

# ClinGen and ClinVar: Complementary Resources

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# ClinGen and ClinVar: What's the Difference?

- ClinGen and ClinVar work together to provide complementary resources to support genomic interpretation
- ClinVar is a DATABASE funded by intramural NIH funding and maintained by the NCBI
  - Goal: Public archive of [*any*] reports of the relationships between [*any*] variants and [*any*] conditions
- ClinGen is a PROGRAM funded by NHGRI
  - Goal: Identifying *clinically relevant* genes and variants for use in precision medicine and research



# What is ClinVar?

- Public archive of variant-phenotype assertions, submitted from a variety of sources, including:
  - Clinical laboratories
  - Research projects
  - Expert panels
  - Other databases, etc.
- Different from dbSNP, dbVar, which primarily maintain information about locations, types of variants

# What does ClinVar DO?

```
ACTGATGGTATGGGGCCAAGAGATATATCT  
CAGGTACGGCTGTCATCACTTAGACCTCAC  
CAGGGCTGGGCATAAAAGTCAGGGCAGAGC  
CCATGGTGCATCTGACTCCTGAGGAGAAGT  
GCAGGTTGGTATCAAGGTTACAAGACAGGT  
GGCACTGACTCTCTGCCTATTGGTCTAT
```

## ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

- Facilitates the evaluation of variant-phenotype assertions by:
  - Archiving submitted interpretations of gene-disease relationships
  - Aggregating data from multiple submitters
  - Determine if there is a consensus about the interpretation
- *ClinVar DOES NOT interpret variants!*

# What's currently in ClinVar?

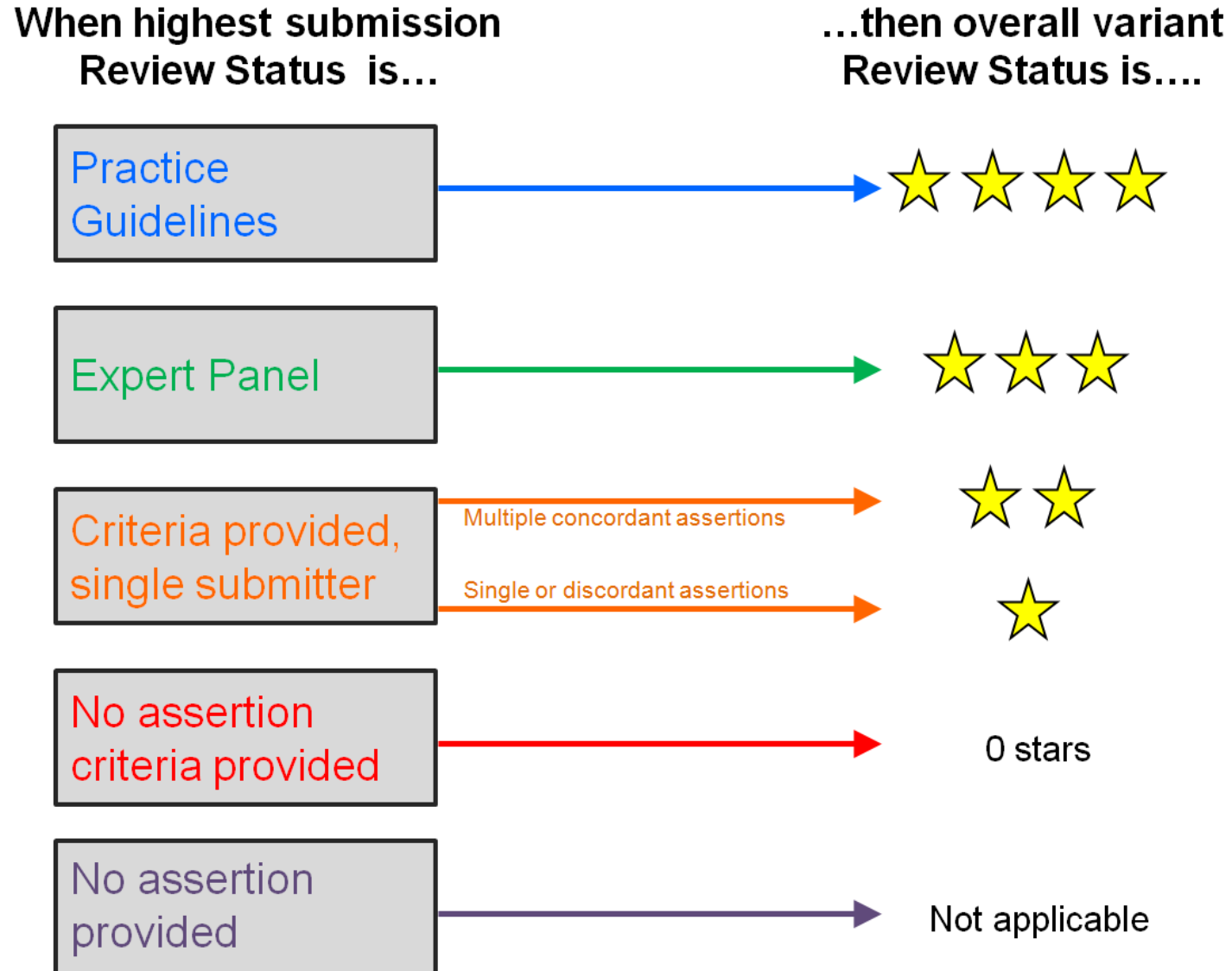
	Category of analysis	Current total (Aug 13, 2018)
→	Records submitted	700611
	Records with assertion criteria	566125
	Records with an interpretation	683254
	Total genes represented	30190
	Unique variation records	441973
→	Unique variation records with interpretations	431693
	Unique variation records with assertion criteria	369351
	Unique variation records with practice guidelines (4 stars)	23
→	Unique variation records from expert panels (3 stars)	10423
	Unique variation records with assertion criteria, multiple submitters, and no conflicts (2 stars)	60340
	Unique variation records with assertion criteria (1 star)	280110
	Unique variation records with assertion criteria and a conflict (1 star)	18455
→	Unique variation records with conflicting interpretations	18608
	Genes with variants specific to one gene	6053
	Genes with variants specific to one protein-coding gene	5942
	Genes included in a variant spanning more than one gene	30153
	Variants affecting overlapping genes	13913
→	Total submitters	1021

# ClinVar is a submitter-driven resource

- There are many pieces of information that ClinVar CAN collect on a variant, but *if a submitter does not submit them, they aren't available.*
- Quality of submissions vary
- When assessing the information you find in ClinVar, you must assess the quality of the submitter/submission itself

# Assessing Quality in ClinVar

- IN GENERAL, one mark of a submission's quality is its review level – at minimum, you should be able to figure out the methods by which the variant was evaluated
- These are known as “assertion criteria”
- When a submitter provides assertion criteria, the submission receives at least 1 star



# <https://www.clinicalgenome.org/lablist/>



Search our Knowledge Base for genes and diseases...



[About ClinGen](#)

[Working Groups & Expert Panels](#)

[Resources & Tools](#)

[GenomeConnect](#)

[Share Your Data](#)

[Curation Activities](#)

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

[▶ Frequently Asked Questions](#)

ClinGen considers the sharing of variant interpretations essential for supporting genomic medicine and a critical part of quality assurance for accurate genetic and genomic testing. Open and transparent sharing allows peer-review and knowledge dissemination to ensure the highest quality care of patients.

Here, we identify clinical laboratories who meet a minimum standard of data sharing:

- Laboratory submissions are registered in [ClinVar](#) as 'Single Submitter, Assertion criteria provided' (single star)
- Laboratory registered in the [Genetic Test Registry \(GTR\)](#) with up-to-date yearly review
- Laboratory submits at least once per year adding new variants and updating reclassified variants as necessary
- Laboratory submits all categories of variants returned to patients (labs are also encouraged to share B/LB/VUS variants even if not returned)
- Laboratory has attested to submitting at least 75% of all sequence and/or copy number variants reported in the past year
- Laboratory has submitted at least 100 variants
- Laboratory is CLIA certified laboratory (USA) or meets an equivalent standard in another country

To apply for status, or to update your status, laboratories can apply [here](#).

Questions about the criteria? Visit our [Frequently Asked Questions](#) or contact [clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org).

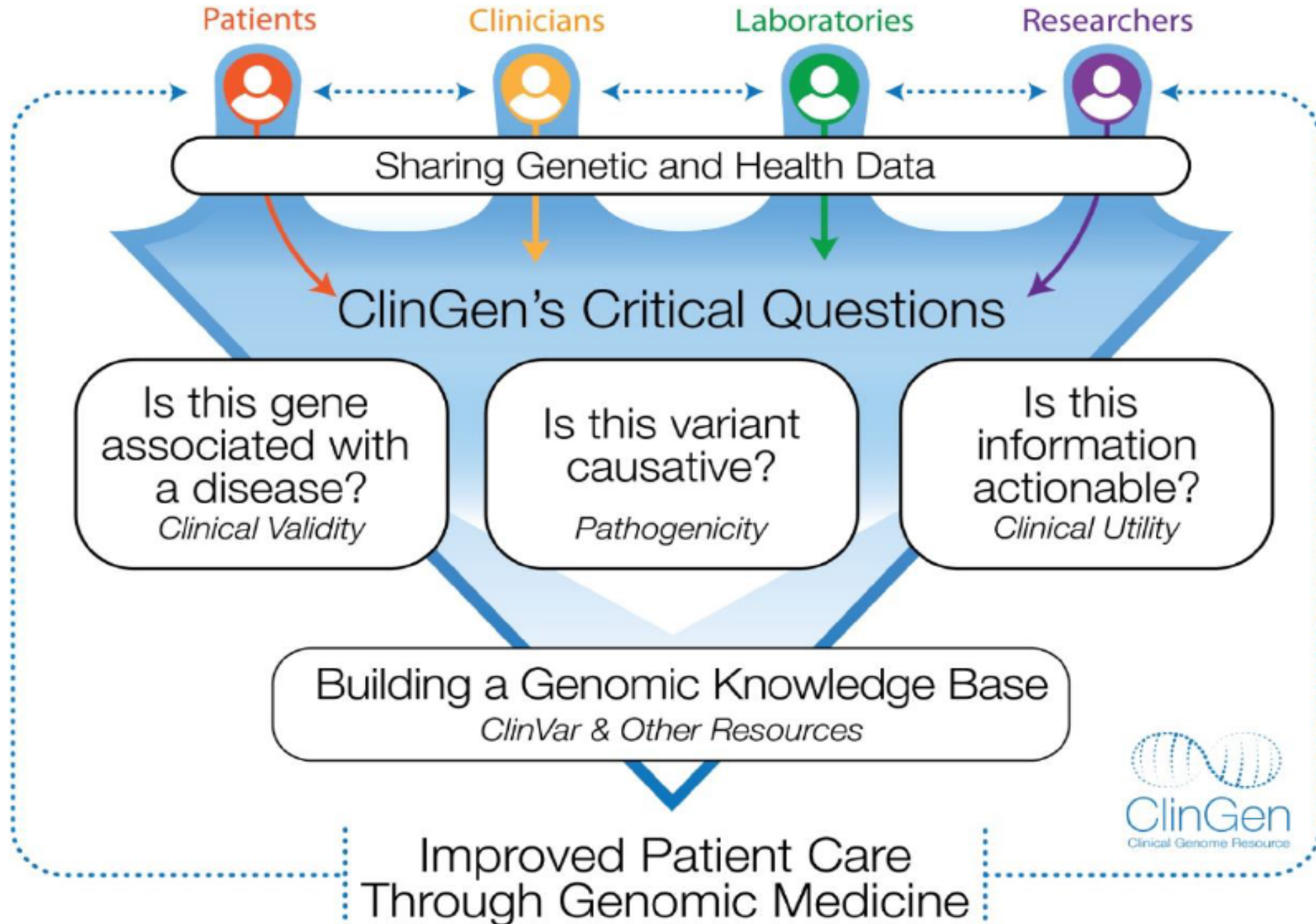


# <https://www.clinicalgenome.org/lablist/>

Laboratory	Meets requirements	Additional Achievements			
		Submitted evidence <sup>1</sup>	>75% from past 5 years <sup>2</sup>	Discrepancy resolution <sup>3</sup>	Consenting mechanism <sup>4</sup>
Ambry					
ARUP					
Athena Diagnostics Inc.					
Centre for Mendelian Genomics, University Medical Centre Ljubljana					
Center for Pediatric Genomic Medicine, Children's Mercy Hospital and Clinics					
Color Genomics, Inc.					
Counsyl					
EGL Genetics (Emory)					

Laboratory	Meets requirements	Additional Achievements			
		Submitted evidence <sup>1</sup>	>75% from past 5 years <sup>2</sup>	Discrepancy resolution <sup>3</sup>	Consenting mechanism <sup>4</sup>
GeneDx					
GeneKor MSA					
Illumina					
Integrated Genetics/Laboratory Corporation of America					
Invitae					
Partners Laboratory for Molecular Medicine					
Phosphorus Diagnostics LLC					
Quest Diagnostics Nichols Institute San Juan Capistrano					
University of Chicago					

# What is the Clinical Genome Resource (ClinGen)?



# ClinGen's Curation Efforts

**Gene-Disease Validity**  
Can variation in this gene cause disease?

[Learn more »](#)



**Variant Pathogenicity**  
Which changes in this gene cause disease?

[Learn more »](#)



**Clinical Actionability**  
How does this genetic diagnosis impact medical management?

[Learn more »](#)



**Dosage Sensitivity**  
Is haploinsufficiency or triplosensitivity an established disease mechanism for this gene?

[Learn more »](#)



# Which variants in a gene actually cause disease?

- Several different efforts going on in this space
  - Addressing existing classification disagreements: Inter-laboratory discrepancy resolution
    - Sequence and copy number variants
  - Preventing future classification disagreements: Modifications of the current ACMG/AMP sequence variant guidelines (Sequence Variant Interpretation WG)
    - General/quantitative specifications of current guidelines
    - Disease-specific modifications


 Unique variation records with conflicting interpretations	18608
 Unique variation records from expert panels (3 stars)	10423

# Discrepancy Resolution Efforts

Genetics  
inMedicine

Original Research Article | Published: 16 March 2017

## Clinical laboratories collaborate to resolve differences in variant interpretations submitted to ClinVar

Steven M. Harrison PhD , Jill S. Dolinsky MS, Amy E. Knight Johnson MS, Tina Pesaran MA, MS, Danielle R. Azzariti MS, Sherri Bale PhD, Elizabeth C. Chao MD, Soma Das PhD, Lisa Vincent PhD & Heidi L. Rehm PhD



Resolved 87.2% of discordant sequence variant classifications between participating labs

Human Mutation  
Variation, Informatics, and Disease



RESEARCH ARTICLE

## Copy number variant discrepancy resolution using the ClinGen dosage sensitivity map results in updated clinical interpretations in ClinVar

Erin R. Riggs , Tristan Nelson, Andrew Merz, Todd Ackley, Brian Bunke, Christin D. Collins, Morag N. Collinson, Yao-Shan Fan, McKinsey L. Goodenberger, Denae M. Golden, Linda Haglund-Hazy, Danijela Krgovic, Allen N. Lamb, Zoe Lewis, Guang Li, Yajuan Liu, Jeanne Meck, Whitney Neufeld-Kaiser, Cassandra K. Runke, Jennifer N. Sanmann, Dimitri J. Stavropoulos, Emma Strong, Meng Su, Marwan K. Tayeh, Nadja Kokalj Vokac, Erik C. Thorland, Erica Andersen, Christa L. Martin, ... See fewer authors 

Updated classifications for 63.8% of CNVs evaluated overlapping dosage sensitive genes

	Strong	Benign	Supporting	Moderate	Pathogenic	Strong	Very Strong
Population Data	MAF is too high for disorder. RAJ/BS1 OR observations in controls inconsistent with disease penetrance BS2				Absent in population databases PM2	Presence in affecteds statistically increased over controls PS4	
Computational And Predictive Data			Multiple lines of computational evidence suggest no impact BNF Misense unless only truncating cause-disease BP5 Silent variant with known predicted splice impact BP7 In-frame indels in respect to last known function BP9	Multiple lines of computational evidence support a deleterious effect on the gene/protein product PS3	Not in exon: change of an amino acid residue where a different pathogenic residue change has been seen before PM5 Protein length changing variant PM6	Same amino acid change as an established pathogenic variant PS2	Predicted null variant in a gene where LOF is a known mechanism of disease PS1
Functional Data	Well established functional studies show no deleterious effect PS1			Misense indels with low rate of benign missense variants and path. missense common BP2	Mutational hot spot or well studied functional domain without benign variation PM3		Well established functional studies show a deleterious effect PS2
Segregation Data	Non-segregation with disease BP4			Co-segregation with disease in multiple affected family members BP2	Increased segregation data		
De novo Data					De novo (without paternity & maternity confirmed) PM4		De novo (paternity & maternity confirmed) PS2
Allelic Data		Observed in homo with a benign variant BP2 Observed in cis with a pathogenic variant BP2			For recessive disorders, detected in homo with a pathogenic variant BP2		
Other Database		Repeatable source without clinical data - benign BP6		Repeatable source - pathogenic BP5			
Other Data		Found in case with an alternate cause BP5		Parent's phenotype fit highly specific for gene/PS4			

# ACMG/AMP Guidelines

## ClinGen Expert Panels

- Cardiovascular
- Neurodevelopmental Disorders
- Hereditary Cancer
- Metabolism
- RASopathies, etc.

**Sequence Variant Interpretation WG**  
 Harmonize recommendations for modifying ACMG guidelines

Gene/Disease Specific ACMG Guidelines


General recommendations to ACMG Guidelines

Slide courtesy of Steven Harrison, PhD

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Is haploinsufficiency or triplosensitivity an established disease mechanism for this gene?

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# Does this gene, when significantly altered, cause this disease?

- Defines the criteria needed to assess (genetic evidence, gene-level experimental evidence)
- Describes the strength evidence supporting a gene-disease relationship in a semi-quantitative manner
- Allows users to methodically classify the validity of a given gene-disease pair

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The American Journal of Human Genetics 100, 895–906, June 1, 2017 895

**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>



## Definitive

Role has been repeatedly demonstrated in research & clinical diagnostic settings

- Upheld over time (in general, at least 3 years)
- No convincing contradictory evidence

## Strong

≥2 independent studies with:

- Multiple pathogenic variants in unrelated probands
- AND
- Several different types of supporting experimental data
- OR
- Excess of pathogenic variants in cases vs. controls
- No convincing contradictory evidence

## Moderate

Several unrelated probands with pathogenic variants

- Some supporting experimental data
- No convincing contradictory evidence

## Limited

<3 unrelated probands with pathogenic variants

- OR
- Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity
- No convincing contradictory evidence

## No Evidence Reported

No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.

## Conflicting Evidence Reported

### Disputed

Convincing evidence disputing a role for this gene in this disease has arisen

- Disputing evidence need not outweigh existing evidence supporting the gene:disease association

### Refuted

Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role

- Applied at the discretion of clinical domain experts after thorough review of available evidence

# Using Gene-Disease Validity in Clinical Practice

- Laboratory: test design
- Clinician: Test ordering – which panel to choose?
  - May consider ordering only panels with established genes
  - Bigger is not always better!
- Clinician: Result interpretation – dealing with results in genes of uncertain significance

# ClinGen's Curation Efforts

**Gene-Disease Validity**  
Can variation in this gene cause disease?

[Learn more »](#)



This panel features a green background with a microscopic view of a tissue surface. It includes a white button with the text "Learn more »" and a circular icon containing the letter "G" and a DNA double helix.

**Variant Pathogenicity**  
Which changes in this gene cause disease?

[Learn more »](#)



This panel features a brown background with a microscopic view of a tissue surface. It includes a white button with the text "Learn more »" and a circular icon containing the letter "V" and a DNA double helix.

**Clinical Actionability**  
How does this genetic diagnosis impact medical management?

[Learn more »](#)



This panel features a blue background with a microscopic view of a tissue surface. It includes a white button with the text "Learn more »" and a circular icon containing the letter "A" and a DNA double helix.

**Dosage Sensitivity**  
Is haploinsufficiency or triplosensitivity an established disease mechanism for this gene?

[Learn more »](#)



This panel features a purple background with a microscopic view of a tissue surface. It includes a white button with the text "Learn more »" and a circular icon containing the letter "D" and a DNA double helix. The entire panel is enclosed in a red border.

# Is a gene or genomic region dosage sensitive?

- Originally created in 2011 as a resource to assist in the interpretation of copy number variants (ISCA, ICCG, ClinGen)
- Evidence-based process to assess genes and regions for dosage sensitivity
  - Haploinsufficiency
  - Triplosensitivity
- Goal: to create a genome-wide dosage sensitivity map




## Towards an evidence-based process for the clinical interpretation of copy number variation

Riggs ER, Church DM, Hanson K, Horner VL, Kaminsky EB, Kuhn RM, Wain KE, Williams ES, Aradhya S, Kearney HM, Ledbetter DH, South ST, Thorland EC, Martin CL. Towards an evidence-based process for the clinical interpretation of copy number variation. *Clin Genet* 2012; 81: 403–412. © John Wiley & Sons A/S, 2011

The evidence-based review (EBR) process has been widely used to develop standards for medical decision-making and to explore complex

ER Riggs<sup>a</sup>, DM Church<sup>b</sup>,  
K Hanson<sup>c\*</sup>, VL Horner<sup>a</sup>,  
EB Kaminsky<sup>a</sup>, RM Kuhn<sup>d</sup>,  
KE Wain<sup>e</sup>, ES Williams<sup>a</sup>,  
S Aradhya<sup>f</sup>, HM Kearney<sup>g</sup>,  
DH Ledbetter<sup>h</sup>, ST South<sup>i</sup>,  
EC Thorland<sup>g</sup> and CL Martin<sup>a,\*</sup>

 **Save** **Sufficient Evidence**



- At least 3 independent loss of function mutations or duplications in unrelated individuals with a similar phenotype and ONE of the following:
  - Mutations are found in at least 2 separate publications, OR
  - Mutations are found in a single publication, but supporting secondary evidence is present
- Role of mutations in normal populations must be understood
  - Mutations are not observed in normal populations, OR
  - Associations between phenotype an incomplete penetrance and/or variable expressivity are well documented

**Potential Clinical Interpretation: Pathogenic**

**2: Emerging Evidence**

- Two independent loss of function mutations or duplications in unrelated individuals with a similar phenotype
- OR**
- More than 2 mutations as described above, but the mutations are either:
    - Inherited from normal parents, and the spectrum of incomplete penetrance/variable expressivity is not understood, OR
    - Not significantly enriched in clinical populations when compared to controls
- OR**
- Observed amongst clinical populations at a statistically significant level in more than one large-scale case control series, without a well-described phenotypic association

**Potential Clinical Interpretation: Uncertain, Likely Pathogenic OR Uncertain**

**1: Little Evidence**

- A single loss of function mutation or duplication in an individual with a clinical phenotype
- OR**
- Observed amongst clinical populations at a statistically significant level in a single large-scale case-control series, without a well-described phenotypic association
- OR**
- Only secondary evidence available to support possible dosage sensitivity

**Potential Clinical Interpretation: Uncertain**

**0: No Evidence**

- No loss of function mutations or duplications reported in probands with a clinical phenotype

**Potential Clinical Interpretation: Uncertain OR Uncertain, Likely Benign**

**Dosage Sensitivity is Unlikely**

- Only evidence refuting the region's dosage sensitivity (e.g., significant observation in normal population, etc.) has been reported

**Potential Clinical Interpretation: Uncertain, Likely Benign OR Benign**

# Using Dosage Sensitivity in Clinical Practice

- Interpreting copy number variants
  - Which genes in the deleted/duplicated region are dosage sensitive?
- Beyond copy number variants...
  - Which diseases are potentially caused by LOF mechanism?

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**Dosage Sensitivity**  
Is haploinsufficiency or triplosensitivity an established disease mechanism for this gene?

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Which genes, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known?



[Genet Med.](#) 2016 Dec; 18(12): 1258–1268.

Published online 2016 Apr 28. doi: [10.1038/gim.2016.40](https://doi.org/10.1038/gim.2016.40)

PMCID: [PMC5085884](#)

NIHMSID: [NIHMS769803](#)

## **A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation**

[Jessica Ezzell Hunter](#), MS, PhD,<sup>1,\*</sup> [Stephanie A. Irving](#), MHS,<sup>1</sup> [Leslie G. Biesecker](#), MD,<sup>2</sup> [Adam Buchanan](#), MS, MPH,<sup>3</sup> [Brian Jensen](#), MD,<sup>4</sup> [Kristy Lee](#), MS,<sup>5</sup> [Christa Lese Martin](#), PhD,<sup>6</sup> [Laura Milko](#), PhD,<sup>5</sup> [Kristin Muessig](#), MS,<sup>1</sup> [Annie D. Niehaus](#), BA,<sup>7</sup> [Julianne O'Daniel](#), MS,<sup>5</sup> [Margaret A. Piper](#), PhD, MPH,<sup>1</sup> [Erin M. Ramos](#), MPH, PhD,<sup>7</sup> [Sheri D. Schully](#), PhD,<sup>8</sup> [Alan F. Scott](#), PhD,<sup>9</sup> [Anne Slavotinek](#), MBBS, PhD,<sup>10</sup> [Nara Sobreira](#), MD, PhD,<sup>9</sup> [Natasha Strande](#), PhD,<sup>5</sup> [Meredith Weaver](#), ScM, PhD,<sup>11</sup> [Elizabeth M. Webber](#), MS,<sup>1</sup> [Marc S. Williams](#), MD,<sup>3</sup> [Jonathan S. Berg](#), MD, PhD,<sup>5</sup> [James P. Evans](#), MD, PhD,<sup>5</sup> [Katrina A.B. Goddard](#), PhD,<sup>1</sup> and ; on behalf of the ClinGen Resource

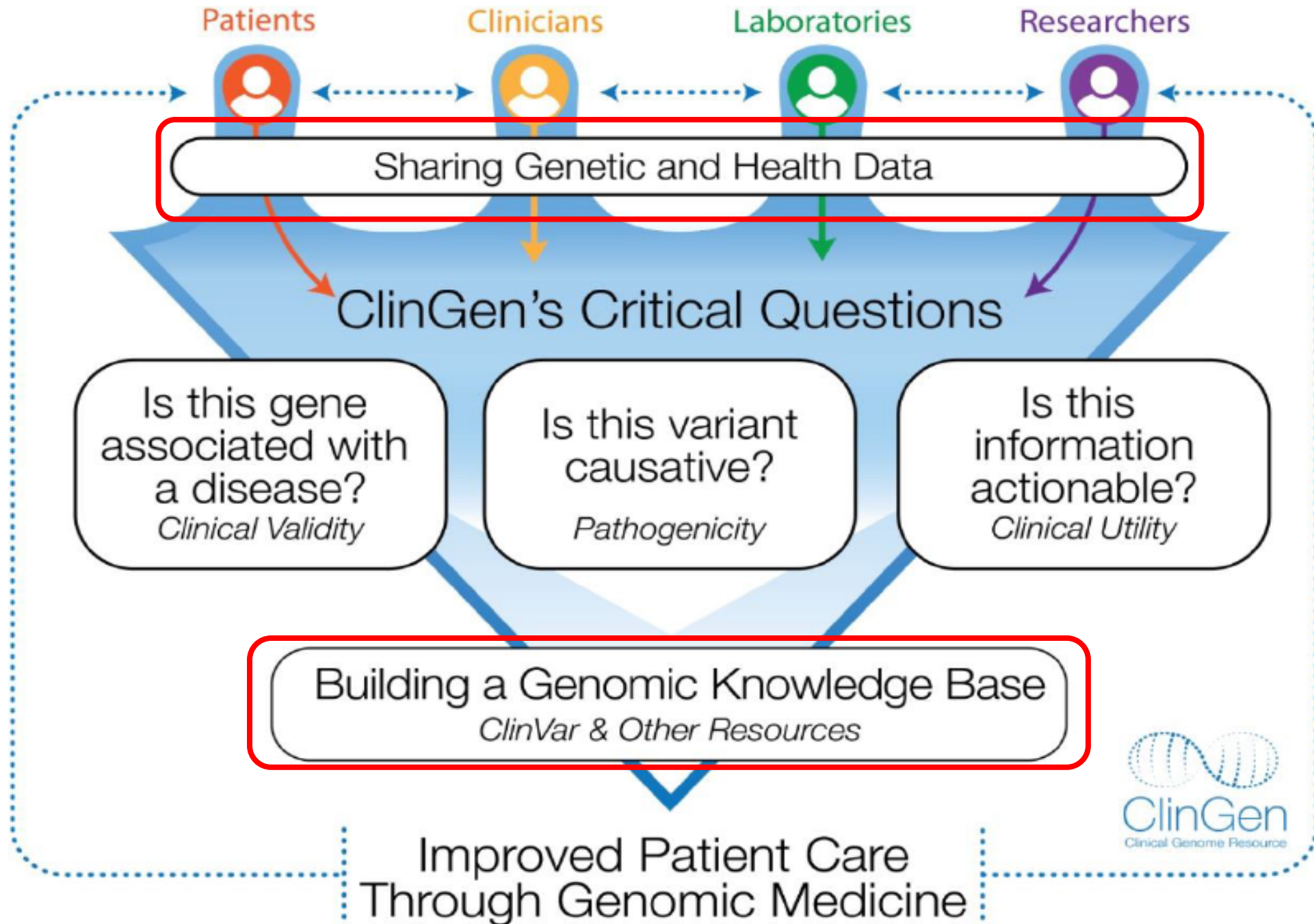


Domain	Scores
<b>Severity:</b> what is the nature of the threat to health to an individual carrying a clearly deleterious allele in this gene?	3 = Reasonable possibility of sudden death 2 = Reasonable possibility of death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity
<b>Likelihood of disease:</b> what is the chance that a serious outcome will materialize given a deleterious variant (akin to penetrance)?	3 = >40% chance 2 = 5–39% chance 1 = 1–4% chance 0 = <1% chance
<b>Effectiveness of specific interventions:</b> how effective is the selected, specific intervention for preventing or significantly diminishing the risk of harm?	3 = Highly effective 2 = Moderately effective 1 = Minimally effective 0 = Controversial or unknown effectiveness IN = Ineffective/no intervention*
<b>Nature of intervention:</b> how risky, medically burdensome, or intensive is a given intervention?	3 = Low risk, or medically acceptable and low-intensity interventions 2 = Moderate risk, moderately acceptable or intensive interventions 1 = Greater risk, less acceptable and substantial interventions 0 = High risk, poorly acceptable or intensive interventions
<b>State of the knowledge base:</b> what is the level of evidence?	A = Substantial evidence, or evidence from a high tier (tier 1) B = Moderate evidence, or evidence from a moderate tier (tier 2) C = Minimal evidence, or evidence from a lower tier (tier 3 or 4) D = Poor evidence, or evidence not provided in the report E = Evidence based on expert contributions (tier 5)

\*Do not score the remaining categories.

# Using Clinical Actionability in Clinical Practice

- May help guide return of secondary or incidental findings
- Actionability reports provide a comprehensive overview of clinical features, natural history, and management recommendations based on published guidelines



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  - >570 individuals from >230 institutions worldwide
  - Funding: NIH/NHGRI U41HG006834, U41HG009649, U41HG009650
- ClinVar staff
  - Team lead: Melissa Landrum
- Questions?
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  - [clingen@clinicalgenome.org](mailto:clingen@clinicalgenome.org)