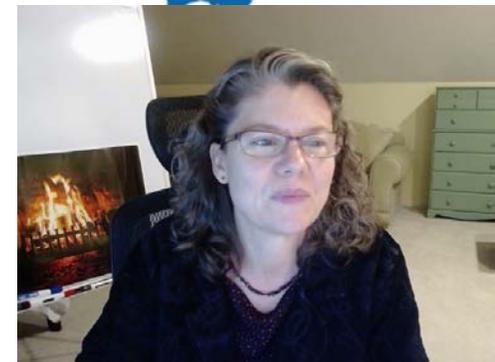
[www.clinicalgenome.org](http://www.clinicalgenome.org)

**Purpose:** Create an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

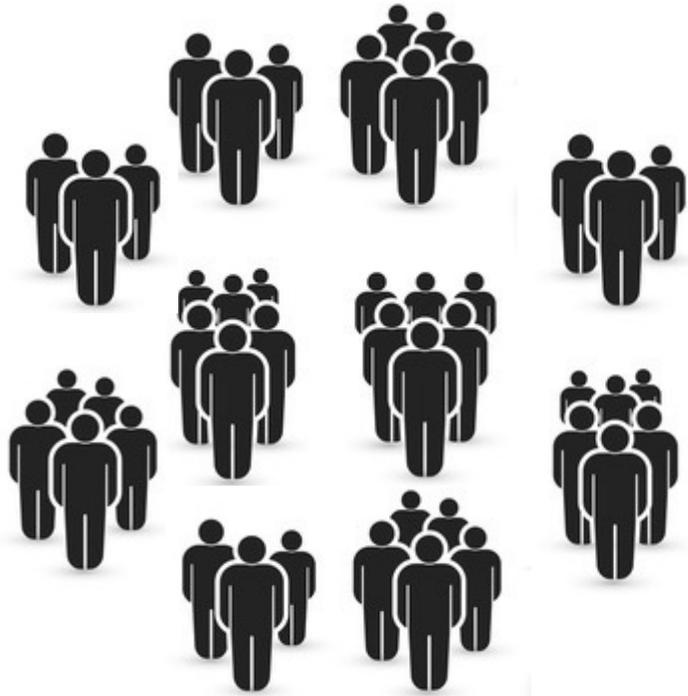
- *Started September 2013*
- *Primarily funded by the NIH*
  - *3 Core U41 Grants (NHGRI)*
  - *Disease-focused U24s (NIH)*



1,557 investigators  
across 36 countries



# What's the difference between ClinGen and ClinVar?



**ClinGen**

(consortium of people sharing data, developing standards and curating knowledge)



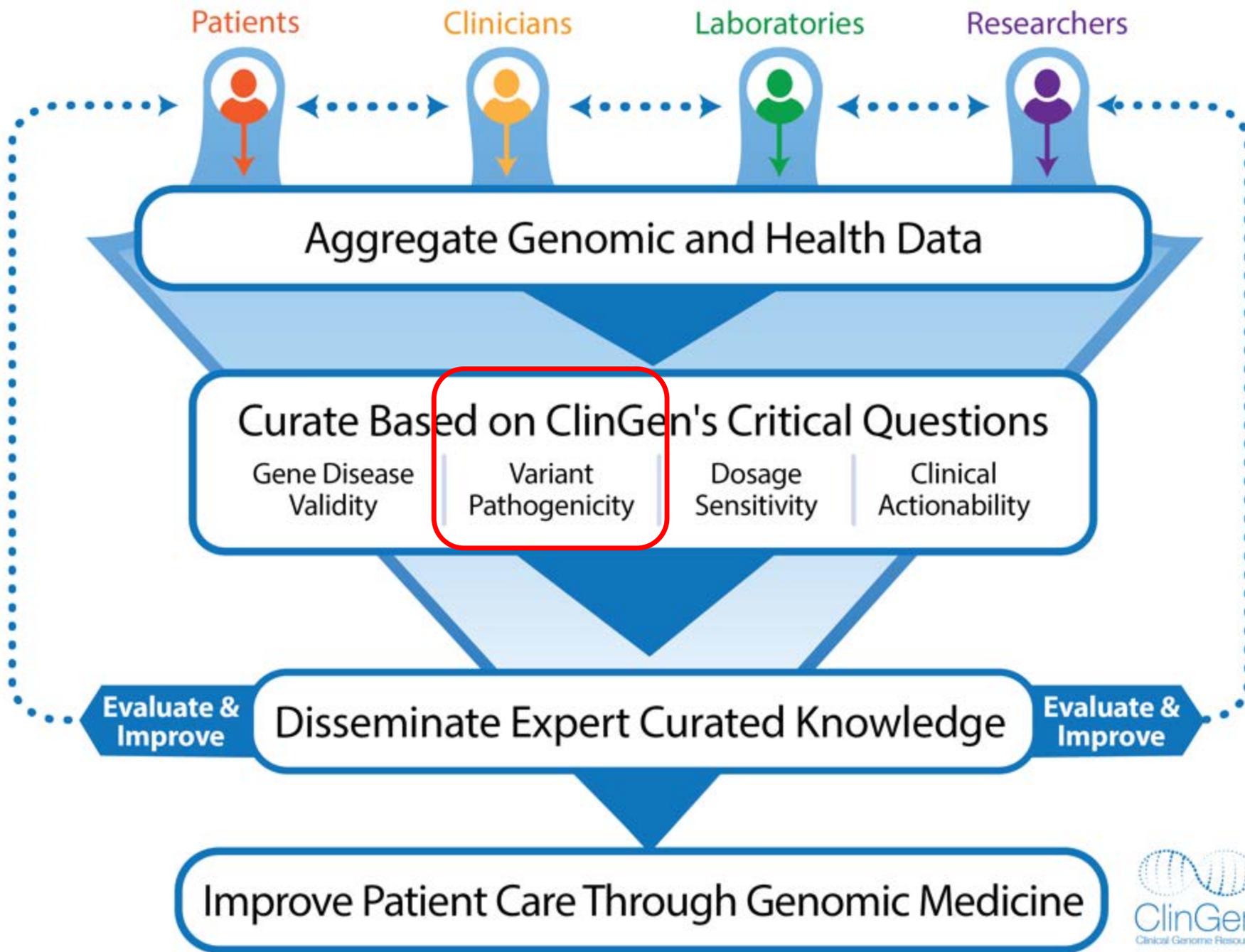
**ClinVar**

(database for sharing variant level knowledge)



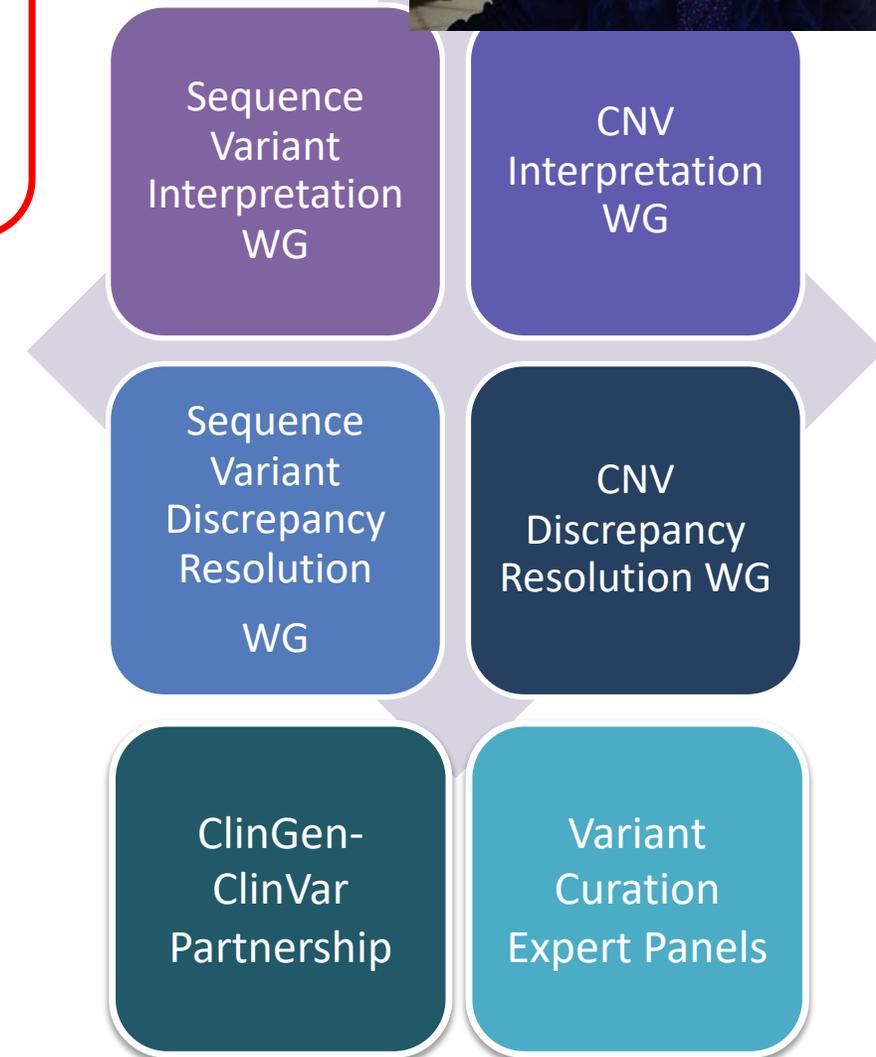
**ClinicalGenome.org**

(database for sharing gene level knowledge)



# Supporting Variant Classification

- Use of common standards
  - Terminology
  - Rules for variant interpretation
- Public sharing of variant classifications
  - Creates transparency and crowd-sources the work
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven classification of variants (Expert Panels)



**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
Population Data	MAF is too high for disorder BAI/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 BP4 Missense when only truncating cause disease BP5 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 PS2	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	Non-segregation with disease BS4		Co-segregation with disease in multiple affected family members PP2	Increased segregation data		
De novo Data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity & 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 BS5	Reputable source = pathogenic PS5			
Other Data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PH4			

Pathogenic  
Likely pathogenic  
Uncertain significance  
Likely benign  
Benign

Adopted worldwide



# ClinGen Sequence Variant Interpretation Working Group



Les Biesecker

Co-Chairs



Steven Harrison

## Goals of ClinGen SVI

1. Refine and evolve the ACMG/AMP guidelines as they are tested and deployed by the community
2. Review and harmonize gene and disease specifications provided by Variant Curation Expert Panels
3. Move the ACMG/AMP guideline towards a more quantitative framework

# Sequence Variant Interpretation

The goal of the Sequence Variant Interpretation Working Group (SVI WG) is to support the refinement and evolution of the [ACMG/AMP Interpreting Sequence Variant Guidelines](#) to develop quantitative approaches to variant interpretation.

Subgroups

Documents

Tools

Membership



Official journal of the American College of Medical Genetics and Genomics

SPECIAL ARTICLE **Genetics  
inMedicine**

Open

## Adaptation and validation of the ACMG/AMP variant classification framework for *MYH7*-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel

Melissa A. Kelly, MS<sup>1</sup>, Colleen Caleshu, MS<sup>2</sup>, Ana Morales, MS<sup>3</sup>, Jillian Buchan, PhD<sup>1</sup>, Zena Wolf, PhD<sup>1</sup>, Steven M. Harrison, PhD<sup>1</sup>, Stuart Cook, MD<sup>4</sup>, Mitchell W. Dillon, MS<sup>1</sup>, John Garcia, PhD<sup>5</sup>, Eden Haverfield, PhD<sup>5</sup>, Jan D.H. Jongbloed, PhD<sup>6</sup>, Daniela Macaya, PhD<sup>7</sup>, Arjun Manrai, PhD<sup>8</sup>, Kate Orland, MS<sup>9</sup>, Gabriele Richard, MD<sup>7</sup>, Katherine Spoonamore, MS<sup>10</sup>, Matthew Thomas, MS<sup>11</sup>, Kate Thomson, BSc<sup>12,13</sup>, Lisa M. Vincent, PhD<sup>7</sup>, Roddy Walsh, PhD<sup>4,14</sup>, Hugh Watkins, MD PhD<sup>13</sup>, Nicola Whiffin, PhD<sup>4,14</sup>, Jodie Ingles, PhD<sup>15</sup>, J. Peter van Tintelen, MD PhD<sup>16</sup>, Christopher Semsarian, MBBS PhD<sup>15</sup>, James S. Ware, PhD MRCP<sup>4,14</sup>, Ray Hershberger, MD<sup>3</sup> and Birgit Funke, PhD<sup>1,17,18</sup>; for the ClinGen Cardiovascular Clinical Domain Working Group<sup>19</sup>

### Chairs

Leslie G. Biesecker, MD  
Steven Harrison, PhD

### Coordinators

Please contact a coordinator for questions.

Danielle Azzariti, MS, Co-Coordinator  
dazzariti@broadinstitute.org

© American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE **Genetics  
inMedicine**

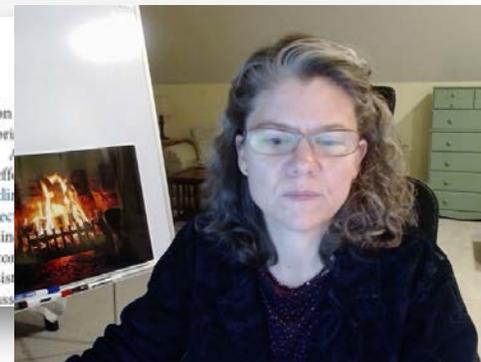
## ClinGen's RASopathy Expert Panel consensus methods for variant interpretation

Bruce D. Gelb, MD<sup>1</sup>, Hélène Cavé, PharmD, PhD<sup>2</sup>, Mitchell W. Dillon, MS<sup>3</sup>, Karen W. Gripp, MD<sup>4</sup>, Jennifer A. Lee, PhD<sup>5</sup>, Heather Mason-Suares, PhD<sup>6</sup>, Katherine A. Rauen, MD, PhD<sup>7</sup>, Bradley Williams, MS<sup>8</sup>, Martin Zenker, MD<sup>9</sup>, Lisa M. Vincent, PhD<sup>10</sup> and for the ClinGen RASopathy Working Group

© American College of Medical Genetics and Genomics

## The ACMG/AMP reputable source criteria for the interpretation of sequence variants

To the Editor: In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) promulgated recommendations for



The Sequence Variant Interpretation WG also consults with and supports Expert Panel groups to develop gene- and disease-specific refinements of the ACMG/AMP Interpreting Sequence Variant Guidelines to increase the uniformity and consistency of the Expert Panel recommendations. The SVI WG has representation from the Biocurators WG, CNV Interpretation WG and Variant Curation Interface development team and all ClinGen Expert Panels.

## 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.

- Guidance on how to rename criteria codes when strength of evidence is modified
- BA1: Updated Recommendation for the ACMG/AMP Stand Alone Pathogenicity Criterion for Variant Classification
  - BA1 Exception List (July 2018)
  - BA1 Exception List Nomination Form
- PVS1: Recommendations for Interpreting the Loss of Function PVS1 ACMG/AMP Variant Criteria
- PS2/PM6: Recommendation for de novo PS2 and PM6 ACMG/AMP criteria (Version 1.0)
- PS3/BS3: Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework
- PM3: Recommendation for in trans Criterion PM3 (Version 1.0)
- PP5/BP6: Recommendation for reputable source PP5 and BP6 ACMG/AMP criteria



SVI Approved Expert Panel Specified ACMG/AMP Variant Interpretation Guidelines

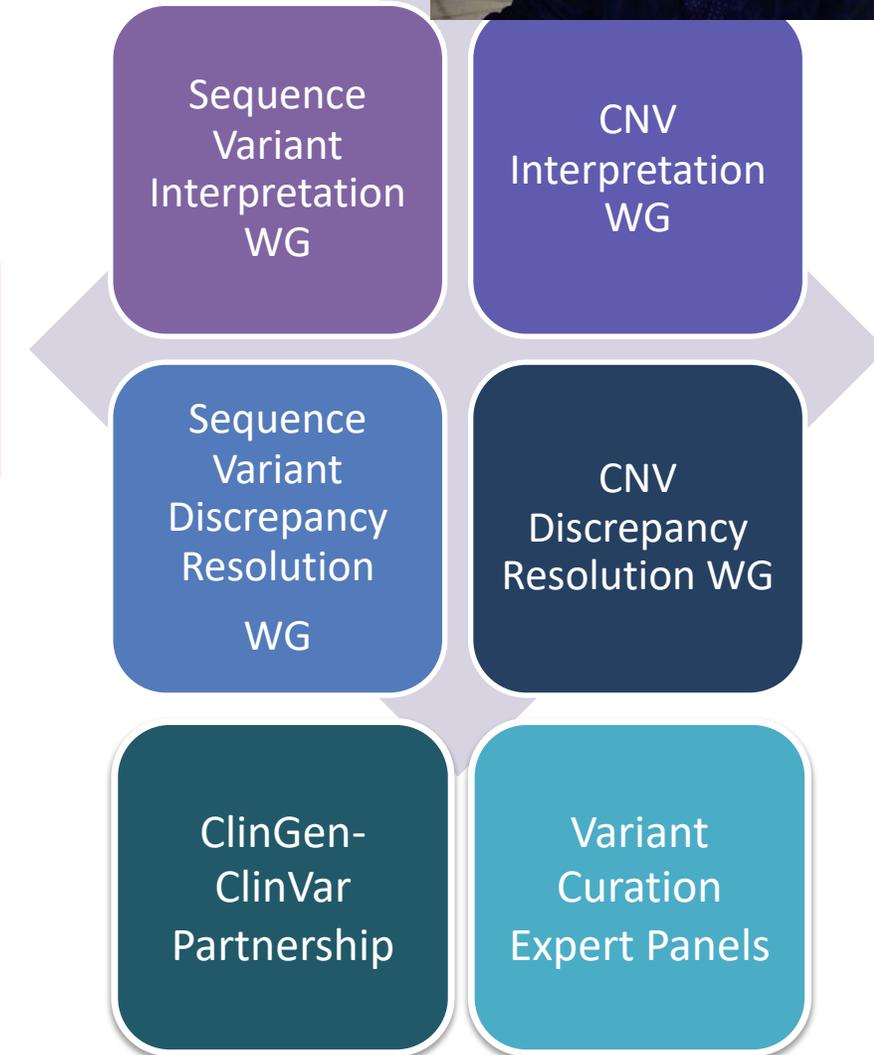


General SVI Publications

► Recommendations for interpreting the lo

# Supporting Variant Classification

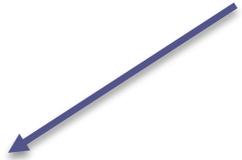
- Use of common standards
  - Terminology
  - Rules for variant interpretation
- Public sharing of variant classifications
  - Creates transparency and crowd-sources the work
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven classification of variants (Expert Panels)



# Rare Variants in African Individuals with Rare Disease



Majority are VUS



Common in Ancestrally  
**Matched** Population



Benign

It is Critical to **Obtain**  
**African** Data for  
African Rare Disease  
Studies



Common in Ancestrally  
**Distinct** Population



Benign

It is Also Critical to **Access**  
**Non-African** Data for  
African Rare Disease  
Studies



Rare in All  
Populations



**Need global data  
sharing of evidence  
and shared efforts in  
variant classification**

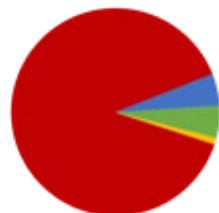
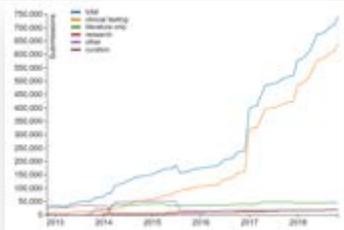
# Global ClinVar Submissions – January 18<sup>th</sup>, 2020

1,341,674 submissions on 858,329 unique variants  
1790 submitters from 80 countries

84% of data in ClinVar are from the top 20 (1.1%) submitters, 14 of which are commercial clinical labs



Invitae	392984
Illumina	208455
GeneDx	121912
Ambry Genetics	72593
Emory/Eurofins	45028
Color	43495
OMIM	32020
Partners LMM	24235
Counsyl	20976
CeGaT - Tuebingen	20219
LabCorp/Integrated	18507
Prevention Genetics	18417
Cincinnati CHMC	17788
Natera	15814



89% Clinical testing  
5% Online resources (OMIM, GeneReviews, UniProt, LSDBs)  
5% Research  
1% Expert Panels and Professional Guidelines

Univ Chicago  
Quest Diagnostics  
Athena Diagnostics  
ARUP Laboratories  
Mendelics  
ENIGMA



# Each country defines arguments for sharing variant-level classifications

## Arguments for Clinical Labs:

- ✓ Improved Variant Classification
- ✓ Shared Evidence Base
- ✓ Standardization and Quality Control
- ✓ Addresses Evolving Regulatory and Medical Standards
- ✓ Keep Providers Up-to-Date with Variant Knowledge



2013

Our AMA: (1) encourages payers, regulators and providers to make clinical assays that assure patient and provider privacy protection; and (2) encourages laboratories to share clinical significance of these results, into the public domain which would allow for the public's health.

2015

### Clinical Data Sharing

The National Society of Genetic Counselors (NSGC) advocates for the sharing of phenotype and interpretation data acquired through genetic and genomic testing. Timely data sharing can improve accuracy of variant interpretation, protect patient confidentiality and should label variants that underlies any variant classification. By sharing variants, data-sharing allows for more consistent interpretation across laboratories. For this reason, responsible data sharing is a key component of any genetic testing plan.

### Benefits of Sharing Variant Classifications and Evidence with ClinVar

Given the rarity of most variants of clinical relevance, it is imperative that genomic variant classifications and supporting evidence are shared in a public, centralized database such as ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) to improve both our understanding of genomic variation and patient care that relies on this information.

#### Improved Variant Classification

Sharing variant classifications with ClinVar allows laboratories to identify classification differences with other ClinVar submitters and work towards consensus, providing more accurate and consistent results to patients.

- ClinVar provides a broader set of clinical classifications than users may have assessed in their own clinical laboratory. Data can be retrieved programmatically via APIs, which allows users to incorporate the information into their own workflows ([https://www.ncbi.nlm.nih.gov/clinvar/docs/maintenance\\_usage/#api](https://www.ncbi.nlm.nih.gov/clinvar/docs/maintenance_usage/#api))
- ClinVar provides a monthly report of conflicting classifications which submitters can use to prioritize reassessment (<https://ftp.ncbi.nlm.nih.gov/pub/clinvar/>)
- Studies of clinical laboratory ClinVar submitters have shown data sharing is a successful approach to prioritizing variant reassessment and resolving classification differences.<sup>1,2,3</sup>

#### Keep Providers Up-to-Date with Variant Knowledge

- Classifications change over time and providers, patients and scientists in the community need to be kept up-to-date. Directing inquiries to ClinVar for current knowledge can reduce resources needed to respond to inquiries on current variant classifications.

#### Adds Value through Standardization and Quality Control

ClinVar adds value to submitted classifications by standardizing descriptions of variants, conditions, and terms for clinical significance.

- Variants are mapped to reference sequences and reported in HGVS. This provides a quality control check for accurate nomenclature.
- Clinical significance terms for Mendelian disorders are converted to standard ACMG-AMP categories (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign), enabling comparison across laboratories.
- As many variants identified in Mendelian disease testing are extremely rare and thus unlikely to be re-observed, sharing variant interpretations in ClinVar is an ongoing quality assurance measure for laboratory reassessment of rare variants.

#### Publicity as a Lab that Shares Data

- ClinGen recognizes submitters meeting minimum requirements for data sharing to support quality assurance (<https://www.clinicalgenome.org/lablist/>).
- Submitters receive recognition by ClinGen at meetings and conferences for sharing data.
- Submitters are displayed on the ClinVar website ([https://www.ncbi.nlm.nih.gov/clinvar/docs/submitter\\_list/](https://www.ncbi.nlm.nih.gov/clinvar/docs/submitter_list/)).

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

© American College of Medical Genetics and Genomics

2017

ACMG STATEMENT | Genetics in Medicine

Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics

ACMG Board of Directors<sup>1</sup>

<https://www.clinicalgenome.org/share-your-data/>

# Laboratories Meeting Minimum Requirements for Data Sharing to Support Quality Assurance

## Goals:

1. To publicly recognize clinical labs who support data sharing and incentivize others to share as well
2. To provide a list of clinical labs to hospitals, healthcare providers, and insurers who wish to only order from, or reimburse, labs meeting a certain standard in data sharing and quality assurance

15 labs meet requirements  
USA(14), Greece

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

Laboratory	Meets Requirements	Additional Achievements		
		>95% from past 5 years <sup>1</sup>	Discrepancy resolution <sup>2</sup>	Consenting mechanism <sup>3</sup>
Ambry	✓	🏆	🏆	🏆
ARUP	✓		🏆	🏆
Athena Diagnostics Inc.	✓		🏆	🏆
Center for Genomics, Ann & Robert H. Lurie Children's Hospital of Chicago	✓	🏆	🏆	🏆
Center for Pediatric Genomic Medicine, Children's Mercy Hospital and Clinics	✓		🏆	
Color Genomics, Inc.	✓	🏆	🏆	🏆
GeneDx	✓		🏆	🏆
GeneKor MSA	✓	🏆	🏆	🏆
Illumina	✓	🏆	🏆	🏆
Integrated Genetics/Laboratory Corporation of America	✓	🏆	🏆	🏆
Invitae	✓	🏆	🏆	🏆
Myriad Women's Health	✓	🏆	🏆	🏆
Partners Laboratory for Molecular Medicine	✓	🏆	🏆	🏆
Quest Diagnostics Nichols Institute San Juan Capistrano	✓		🏆	🏆
University of Chicago	✓	🏆	🏆	🏆

Some requirements and additional achievements based on self-reported data by laboratory

\*Most recent submission pending ClinVar processing

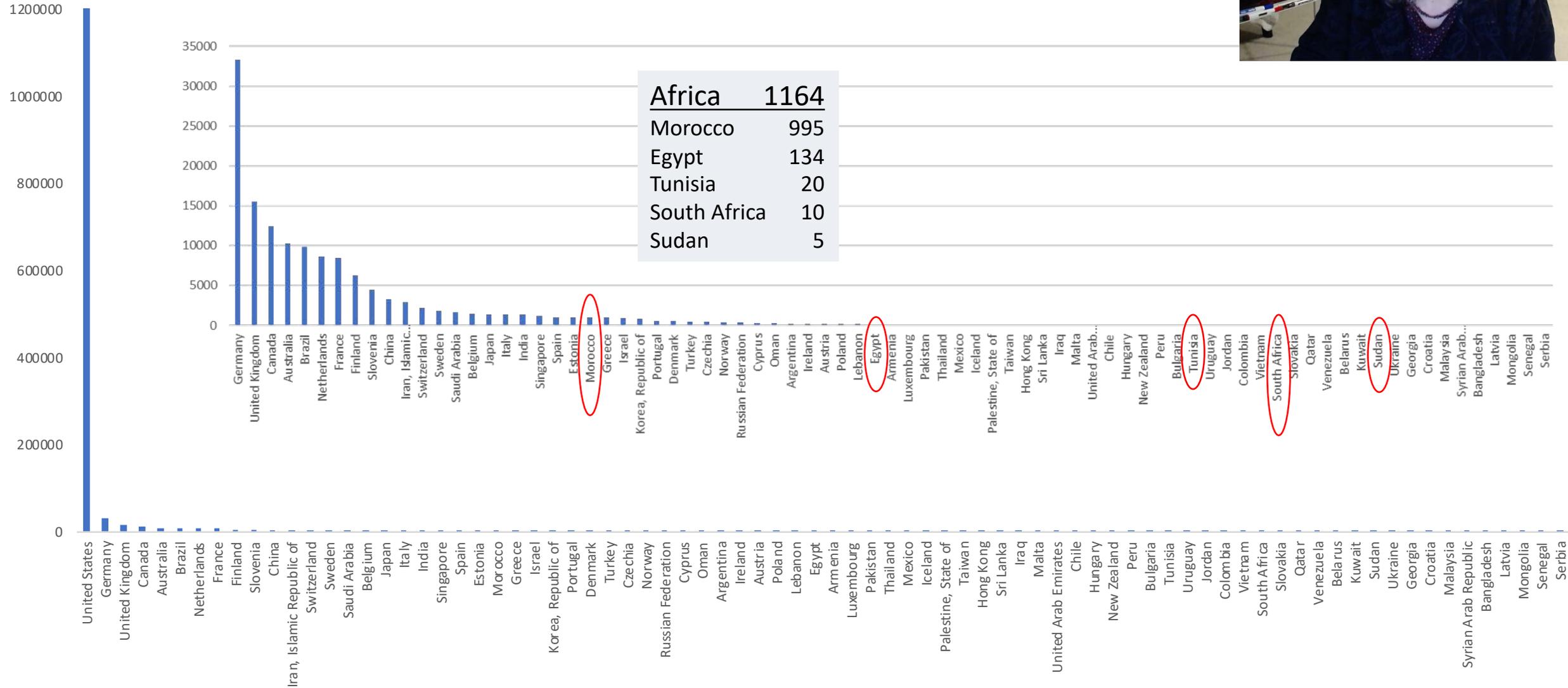
<sup>1</sup>>95% of classified sequence and/or copy number variants from past 5 years submitted

<sup>2</sup>Actively working to resolve interlab interpretation differences

<sup>3</sup>Laboratory actively supports use of a consenting mechanism to enable patients to directly consent to share detailed, individual-level clinical data (e.g., an internal patient registry made available for collaborative research, or report language highlighting external registries such as GenomeConnect)



# Submissions to ClinVar by Country



<b>Africa</b>	<b>1164</b>
Morocco	995
Egypt	134
Tunisia	20
South Africa	10
Sudan	5

# Shariant - A Country-Specific Variant-Level Database



## Shariant = share variants

### VARIANT CLASSIFICATION SHARING PLATFORM

Share clinically curated variants with structured supporting evidence and phenotypes between Australian labs

Allow collaborative monitoring & review of curated variants

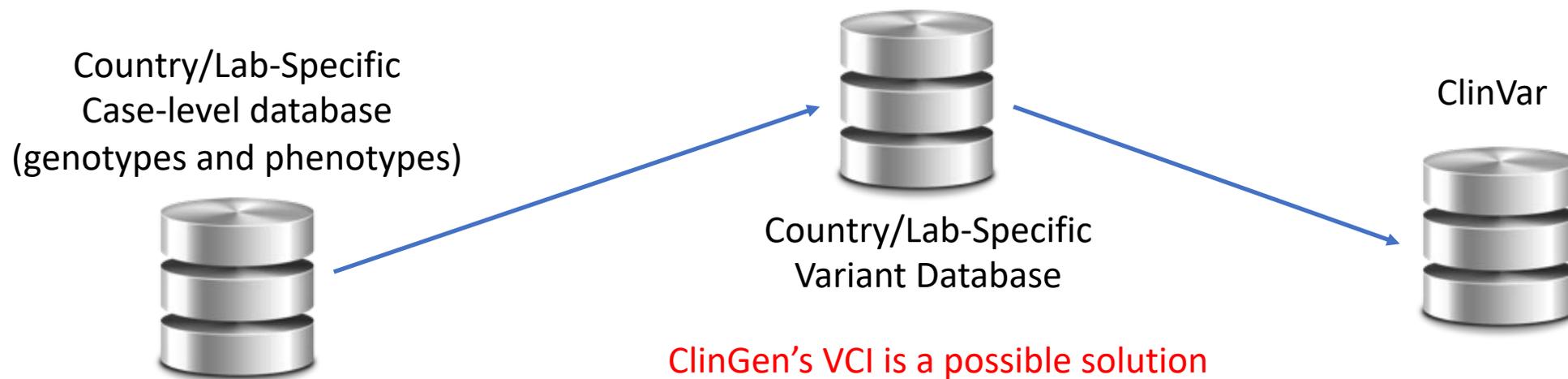
Act as a central administrative node for submission to international databases such as ClinVar



# Database Ecosystems Needed for Each Country



- Every lab/country needs a place to maintain their own variant classifications (often with case-level data) that can be managed on a daily basis. ClinVar does not serve this purpose.
- **Case-level data** storage requires additional protections (e.g. controlled access).
- ClinVar has become the primary database for “sharing, comparing, distributing and accessing” variant interpretations with the community



## Points to consider for sharing variant-level information from clinical genetic testing with ClinVar

Danielle R. Azzariti,<sup>1,6</sup> Erin Rooney Riggs,<sup>2,6</sup> Annie Niehaus,<sup>3</sup> Laura Lyman Rodriguez,<sup>3</sup> Erin M. Ramos,<sup>3</sup> Brandi Kattman,<sup>4</sup> Melissa J. Landrum,<sup>4</sup> Christa L. Martin,<sup>2,6</sup> and Heidi L. Rehm<sup>1,5,6</sup>

<sup>1</sup>Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine, Cambridge, Massachusetts 02139, USA; <sup>2</sup>Autism & Developmental Medicine Institute, Geisinger, Danville, Pennsylvania 17837, USA; <sup>3</sup>National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20894, USA; <sup>4</sup>National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Rockville, Maryland 20894, USA; <sup>5</sup>Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA

**Abstract** Data sharing between laboratories, clinicians, researchers, and patients is essential for improvements and standardization in genomic medicine; encouraging genomic data sharing (GDS) is a key activity of the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen). The ClinGen initiative is dedicated to evaluating the clinical relevance of genes and variants for use in precision medicine and research. Currently, data originating from each of the aforementioned stakeholder groups is represented in ClinVar, a publicly available repository of genomic variation, and its relationship to human health hosted by the National Center for Biotechnology Information at the NIH. Although policies such as the 2014 NIH GDS policy are clear regarding the mandate for informed consent for broad data sharing from research participants, no clear guidance exists on the level of consent appropriate for the sharing of information obtained through clinical testing to advance knowledge. ClinGen has collaborated with ClinVar and the National Human Genome Research Institute to develop points to consider for clinical laboratories on sharing de-identified variant-level data in light of both the NIH GDS policy and the recent updates to the Common Rule. We propose specific data elements from interpreted genomic variants that are appropriate for submission to ClinVar when direct patient consent was not sought and describe situations in which obtaining informed consent is recommended.

### INTRODUCTION

The benefits of genomic data sharing (GDS), including the potential to improve clinical interpretation of genomic variants and advance genomic medicine, are widely recognized, and the practice has been endorsed by both professional societies and funding agencies (American Medical Association 2013; National Institutes of Health 2014; National Society of Genetic Counselors 2015; ACMG Board of Directors 2017). One of the aims of the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen) (Rehm et al. 2015) is to create a publicly available knowledge base of clinically relevant genes and variants for use in precision medicine and research. As shared genomic data help

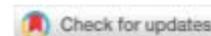
\*These authors contributed equally to this work.

Corresponding author:  
dazzariti@partners.org

© 2018 Azzariti et al. This article is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted reuse and redistribution provided that the original author and source are credited.

Published by Cold Spring Harbor Laboratory Press

doi: 10.1101/mcs.a002345



### OPEN LETTER

## Genomic variant sharing: a position statement [version 1; referees: 1 approved, 1 approved with reservations]

Caroline F. Wright<sup>1</sup>, James S. Ware<sup>2</sup>, Anneke M. Lucassen<sup>3</sup>, Alison Hall<sup>4</sup>, Anna Middleton<sup>5,6</sup>, Nazneen Rahman<sup>7</sup>, Sian Ellard<sup>1</sup>, Helen V. Firth<sup>8,9</sup>

<sup>1</sup>Institute of Biomedical and Clinical Science, University of Exeter, Exeter, UK

<sup>2</sup>National Heart and Lung Institute, Imperial Centre for Translational and Experimental Medicine, London, UK

<sup>3</sup>Department of Clinical Ethics and Law, Faculty of Medicine, University of Southampton, Southampton, UK

<sup>4</sup>PHG Foundation, Cambridge, UK

<sup>5</sup>Faculty of Education, University of Cambridge, Cambridge, UK

<sup>6</sup>Connecting Science, Wellcome Genome Campus, Cambridge, UK

<sup>7</sup>Division of Genetics and Epidemiology, Institute of Cancer Research, UK, London, UK

<sup>8</sup>Department of Clinical Genetics, University of Cambridge Addenbrooke's Hospital Cambridge, Cambridge, UK

<sup>9</sup>Wellcome Trust Sanger Institute, Cambridge, UK

**V1** First published: 05 Feb 2019, 4:22 (<https://doi.org/10.12688/wellcomeopenres.15090.1>)

Latest published: 05 Feb 2019, 4:22 (<https://doi.org/10.12688/wellcomeopenres.15090.1>)

### Abstract

Sharing de-identified genetic variant data is essential for the practice of genomic medicine and is demonstrably beneficial to patients. Robust genetic diagnoses that inform medical management cannot be made accurately without reference to genetic test results from other patients, as well as population controls. Errors in this process can result in delayed, missed or erroneous diagnoses, leading to inappropriate or missed medical interventions for the patient and their family. The benefits of sharing individual genetic variants, and the harms of *not* sharing them, are numerous and well-established. Databases and mechanisms already exist to facilitate deposition and sharing of pseudonomised genetic variants, but clarity and transparency around best practice is needed to encourage widespread use, prevent inconsistencies between different communities, maximise individual privacy and ensure public trust. We therefore recommend that widespread sharing of a small number of individual genetic variants associated with limited clinical information should become standard practice in genomic medicine. Information robustly linking genetic variants with specific conditions is fundamental biological knowledge, not personal information, and therefore should not require consent to share. For additional case-level detail about individual patients or more extensive genomic information, which is often essential for clinical interpretation, it may be more appropriate to use a controlled-access model for data sharing, with the ultimate aim of making as much information as open and de-identified as possible with appropriate consent.

### Keywords

medical genomics, variant, data sharing, data ethics

### Open Peer Review

Referee Status: ? ✓

	Invited Referees	
	1	2
version 1 published 05 Feb 2019	? report	✓ report
1	Gert Matthijs <sup>1</sup> , KU Leuven, Belgium	
2	Christa L. Martin, Geisinger Health	





# When is consent required for sharing?

- Consent is **not required** for sharing **variant interpretations with summarized evidence**
- Individual consent allows more detailed sharing
- ClinGen videos in English, French, Spanish and Chinese explain the difference

English - Clinical Broad Data Sharing Consent Video

GENE	VARIANT	TOTAL	SEX	RACE/ETHNICITY	HEALTH DETAILS
BRCA1	R1495M	5	4 Female	2 Caucasian	4 Breast cancer
			1 Male	1 African American	1 Ovarian cancer
				2 Not specified	1 Developmental Delay

Summary Information

00:03:05:24

Consent not required

English - Clinical Broad Data Sharing Consent Video

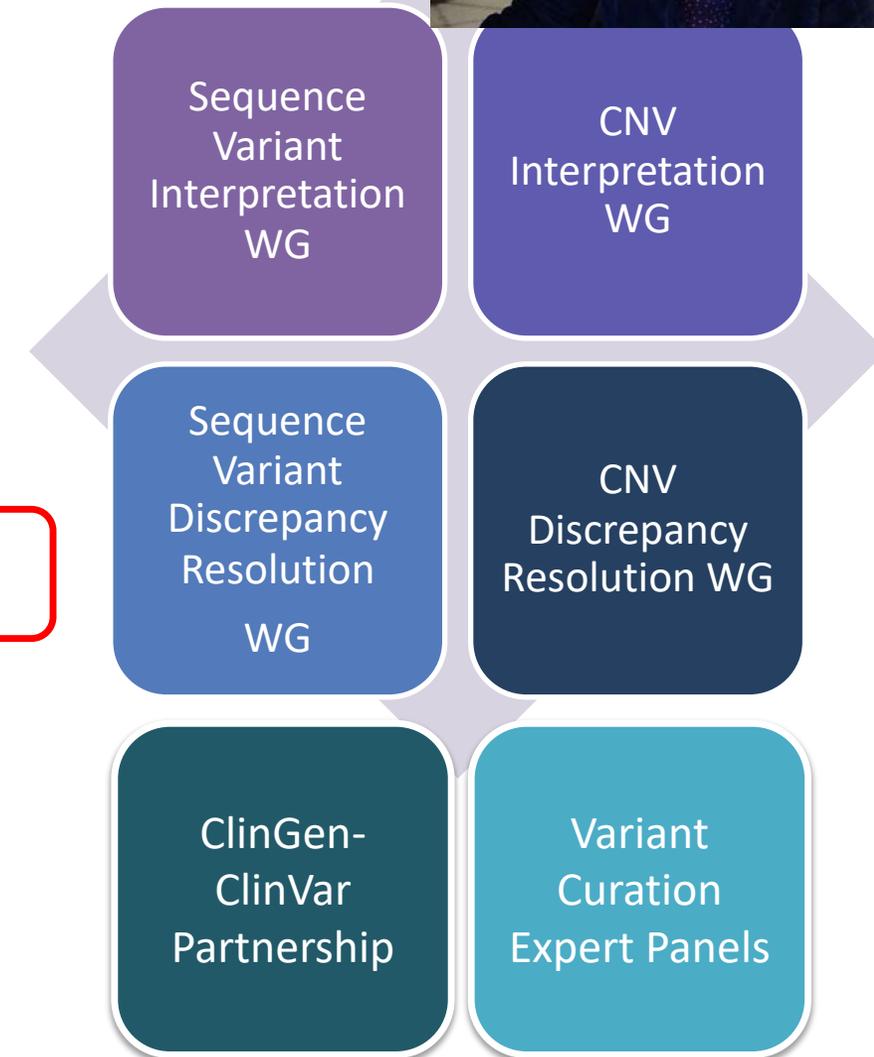
### Individual Information

GENE	PARTICIPANT	SEX	AGE	RACE/ETHNICITY	HEALTH DETAILS	OTHER GENETIC CHANGES
BRCA1 Variant R1495M	343Ds2	Female	50	African American	Breast cancer	No
	574GC1	Female	35	Caucasian	Breast cancer	No
	854GE1	Female	34	Unknown	Ovarian cancer	No
	CF234H	Female	23	Caucasian	Breast cancer Developmental delay	Yes chr8:103066066-104430435 x 1 (GRCh37/hg19)
	917HB1	Male	45	Unknown	Breast cancer	No

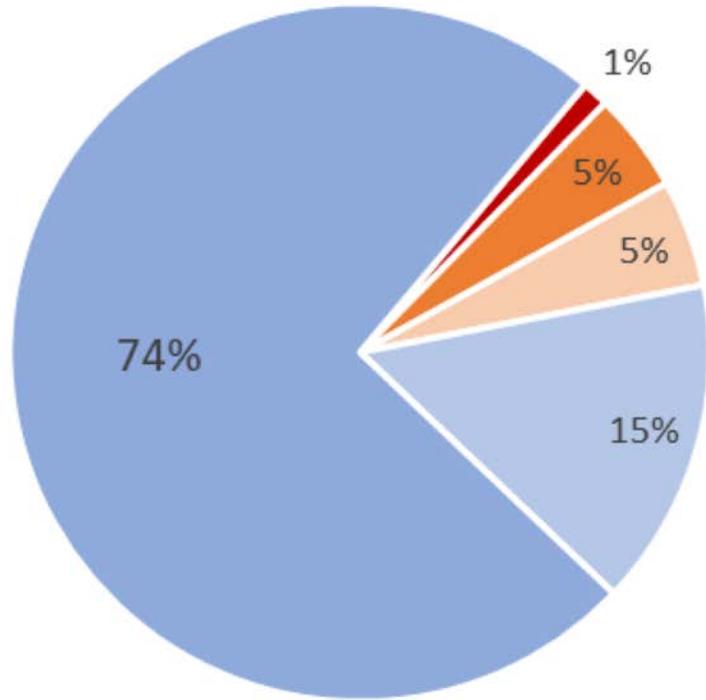
Consent required

# Supporting Variant Classification

- Use of common standards
  - Terminology
  - Rules for variant interpretation
- Public sharing of variant classifications
  - Creates transparency and crowd-sources the work
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven classification of variants (Expert Panels)



# Concordance in ClinVar



- P/LP vs VUS/LB/B → 10,640 medically significant conflicts
- VUS vs LB/B
- confidence conflict (P vs LP OR B vs LB)
- ≥2 concordant submissions
- 1 submission

5594 medically significant conflicts from 1 star clinical lab submitters

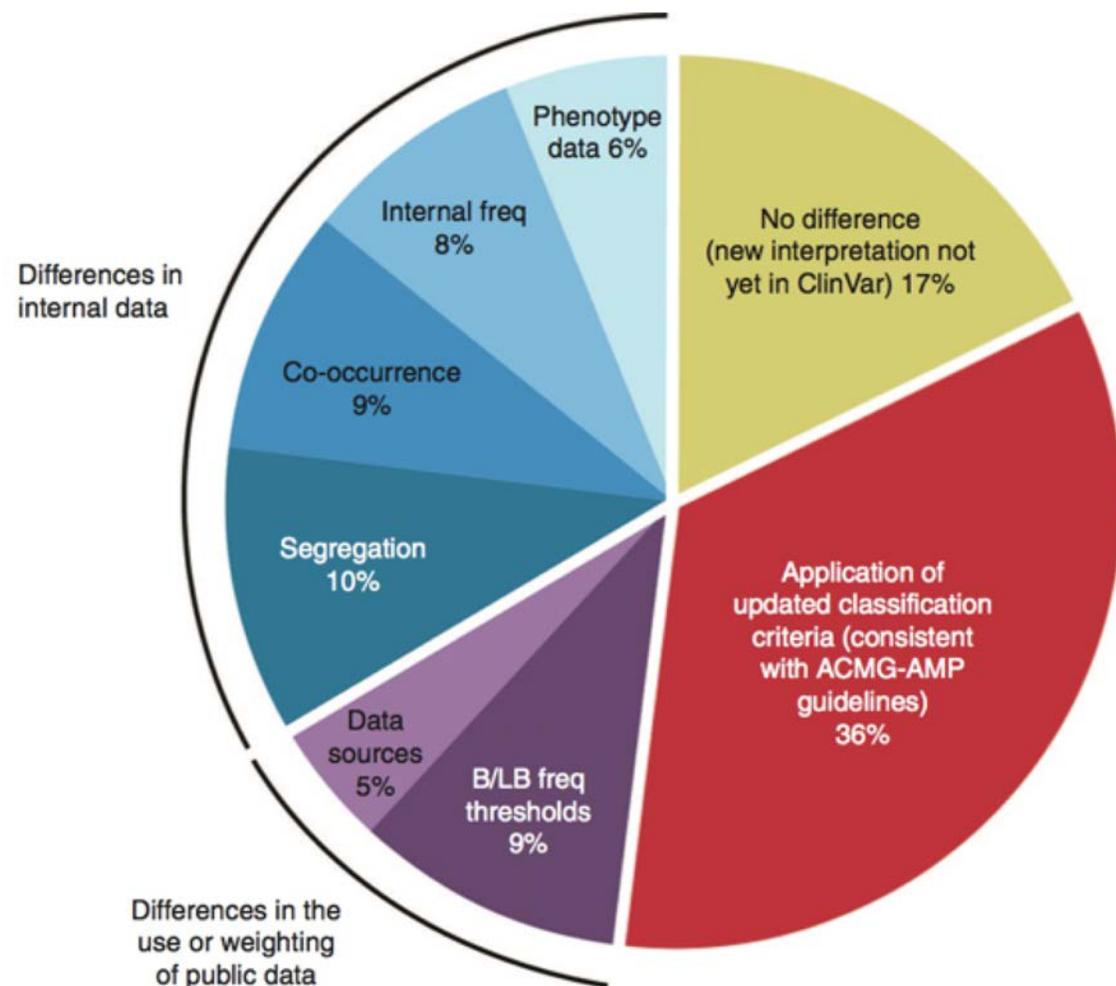
ClinVar Review Levels

Practice Guideline	★★★★★
Expert Panel (EP) Submitter	★★★★
Multiple Non-EP Submitters Agree	★★★
Single Non-EP Submitter OR Multiple Non-EP Submitters Disagree	★
No Assertion Criteria Submitter(s) Only	0 Stars

Data from ClinVar Miner on January 25<sup>th</sup>, 2021



# Variant Discrepancy Resolution - Phase 1



- **87% resolution (211/242)**
- Major time commitment (an estimated 1-2 hours per variant per laboratory)

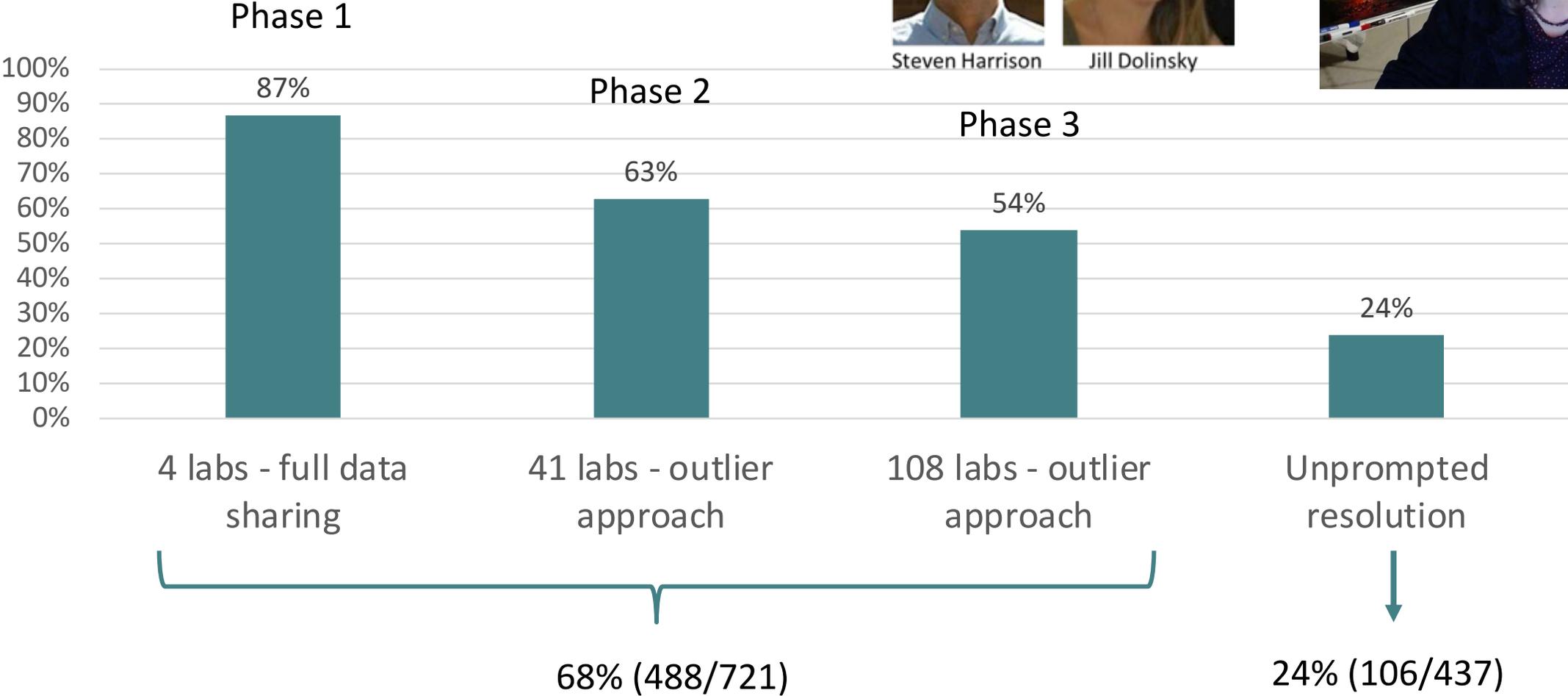
# ClinVar Variant Discrepancy Resolution



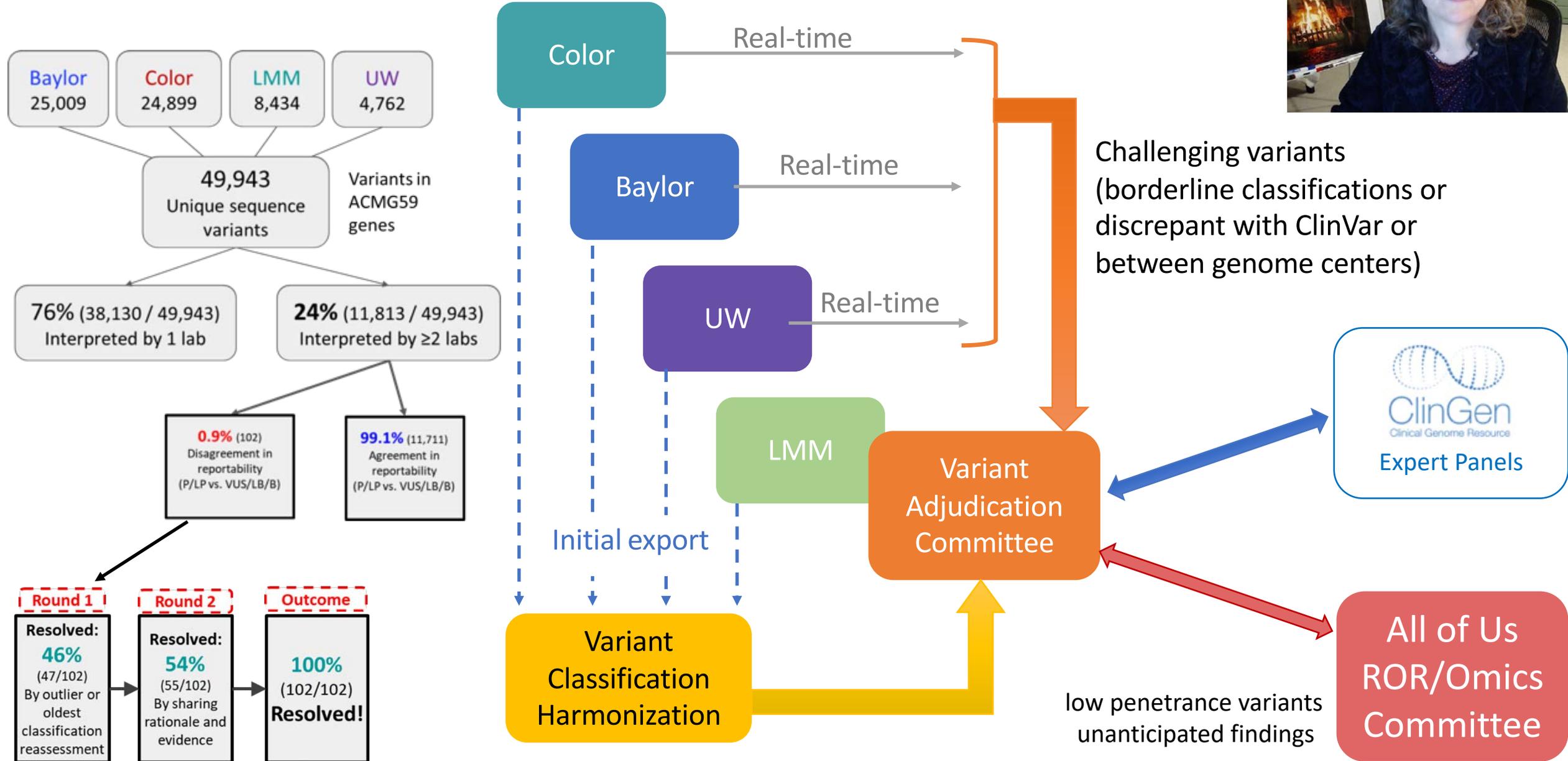
Steven Harrison



Jill Dolinsky

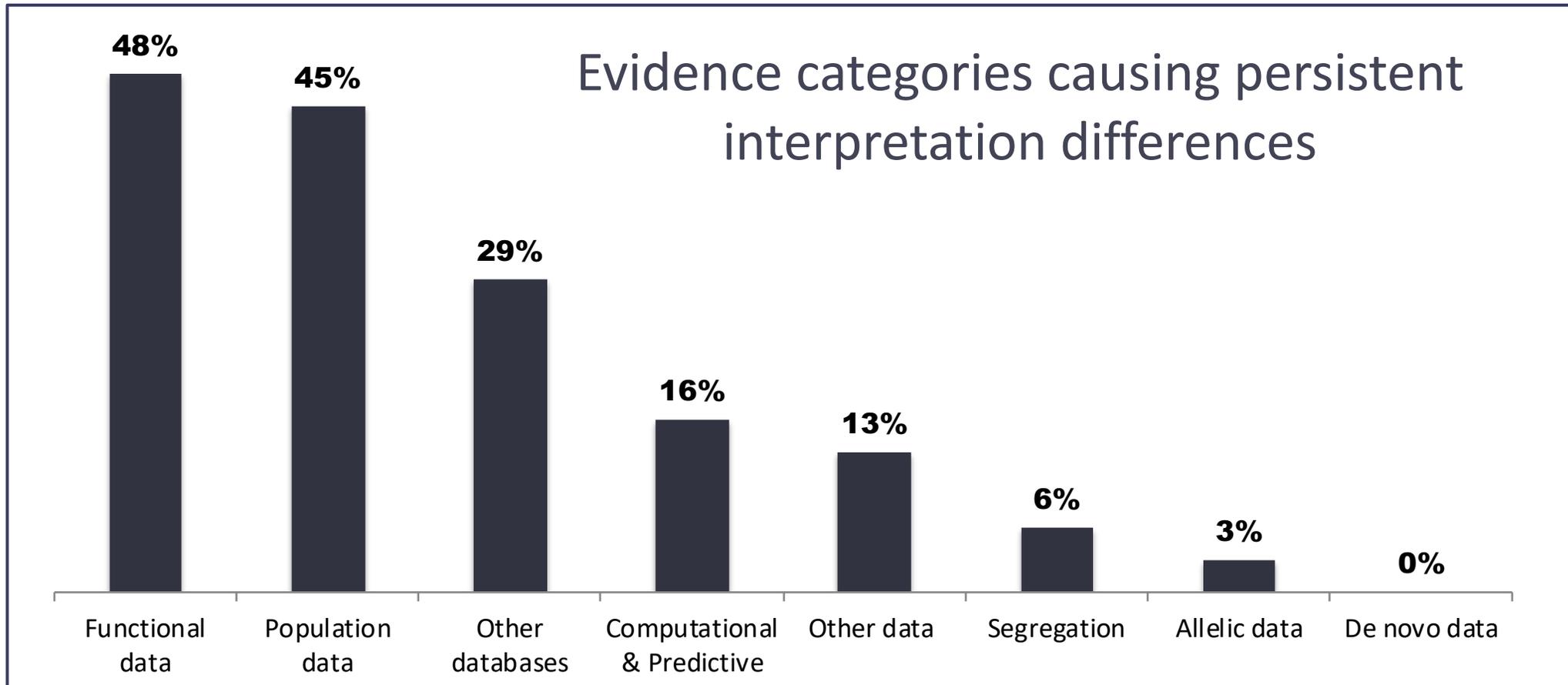


# All of Us Variant Classification Harmonization



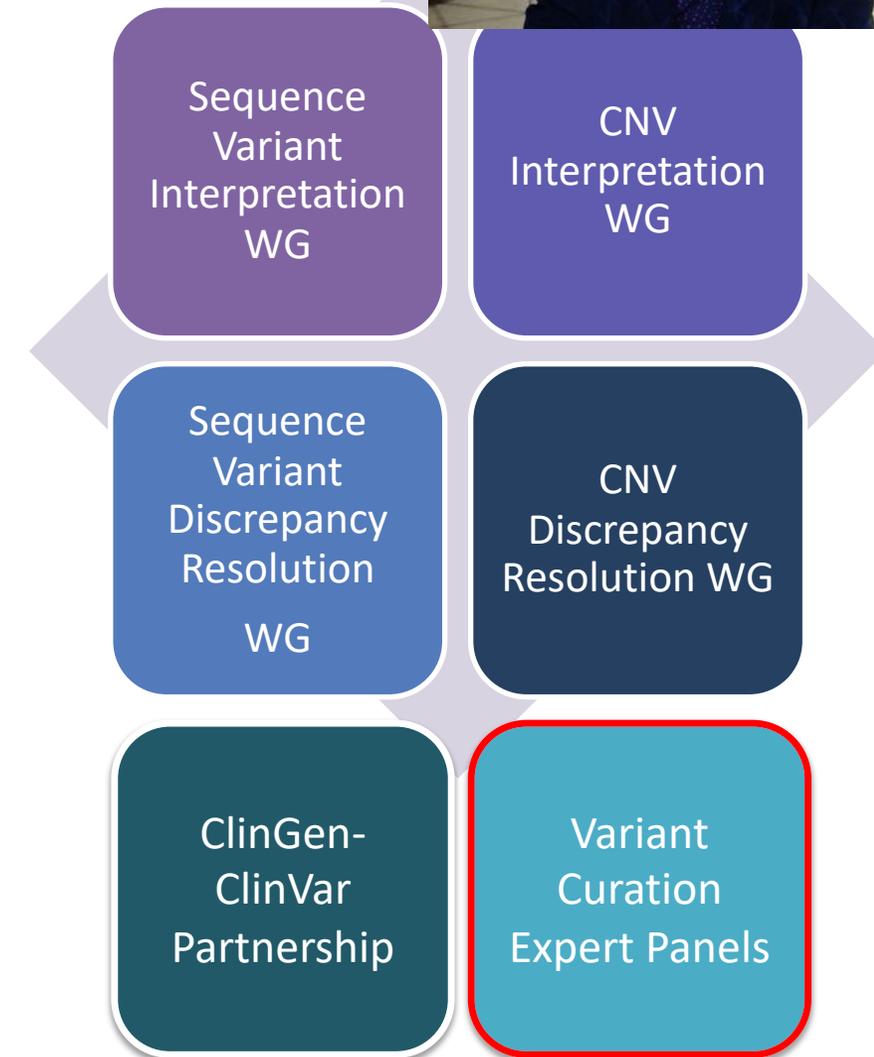
## We don't expect 100% concordance

- Goal to resolve interpretation differences due to differences in data sources, out-dated data, or older classification algorithms
- Resolving remaining interpretation differences will require expert consensus



# Supporting Variant Classification

- Use of common standards
  - Terminology
  - Rules for variant interpretation
- Public sharing of variant classifications
  - Creates transparency and crowd-sources the work
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven classification of variants (Expert Panels)



# Expert Panel Submissions Can Resolve Differences in Classification in ClinVar



## NM\_004004.6(GJB2):c.101T>C (p.Met34Thr)

**Interpretation:** Pathogenic

**Review status:** ★★☆☆ reviewed by expert panel

**Submissions:** 33 (Most recent: Nov 26, 2020)

**Last evaluated:** Jun 24, 2019

**Accession:** VCV000017000.25

**Variation ID:** 17000

**Description:** single nucleotide variant

FDA RECOGNIZED DATABASE

22 Pathogenic  
4 Likely Pathogenic  
2 VUS  
2 Likely Benign  
2 Benign

Practice Guideline	★★★★★
Expert Panel (EP) Submitter	★★★★
Multiple Non-EP Submitters Agree	★★★
Single Non-EP Submitter OR Multiple Non-EP Submitters Disagree	★
No Assertion Criteria Submitter(s) Only	0 Stars

# About ClinGen Expert Panels

ClinGen's Expert Panels are implementing the standards developed by our curation activities to improve genomics knowledge.



## Clinical Domain Working Groups

Gene Curation Expert Panels

Variant Curation Expert Panels

## Gene Curation Working Group

## Dosage Sensitivity Working Group

<b>Cardiovascular CDWG</b>	Arrhythmogenic Right Ventricular Cardiomyopathy Gene Curation Expert Panel <small>In Progress</small>	<input type="checkbox"/>
	Brugada Syndrome Gene Curation Expert Panel	<input checked="" type="checkbox"/>
	Cardiomyopathy Variant Curation Expert Panel	<input checked="" type="checkbox"/>
	Familial Hypercholesterolemia Variant Curation Expert Panel <small>In Progress</small>	<input checked="" type="checkbox"/>
	Familial Thoracic Aortic Aneurysm and Dissection Gene Curation Expert Panel	<input checked="" type="checkbox"/>
	FBN1 Variant Curation Expert Panel <small>In Progress</small>	<input checked="" type="checkbox"/>
	Hypertrophic Cardiomyopathy Gene Curation Expert Panel	<input checked="" type="checkbox"/>
	KCNQ1 Variant Curation Expert Panel <small>In Progress</small>	<input checked="" type="checkbox"/>
	Long QT Syndrome Gene Curation Expert Panel <small>In Progress</small>	<input type="checkbox"/>
<b>Hearing Loss CDWG</b>	Hearing Loss Gene Curation Expert Panel	<input checked="" type="checkbox"/>
	Hearing Loss Variant Curation Expert Panel	<input checked="" type="checkbox"/>
<b>Hemostasis/Thrombosis CDWG</b>	Coagulation Factor Deficiency Variant Curation Expert Panel <small>In Progress</small>	<input type="checkbox"/>
	Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel <small>In Progress</small>	<input type="checkbox"/>
	Platelet Disorder Variant Curation Expert Panel <small>In Progress</small>	<input checked="" type="checkbox"/>
<b>Hereditary Cancer CDWG</b>	Breast/Ovarian Cancer Gene Curation Expert Panel	<input checked="" type="checkbox"/>
	CDH1 Variant Curation Expert Panel	<input checked="" type="checkbox"/>
	Colorectal Cancer Gene Curation Expert Panel	<input checked="" type="checkbox"/>

### 13 Clinical Domain Working Groups

- Cardiovascular CDWG
- Hearing Loss CDWG
- Hemostasis/Thrombosis CDWG
- Hereditary Cancer CDWG
- Inborn Errors of Metabolism CDWG
- Neurodevelopmental Disorders CDWG
- RASopathy CDWG
- Neuromuscular CDWG
- Ocular CDWG
- Skeletal Disorders CDWG
- Kidney Disease CDWG
- Immunology CDWG
- Somatic Cancer CDWG

### 32 Gene Curation Expert Panels

### 37 Variant Curation Expert Panels

# ClinGen Expert Panels Span Many Time Zones!



**1557 researchers & clinicians from 36 countries**

[Map by Natalie Pino; Time-zone videos from Birgit Funke]

# ClinGen Variant Curation Expert Panel Approval Steps



*ClinGen affiliated groups*

- A. Identify EP leadership and membership
- B. Define scope (disease focus and gene list)
- C. Address COI

## Step 1: Define WG and plans

Submit completed Step 1 application materials

- D. Specify ACMP/AMP rules for genes in scope
- Review SVI guidance and other EP disease-specific rule specification as examples

## Step 2: Develop Variant Classification Rules

Submit completed Step 2 application materials and present to the SVI WG

- E. Validate specified rules with known variants and refine as needed
- 10-12 P/LP per gene
- 10-12 B/LB per gene
- 10-12 VUS per gene

## Step 3: Pilot Rules

Submit completed Step 3 application materials

- F. Define plans for ongoing variant review and reanalysis and discrepancy resolution
- G. Provide example evidence summaries
- H. & I. Provide attestations for these sections

## Step 4: Final VCEP approval

Submit fully completed VCEP application and present to the CDWG OC

# Criteria requiring gene/disease specification

Gene-specific data, such as:

PM1: Functional domains / hot spots

PS3/BS3: Validated functional assays

Disease specific data, such as:

BA1/BS1/BS2/PM2/BS4:

MAF/Prevalence/penetrance

PP4: Phenotype specificity

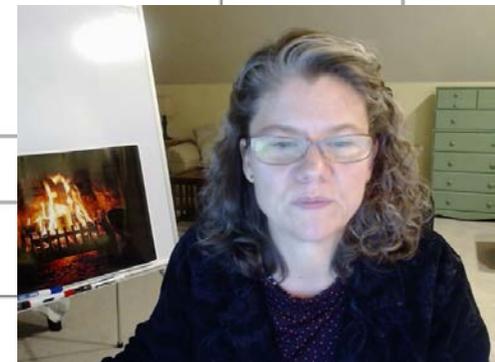
PVS1: Pathogenicity mechanism

RASopathy VCEP:

Final classification of >60% of RASopathy variants were impacted by the specified criteria.

Labs reached **100%** concordance for discrepancies reassessed with RASopathy-specific criteria

	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 <i>trans</i> with a dominant variant BP2 Observed in <i>cis</i> with a pathogenic variant BP2		For recessive disorders, detected in <i>trans</i> 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			



# Sequence Variant Interpretation

The goal of the Sequence Variant Interpretation Working Group (SVI WG) is to support the refinement and evolution of the [ACMG/AMP Interpreting Sequence Variant Guidelines](#) to develop quantitative approaches to variant interpretation.

[Subgroups](#) [Documents](#) [Tools](#) [Membership](#)



The Sequence Variant Interpretation WG also consults with and supports Expert Panel groups to develop gene- and disease-specific refinements of the ACMG/AMP Interpreting Sequence Variant Guidelines to increase the uniformity and consistency of the Expert Panel recommendations. The SVI WG has representation from the Biocurators WG, CNV Interpretation WG and Variant Curation Interface development team and all ClinGen Expert Panels.

## 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.

- [Guidance on how to rename criteria codes when strength of evidence is modified](#)
- [BA1: Updated Recommendation for the ACMG/AMP Stand Alone Pathogenicity Criterion for Variant Classification](#)
  - [BA1 Exception List \(July 2018\)](#)
  - [BA1 Exception List Nomination Form](#)
- [PVS1: Recommendations for Interpreting the Loss of Function PVS1 ACMG/AMP Variant Criteria](#)
- [PS2/PM6: Recommendation for de novo PS2 and PM6 ACMG/AMP criteria \(Version 1.0\)](#)
- [PS3/BS3: Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework](#)
- [PM3: Recommendation for in trans Criterion PM3 \(Version 1.0\)](#)
- [PP5/BP6: Recommendation for reputable source PP5 and BP6 ACMG/AMP criteria](#)



SVI Approved Expert Panel Specified  
ACMG/AMP Variant Interpretation  
Guidelines



General SVI Publications

[► Recommendations for interpreting the lo](#)  
[cations of the ACMG/AMP](#)

### Chairs

**Leslie G. Biesecker, MD**  
**Steven Harrison, PhD**

### Coordinators

Please contact a coordina  
questions.

**Danielle Azzariti, MS, Co**  
[dazzariti@broadinstitute.c](mailto:dazzariti@broadinstitute.c)

Official journal of the American College of Medical Genetics and Genomics

SPECIAL ARTICLE | Genetics  
inMedicine

Open

### Adaptation and validation of the ACMG/AMP variant classification framework for *MYH7*-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel

Melissa A. Kelly, MS<sup>1</sup>, Colleen Caleshu, MS<sup>2</sup>, Ana Morales, MS<sup>3</sup>, Jillian Buchan, PhD<sup>1</sup>, Zena Wolf, PhD<sup>1</sup>, Steven M. Harrison, PhD<sup>1</sup>, Stuart Cook, MD<sup>4</sup>, Mitchell W. Dillon, MS<sup>1</sup>, John Garcia, PhD<sup>5</sup>, Eden Haverfield, PhD<sup>5</sup>, Jan D.H. Jongbloed, PhD<sup>6</sup>, Daniela Macaya, PhD<sup>7</sup>, Arjun Manrai, PhD<sup>8</sup>, Kate Orland, MS<sup>9</sup>, Gabriele Richard, MD<sup>7</sup>, Katherine Spoonamore, MS<sup>10</sup>, Matthew Thomas, MS<sup>11</sup>, Kate Thomson, BSc<sup>12,13</sup>, Lisa M. Vincent, PhD<sup>7</sup>, Roddy Walsh, PhD<sup>4,14</sup>, Hugh Watkins, MD PhD<sup>13</sup>, Nicola Whiffin, PhD<sup>4,14</sup>, Jodie Ingles, PhD<sup>15</sup>, J. Peter van Tintelen, MD PhD<sup>16</sup>, Christopher Semsarian, MBBS PhD<sup>15</sup>, James S. Ware, PhD MRCP<sup>4,14</sup>, Ray Hershberger, MD<sup>3</sup> and Birgit Funke, PhD<sup>1,17,18</sup>; for the ClinGen Cardiovascular Clinical Domain Working Group<sup>19</sup>

© American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE | Genetics  
inMedicine

### ClinGen's RASopathy Expert Panel consensus methods for variant interpretation

Bruce D. Gelb, MD<sup>1</sup>, H el ene Cav e, PharmD, PhD<sup>2</sup>, Mitchell W. Dillon, MS<sup>3</sup>, Karen W. Gripp, MD<sup>4</sup>, Jennifer A. Lee, PhD<sup>5</sup>, Heather Mason-Suares, PhD<sup>6</sup>, Katherine A. Rauen, MD, PhD<sup>7</sup>, Bradley Williams, MS<sup>8</sup>, Martin Zenker, MD<sup>9</sup>, Lisa M. Vincent, PhD<sup>8</sup> and for the ClinGen RASopathy Working Group

# ClinGen VCEP Classified Variants in ClinVar

## Resolve Conflicts

11,579 Expert Classified Variants in ClinVar



	CDH1	Hearing Loss	Cardio-myopathy	Myeloid Malignancy	PAH	PTEN	RASopathy	Total
Total Submission	50	77	102	52	158	111	254	804
P/LP vs VUS/LB/B overwritten	5	19	14	3	10	18	10	79
VUS vs LB/B overwritten	12	14	12	2	2	10	52	104

- PAH VCEP 489
- PTEN VCEP 145
- CDH1 VCEP 229
- TP53 VCEP 58
- RASopathy VCEP 329
- Hearing Loss VCEP 169
- Myeloid Maligna... 145
- Platelet Disord... 2
- Lysosomal Stora... 138
- Cardiovascular ... 101

14	4	117	145	209
10	18	42	37	38
48	26	32	55	68
6	17	11	10	14
128	61	38	19	83
26	23	53	41	26
52	15	28	25	25
				2
11	2	16	43	66
46	1	16	18	20

To track ClinGen FDA-recognized submissions go to:

<https://erepo.clinicalgenome.org/evrepo/>

- Benign 341
- Likely Benign 167
- Uncertain Significance 353
- Likely Pathogenic 393
- Pathogenic 551

# VCEP Classifications in ClinVar



**NM\_206933.3(USH2A):c.11241C>A (p.Tyr3747Ter)** Cite this record

**Interpretation:** Pathogenic

**Review status:** ★★☆☆ reviewed by expert panel **FDA RECOGNIZED DATABASE**

**Submissions:** 2 (Most recent: Mar 21, 2019)

**Last evaluated:** Sep 17, 2018

**Accession:** VCV000506273.2

**Variation ID:** 506273

**Description:** single nucleotide variant

## Submitted interpretations and evidence

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Sep 17, 2018)	reviewed by expert panel (ClinGen HL ACMG Specifications v1) Method: curation	<b>Usher syndrome</b> (Autosomal recessive inheritance) Allele origin: germline	<b>ClinGen Hearing Loss Variant Curation Expert Panel,</b> <b>FDA RECOGNIZED DATABASE</b> Accession: SCV000840528.3 Submitted: (Feb 27, 2019)	<b>Evidence details</b> <b>Other databases</b> <a href="https://erepo.clinicalgenome.o...">https://erepo.clinicalgenome.o...</a> Comment: The p.Tyr3747X variant in USH2A is predicted to cause a premature stop codon in biologically-relevant-exon 58/72 that leads to a truncated or absent protein in a gene in which loss-of-function is an established mechanism (PVS1). The allele frequency of the p.Tyr3747X variant in the Ush2A gene is 0.017% (4/24020) of African chromosomes by the Genome Aggregation Database ( <a href="http://gnomad.broadinstitute.org">http://gnomad.broadinstitute.org</a> ), which is a low enough frequency to award PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_Supporting). This variant has been detected in 1 patient with hearing loss in trans with a suspected pathogenic variant (PM3_Supporting, Partners LMM internal data SCV000713838.1). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied: PVS1, PM2_Supporting, PM3_Supporting. (less)



View structured evidence in ClinGen's Evidence Repository



# ClinGen Variant & Gene Curation

Variant Curation is available for public use. To register, create an account via "Login", and then contact our helpdesk at [clingen-helpdesk@lists.stanford.edu](mailto:clingen-helpdesk@lists.stanford.edu).

Gene Curation is currently restricted to ClinGen curators. To collaborate on gene curation contact [clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org)



## ClinGen Variant Curation Interface (VCI)

Used by VCEPs, laboratories and individuals to facilitate the classification of variants

Breakout on VCI Training on Day 3



**Variant Interpretation Record**

Navigation: 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

Classification: **Not Met** (BP3) **Not Applied** (BP4) **Met** (PM2)

Benign: No criteria met | Pathogenic: Strong: 3, Moderate: 1 | Calculated Pathogenicity: Pathogenic

Basic Information | Population | Predictors | Experimental | Segregation/Case | Gene-centric

Missense | Loss of Function | Silent & Intron | In-frame Indel

**Functional, Conservation, and Splicing Predictors**

**PP3:** Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.) (has caveat) **Not Evaluated** (dropdown menu open: Not Evaluated, Met, Not Met, PP3\_Moderate, **PP3\_Strong**) **Explanation:** [Text area]

**BP4:** Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc.) (has caveat) **Not Evaluated** (dropdown menu)

**BP1:** Missense variant in a gene for which primarily truncating variants are known to cause disease **Not Evaluated** (dropdown menu) **Explanation:** [Text area]

**PP2:** Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease **Not Evaluated** (dropdown menu)

Evaluations for PP3, BP4, BP1, PP2 saved successfully! **Update**

# Expert panels also combine evidence to reclassify VUSs

## NM\_000257.4(MYH7):c.2678C>T (p.Ala893Val)

**Interpretation:** Likely pathogenic

**Review status:** ★★★☆ reviewed by expert panel **FDA RECOGNIZED DATABASE**

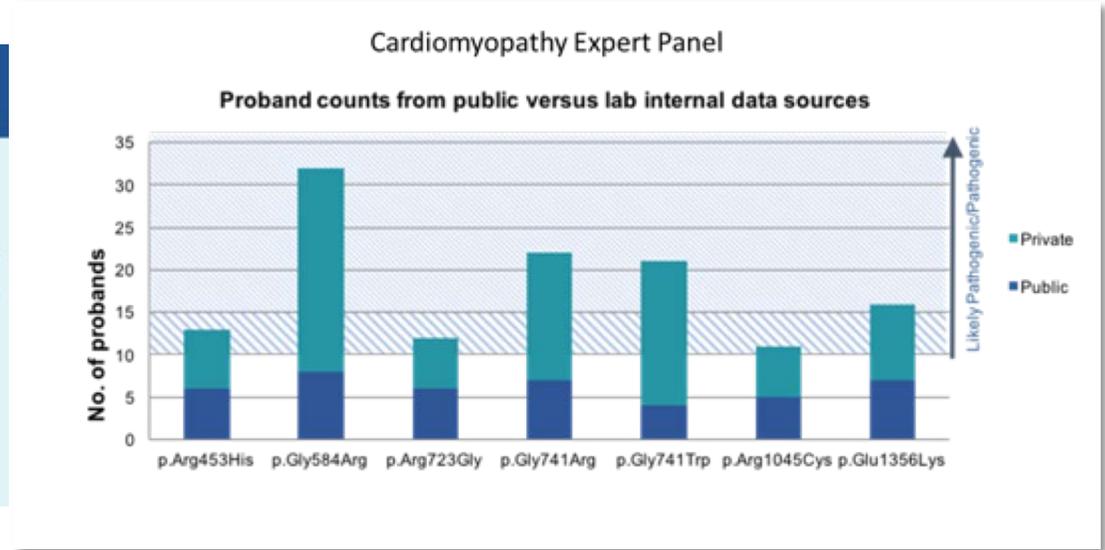
**Submissions:** 4 (Most recent: Jun 3, 2020)

**Last evaluated:** Dec 15, 2016

**Accession:** VCV000177763.5

**Variation ID:** 177763

**Description:** single nucleotide variant



Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Likely pathogenic (Dec 15, 2016)	reviewed by expert panel - <a href="#">ACMG variant classification (MYH7)</a>	curation	Primary dilated cardiomyopathy (Autosomal dominant inheritance) [ <a href="#">MedGen</a>   <a href="#">Orphanet</a> ]	germline		<a href="#">ClinGen Inherited Cardiomyopathy Expert Panel</a>	SCV000564435.2
Uncertain significance (Jan 21, 2016)	criteria provided, single submitter - <a href="#">LMM Criteria</a>	clinical testing	not specified [ <a href="#">MedGen</a> ]	germline	- <a href="#">PubMed (2)</a> [ <a href="#">See all records that cite these PMIDs</a> ]	<a href="#">Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine</a>	SCV000201216.2
Uncertain significance (Oct 24, 2016)	criteria provided, single submitter - <a href="#">GeneDx Variant Classification (06012015)</a>	clinical testing	not specified [ <a href="#">MedGen</a> ]	germline		<a href="#">GeneDx</a>	SCV000177763.5



# ClinGen VCEPs do not review all variants!

VCEPs priorities include:

1. Resolving discrepancies
2. Classifying the most prevalent pathogenic variants
3. Examining variants that have been observed in multiple cases through which combining data can move them from VUS or LP to Pathogenic or Benign



# Opportunities to get Involved in ClinGen

<https://clinicalgenome.org/start/>

## Want to get involved in ClinGen activities?

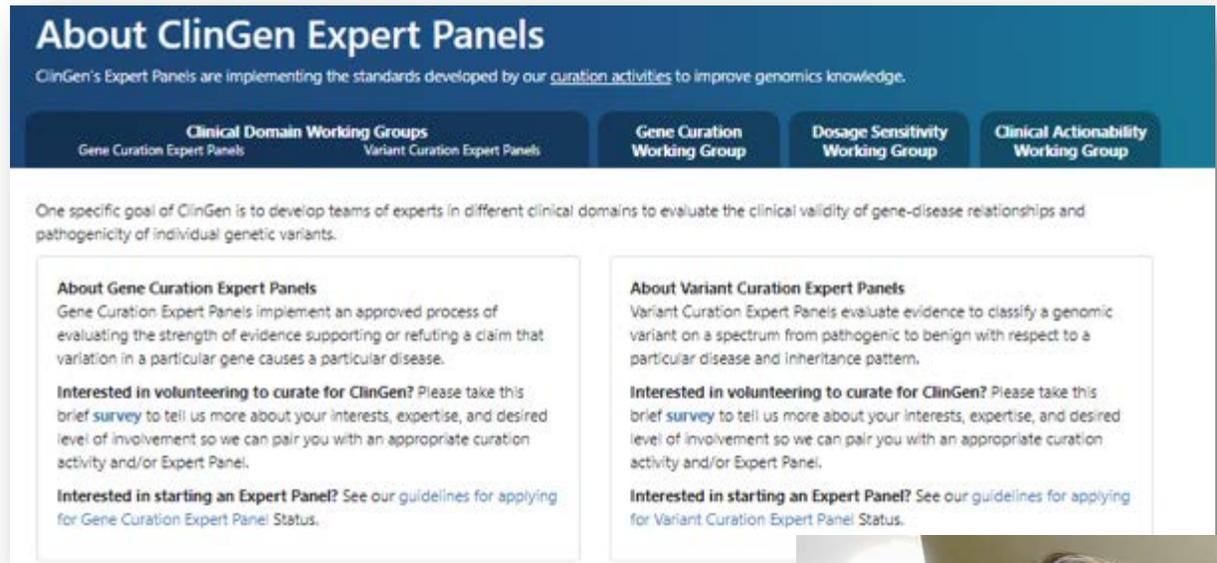
We look forward to collaborating with you! Here are some ways to participate:

- **Sign up for our Mailing List**  
Sign up to get ClinGen news and updates delivered to your inbox.
- **Attend ClinGen Events**  
Find when and where ClinGen is exhibiting and hosting events.
- **Volunteer to Curate**  
Interested in volunteering to curate for ClinGen? Please complete this brief survey
- **Join the ClinVar Community Call**  
Join a monthly call bringing together Clinvar users to discuss topics related to ClinVar.
- **Share Your Data**  
Learn how clinicians, laboratories and patients can share their data.
- **Part IV Practice Improvement**  
Learn about a module towards Part IV Practice Improvement for clinical laboratory geneticists.

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

If you want to volunteer as a biocurator and learn gene and variant curation, fill out our survey:

- If you have specific expertise and would like to join one of our Gene or Variant Curation Expert Panels as an expert:



The screenshot shows the 'About ClinGen Expert Panels' page. At the top, it states: 'ClinGen's Expert Panels are implementing the standards developed by our curation activities to improve genomics knowledge.' Below this, there are four navigation buttons: 'Clinical Domain Working Groups' (with sub-items 'Gene Curation Expert Panels' and 'Variant Curation Expert Panels'), 'Gene Curation Working Group', 'Dosage Sensitivity Working Group', and 'Clinical Actionability Working Group'. The main content area has a heading: 'One specific goal of ClinGen is to develop teams of experts in different clinical domains to evaluate the clinical validity of gene-disease relationships and pathogenicity of individual genetic variants.' There are two columns of text. The left column is titled 'About Gene Curation Expert Panels' and describes the process of evaluating evidence for gene-disease relationships. The right column is titled 'About Variant Curation Expert Panels' and describes the process of classifying genomic variants. Both columns include a call to action: 'Interested in volunteering to curate for ClinGen? Please take this brief survey...' and 'Interested in starting an Expert Panel? See our guidelines for applying for Gene Curation Expert Panel Status.' and 'Interested in starting an Expert Panel? See our guidelines for applying for Variant Curation Expert Panel Status.'

For a full list of Expert Panels, visit this page:

<https://clinicalgenome.org/working-groups/clinical-domain/>





# Clinical Genome Resource

**WG and EP Members:** >1,557 people from >36 countries



Applications & Infrastructure	Education, Engagement & Outreach	Core Standards & Oversight	Expert Curation
<b>Data Platform</b> L. Babb, L. Madhavrao, T. Nelson, K. Riehle, C. Thaxton	<b>Education, Coordination and Training</b> E. Riggs & D. Azzariti	<b>CDWG Oversight</b> J. Berg, S. Plon & H. Rehm	<b>Clinical Domain Working Groups</b> Gene Curation Expert Panels Variant Curation Expert Panels
<b>ClinVar Partnership</b> M. Landrum & H. Rehm	<b>Biocurators</b> J. Goldstein	<b>Gene Curation</b> C Thaxton & E. Riggs	
<b>Electronic Health Record</b> M. Williams	<b>Stakeholders Partnership</b> L. Milko & M. Watson	<b>Lumping and Splitting</b> J. Goldstein & C. Thaxton	<b>Dosage Sensitivity</b> E. Andersen & E. Thorland
<b>Application Stakeholder Feedback</b>	<b>Regulatory</b> C. Thaxton	<b>Sequence Variant Interpretation</b> L. Biesecker & S. Harrison	
<b>ClinGen Program Coordinators</b> Danielle Azzariti Julie Kim Hannah Dziadzio Kristy Lee Miranda Hallquist Xi Luo Meredith Weaver Emma Owens Deborah Ritter Brooke Palus Liz Kearns Natalie Pino	<b>Community Curation</b> C. Thaxton	<b>CNV Interpretation</b> S. Aradhya & D. Pineda-Alvarez	<b>Adult Actionability</b> J. Hunter & A. Buchanan
	<b>Data Access, Protection and Confidentiality</b> A. Popejoy	<b>Low Penetrance/Risk Alleles</b> M. Lebo & R. Schmidt	<b>Pediatric Actionability</b> K. Goddard & B. Powell
	<b>Consent and Disclosure Recommendations (CADRe)</b> A. Buchanan, M. Hallquist	<b>Complex Diseases</b> K. Goddard, G. Wojcik	<b>External Scientific Panel</b> John Carpten Richard Sharp Rex Chisholm Peter Tarczy-Hornach Deb Leonard Holly Peay Georgia Wiesner
		<b>Ancestry and Diversity</b> A. Popejoy & K. Ormond	

- Steering Committee (\*PIs)**
- Jonathan Berg, UNC\*
  - Thomas Montine, Stanford\*
  - Katrina Goddard, Kaiser\*
  - David Ledbetter, Geisinger\*
  - Christa Lese Martin, Geisinger\*
  - Sharon Plon, Baylor\*
  - Heidi Rehm, Broad\*
  - Marc Williams, Geisinger\*
  - Matt Wright, Stanford
  - Adam Buchanan, Geisinger
  - Carlos Bustamante, Stanford\*
  - Andy Freedman, NCI
  - Steven Harrison, Broad
  - Aleksandar Milosavljevic, Baylor
  - Kelly Ormond, Stanford
  - Erin Riggs, Geisinger
  - Brandi Kattman, NCBI
  - Melissa Landrum, NCBI
  - Erin Ramos, NHGRI