ClinGen and ClinVar: Complementary Resources

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ClinGen
Clinical Genome Resource

NCBI ClinVar

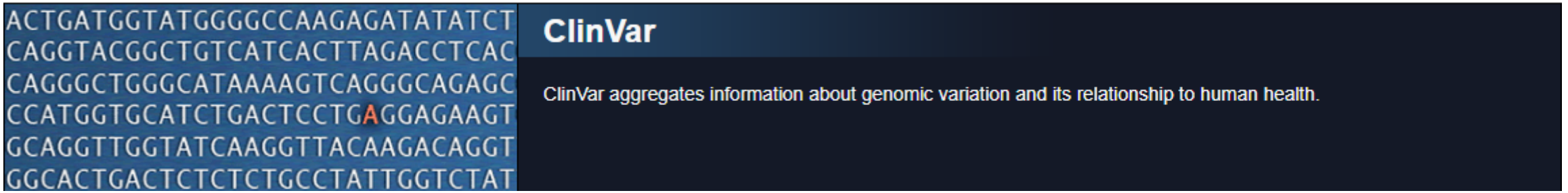
ClinGen and ClinVar: What's the Difference?

- 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?



- 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

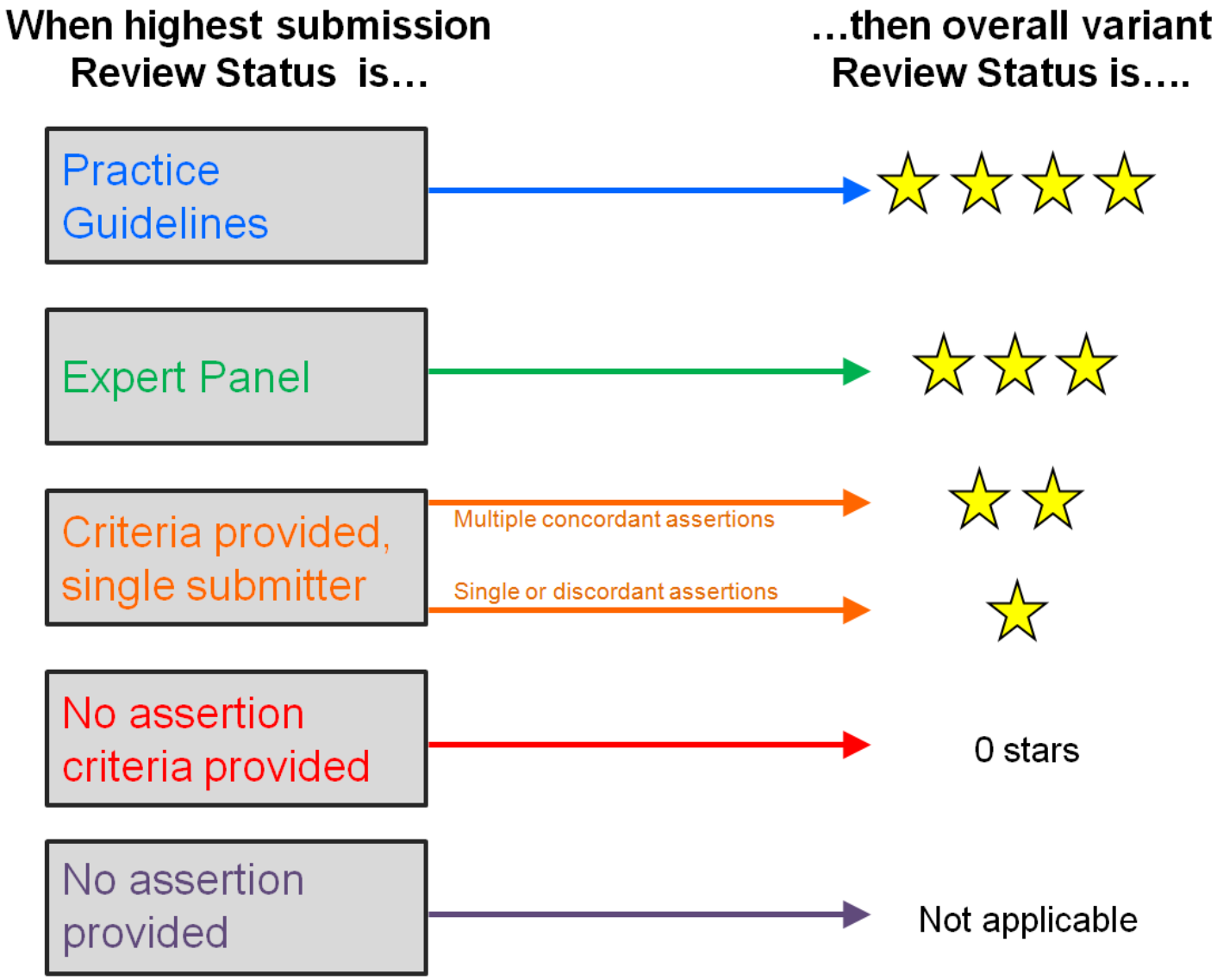
- There are many pieces of information that ClinVar CAN collect on a variant, but *if a submitter does not submit them, they aren't available.*

- Quality of submissions vary

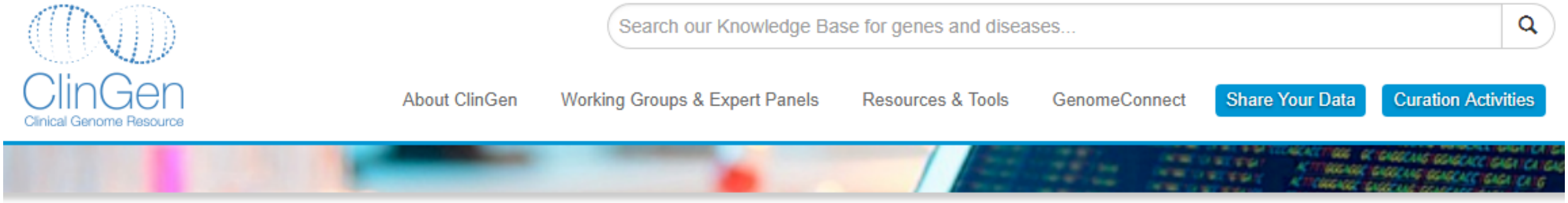
- When assessing the information you find in ClinVar, you must assess the quality of the submitter/submission itself

Assessing Quality in ClinVar

- IN GENERAL, one mark of a submission's quality is it's 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/



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.

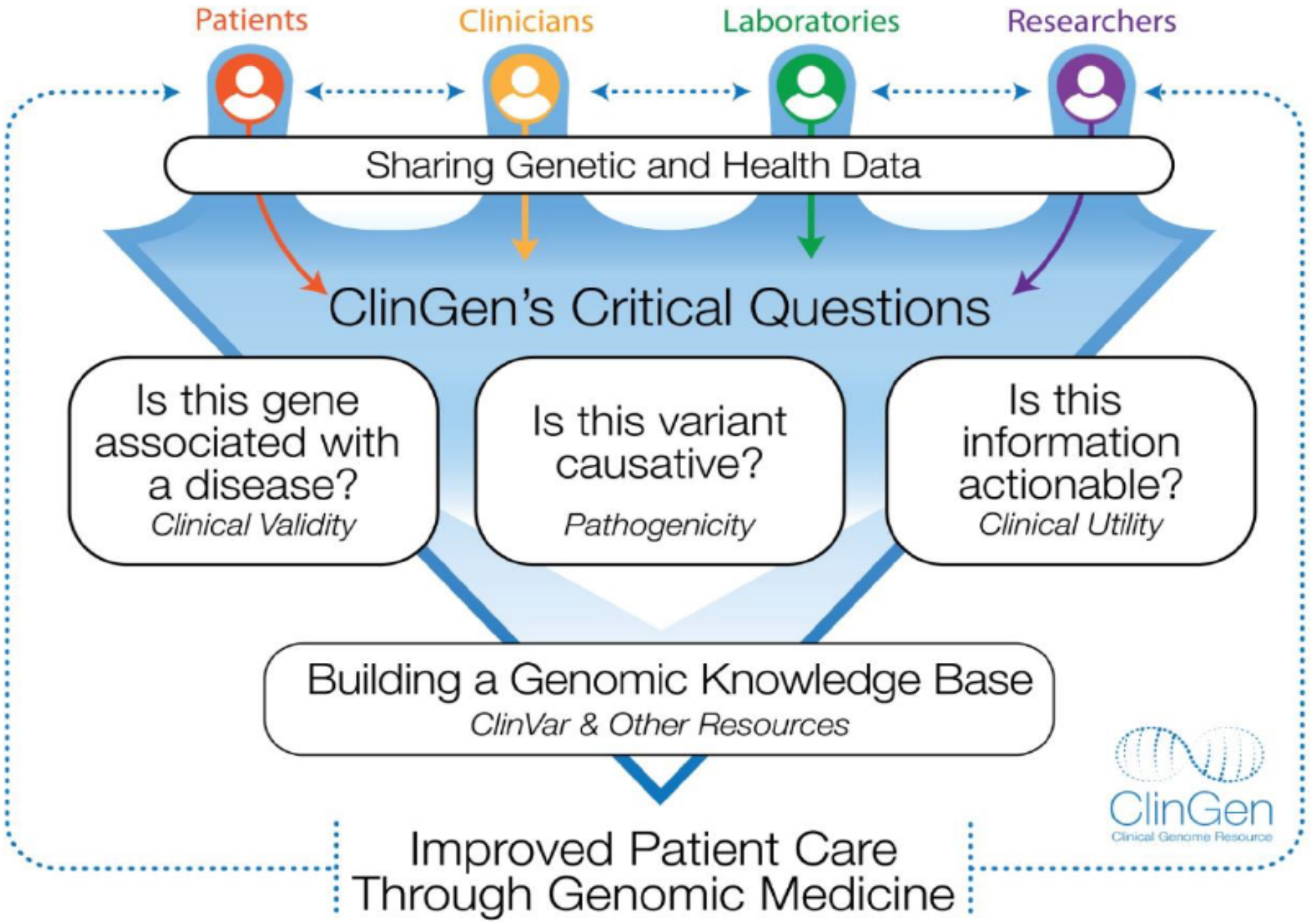
Questions about the criteria? Visit our Frequently Asked Questions or contact clingen@clinicalgenome.org.

https://www.clinicalgenome.org/lablist/

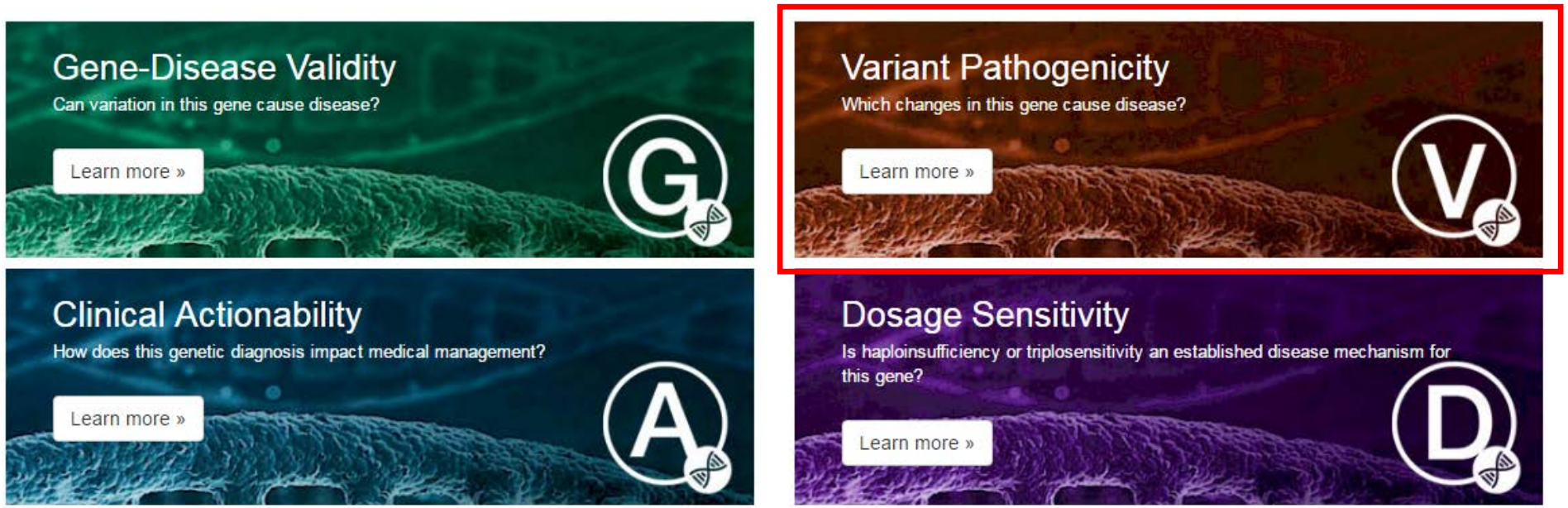
Laboratory	Meets requirements	Additional Achievements			
		Submitted evidence[1]	>75% from past 5 years[2]	Discrepancy resolution[3]	Consenting mechanism[4]
Ambry	✓	✓	✓	✓	✓
ARUP	✓			✓	
Athena Diagnostics Inc.	✓			✓	
Centre for Mendelian Genomics, University Medical Centre Ljubljana	✓		✓	✓	
Center for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

Laboratory	Meets requirements	Additional Achievements			
		Submitted evidence[1]	>75% from past 5 years[2]	Discrepancy resolution[3]	Consenting mechanism[4]
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



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

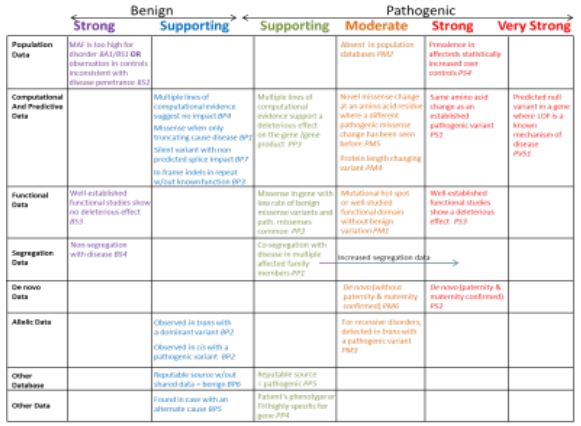
OFFICIAL JOURNAL HGV HUMAN GENOME VARIATION SOCIETY

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



ACMG/AMP Guidelines

ClinGen Expert Panels

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

Gene/Disease Specific ACMG Guidelines

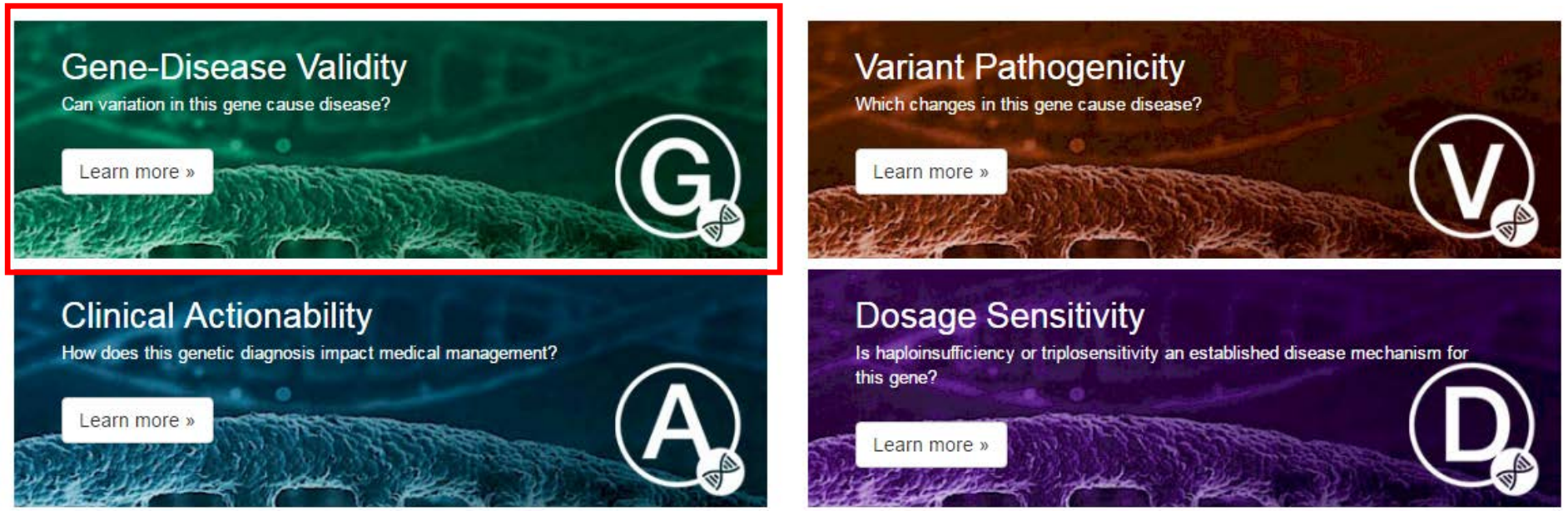
Sequence Variant Interpretation WG

Harmonize recommendations for modifying ACMG guidelines

General recommendations to ACMG Guidelines

Slide courtesy of Steven Harrison, PhD

ClinGen's Curation Efforts



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

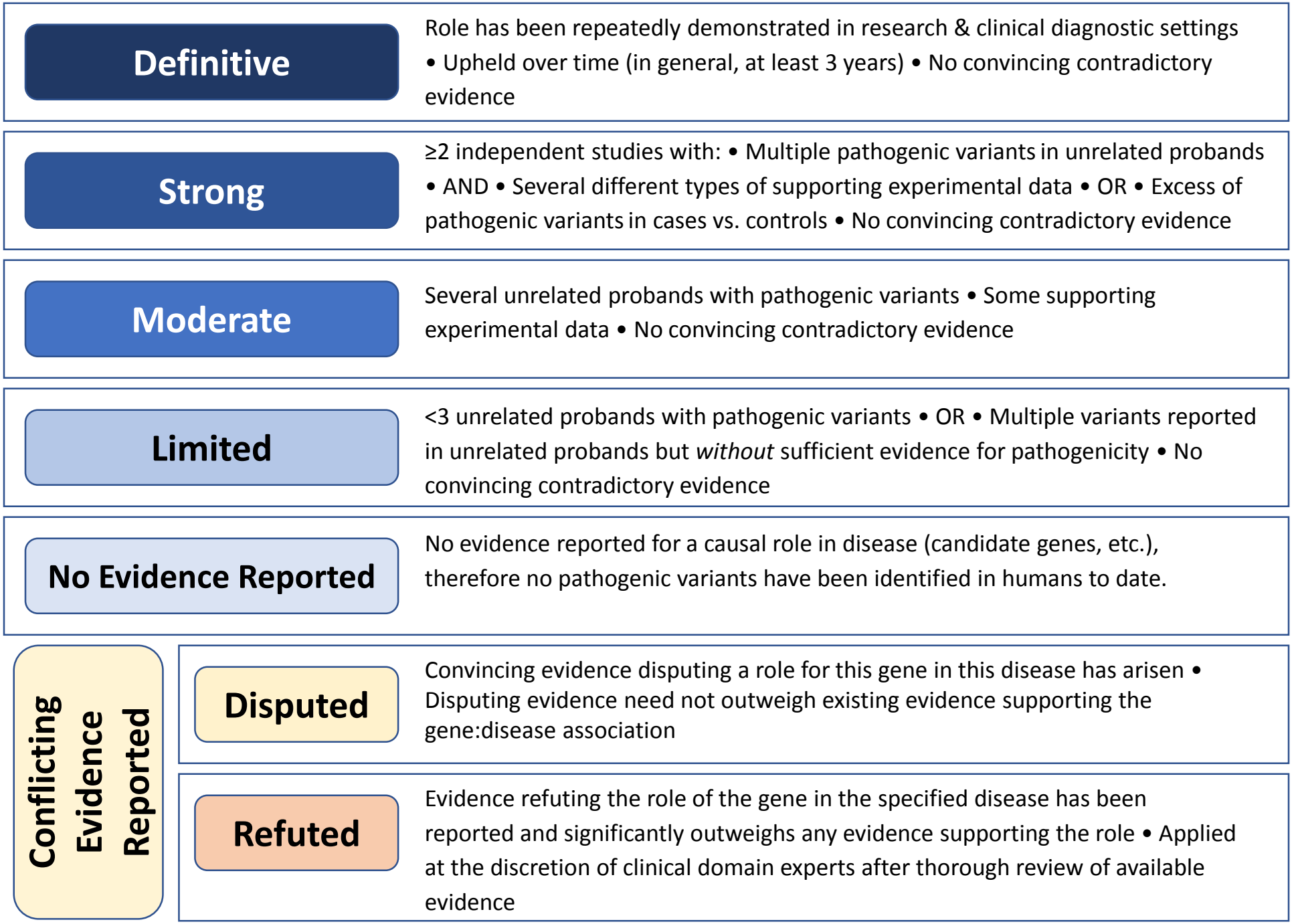
- Defines the criteria needed to assess (genetic evidence, gene-level experimental evidence)
- Describes the strength evidence supporting a gene-disease relationship in a semi-quantitative manner
- Allows users to methodically classify the validity of a given gene-disease pair

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

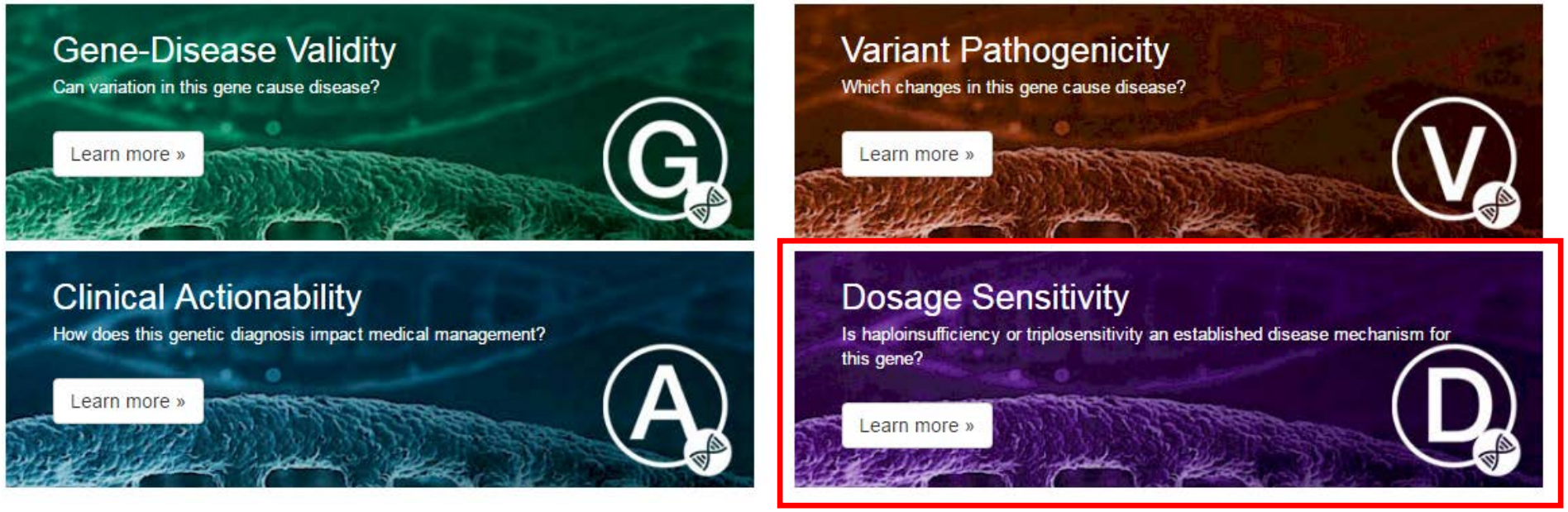
Natasha T. Strande,[1,14] Erin Rooney Riggs,[2,14] Adam H. Buchanan,[3] Ozge Ceyhan-Birsoy,[4,5,6,7] Marina DiStefano,[4] Selina S. Dwight,[8] Jenny Goldstein,[1] Rajarshi Ghosh,[9] Bryce A. Seifert,[1] Tam P. Sneddon,[8] Matt W. Wright,[8] Laura V. Milko,[1] J. Michael Cherry,[8] Monica A. Giovanni,[3]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


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



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

Clin Genet 2012: 81: 403–412
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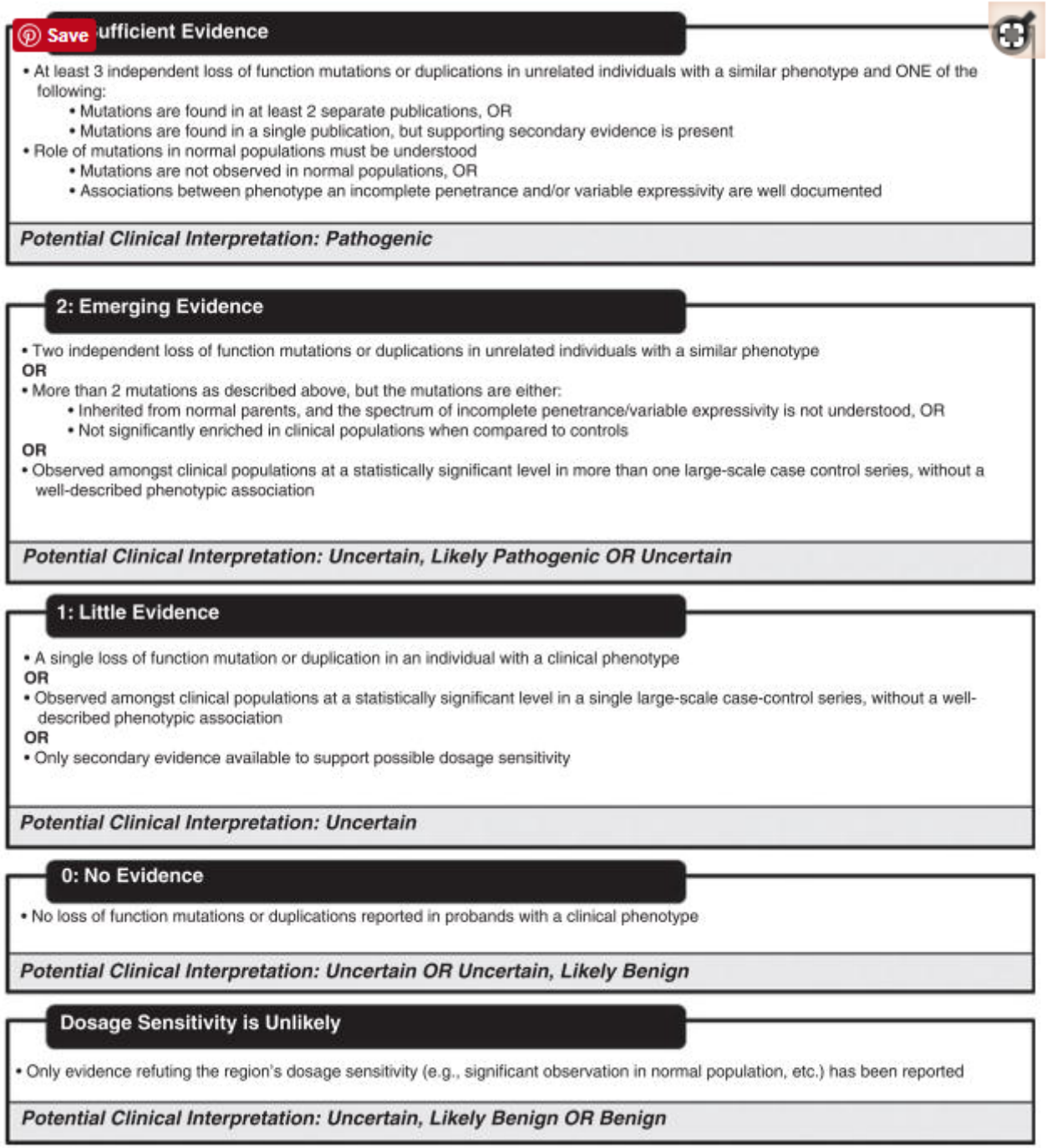
CLINICAL GENETICS

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

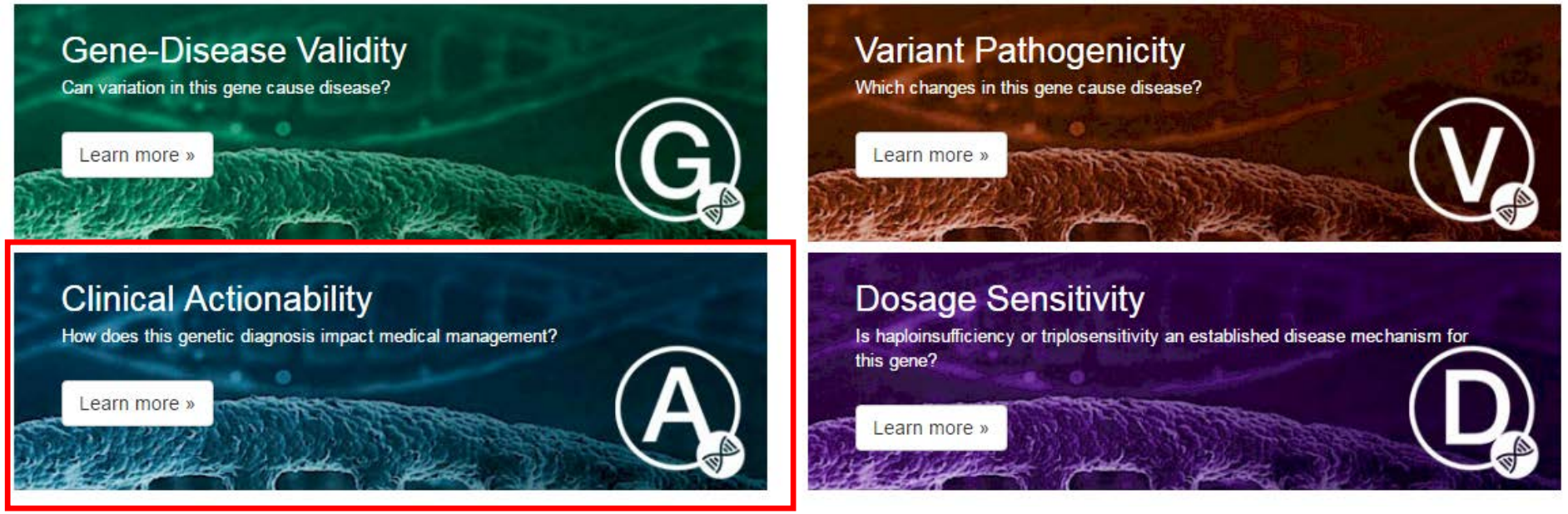


Riggs et al. *Clin Genet* 2012

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?

ClinGen's Curation Efforts



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

GENETICS IN MEDICINE
An open access paper
www.nature.com

Genet Med. 2016 Dec; 18(12): 1258–1268.
Published online 2016 Apr 28. doi: 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,[1,*] Stephanie A. Irving, MHS,[1] Leslie G. Biesecker, MD,[2] Adam Buchanan, MS, MPH,[3] Brian Jensen, MD,[4] Kristy Lee, MS,[5] Christa Lese Martin, PhD,[6] Laura Milko, PhD,[5] Kristin Muessig, MS,[1] Annie D. Niehaus, BA,[7] Julianne O'Daniel, MS,[5] Margaret A. Piper, PhD, MPH,[1] Erin M. Ramos, MPH, PhD,[7] Sheri D. Schully, PhD,[8] Alan F. Scott, PhD,[9] Anne Slavotinek, MBBS, PhD,[10] Nara Sobreira, MD, PhD,[9] Natasha Strande, PhD,[5] Meredith Weaver, ScM, PhD,[11] Elizabeth M. Webber, MS,[1] Marc S. Williams, MD,[3] Jonathan S. Berg, MD, PhD,[5] James P. Evans, MD, PhD,[5] Katrina A.B. Goddard, PhD,[1] and ; on behalf of the ClinGen Resource

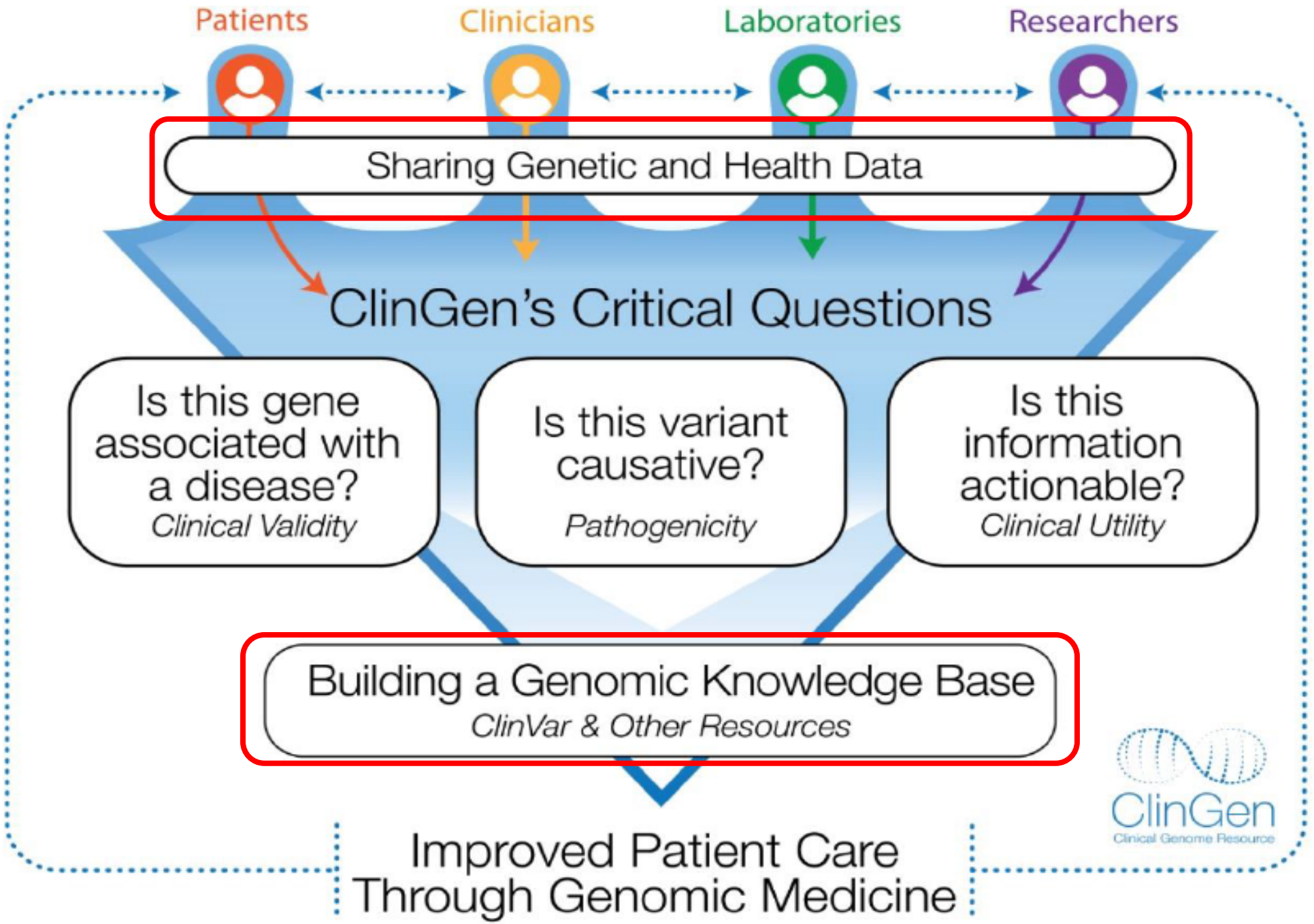
Domain	Scores
Severity: what is the nature of the threat to health to an individual carrying a clearly deleterious allele in this gene?	3 = Reasonable possibility of sudden death 2 = Reasonable possibility of death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity
Likelihood of disease: 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
Effectiveness of specific interventions: 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[a]
Nature of intervention: 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
State of the knowledge base: 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)

[a]Do not score the remaining categories.

Hunter *et al. Genet Med* 2016

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


Patients
Clinicians
Laboratories
Researchers
Sharing Genetic and Health Data
ClinGen's Critical Questions
Is this gene associated with a disease?
Clinical Validity
Is this variant causative?
Pathogenicity
Is this information actionable?
Clinical Utility
Building a Genomic Knowledge Base
ClinVar & Other Resources
ClinGen
Clinical Genome Resource
Improved Patient Care Through Genomic Medicine

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- ClinGen PIs and working group members
  - >570 individuals from >230 institutions worldwide
  - Funding: NIH/NHGRI U41HG006834, U41HG009649, U41HG009650
- ClinVar staff
  - Team lead: Melissa Landrum

- Questions?
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