Panel 2: Consistency of Interpretation of Variants Across Expert Labs / Groups, ClinVar Submissions?

Gail Jarvik, Heidi Rehm, Dan Roden

Genomic Medicine VIII

June 8-9, 2015

Rockville, Maryland

Mendelian Disease Variant Classification Terminology

ACMG Recommendation:

- Pathogenic (≠ mutation)
- Likely pathogenic (90%)
- Uncertain significance (VUS)
- Likely benign
- Benign (≠ polymorphism)

Defining the Challenge

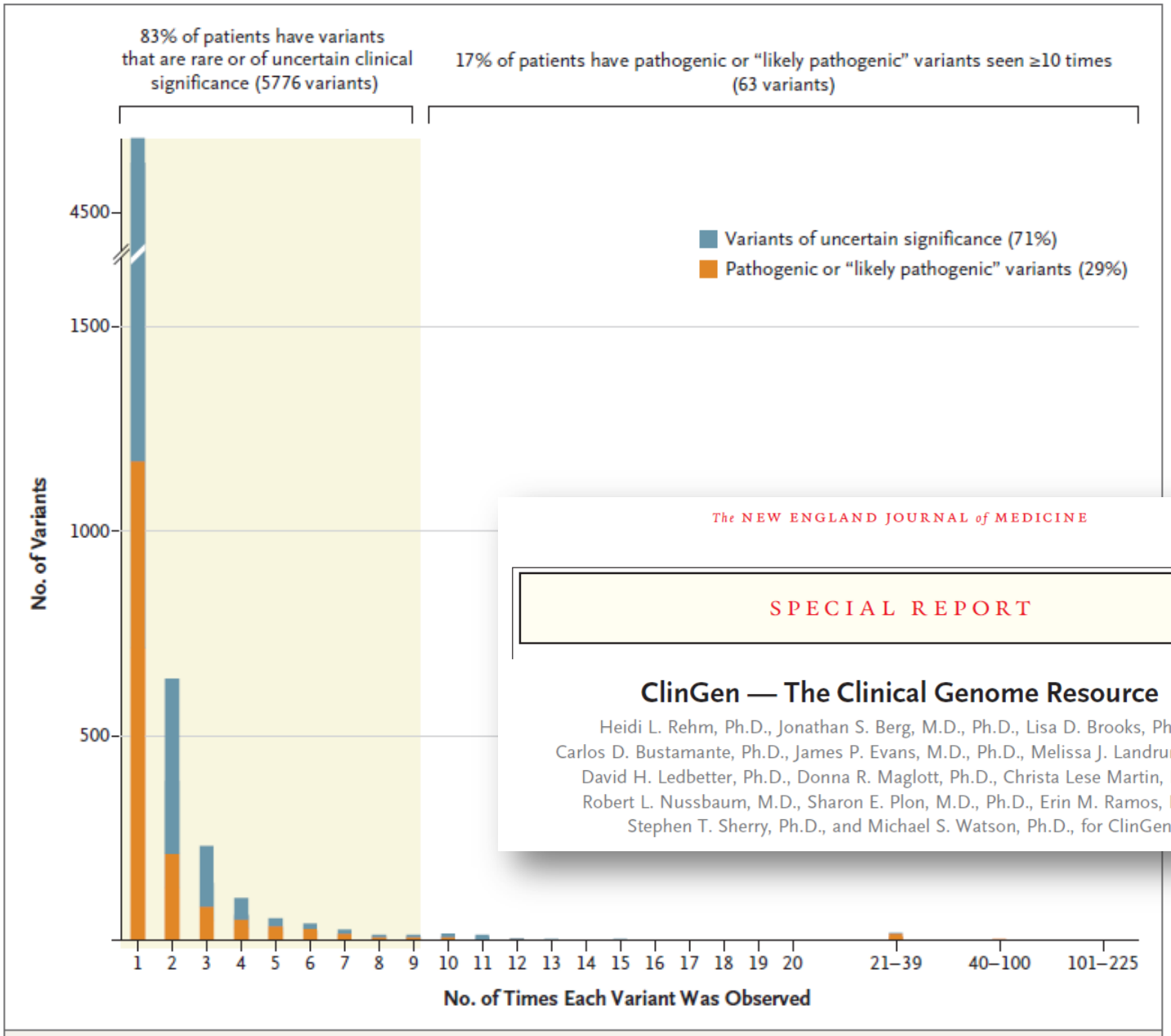


Figure 1. Variant Histogram from Mendelian Disease Testing of 15,000 Probands.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

ClinGen — The Clinical Genome Resource

Heidi L. Rehm, Ph.D., Jonathan S. Berg, M.D., Ph.D., Lisa D. Brooks, Ph.D., Carlos D. Bustamante, Ph.D., James P. Evans, M.D., Ph.D., Melissa J. Landrum, Ph.D., David H. Ledbetter, Ph.D., Donna R. Maglott, Ph.D., Christa Lese Martin, Ph.D., Robert L. Nussbaum, M.D., Sharon E. Plon, M.D., Ph.D., Erin M. Ramos, Ph.D., Stephen T. Sherry, Ph.D., and Michael S. Watson, Ph.D., for ClinGen

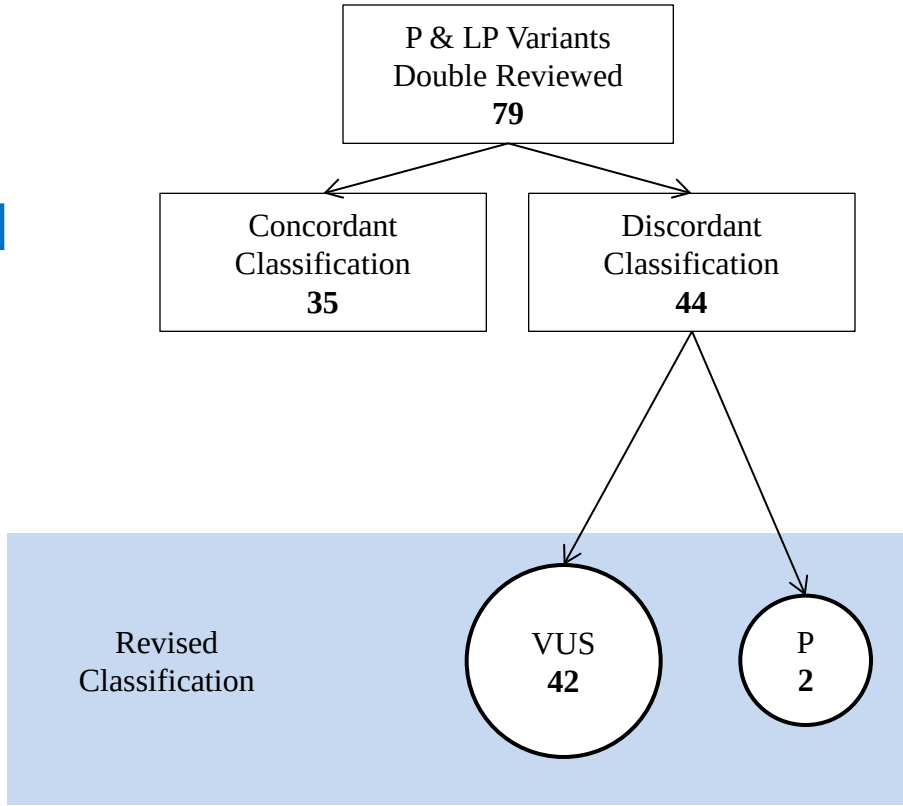
2014 Cross-Consortium Classification of 6 Variants (early ACMG rules)

Site	MSH6 c.2731C>T; p.Arg911*	RYR1 c.1840C>T; p.Arg614Cys	FBN1 c.4270C>G; p.Pro1424Ala	TSC2 c.736A>G; p.Thr246Ala	TNNT2 c.732G>T; p.Glu244Asp	LDLR c.967G>A; p.Gly323Ser
1	Pathogenic	Likely pathogenic/	VUS	VUS	VUS	VUS
2	Pathogenic	Pathogenic	Likely pathogenic/ VUS	VUS	VUS	VUS
3	Pathogenic	Pathogenic	VUS	VUS	VUS	VUS
4	Pathogenic	Pathogenic	VUS	VUS	Likely pathogenic	VUS
5	Pathogenic	Likely pathogenic/	Likely pathogenic/ VUS	Likely pathogenic	VUS	VUS
6	Pathogenic	Likely pathogenic	Pathogenic/ Likely pathogenic/	Likely pathogenic	VUS	Likely pathogenic/ VUS

Amendola et al., *Genome Res* 2015. PMID: 25637381

EVS 6500 Variant Classification QC: Overcalling

- Recalled all pathogenic & likely pathogenic variants:
  - 56% discordant;
  - 42/44 (95%) overcalled (final call VUS)
- Final calls matched experts
  - 142/144 (99%)



Amendola et al. *Genome Res* 2015. *PMID: 25637381*

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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

The American College of Medical Genetics and Genomics (ACMG) previously developed guidance for the interpretation of sequence variants.[1] In the past decade, sequencing technology has evolved rapidly with the advent of high-throughput next-generation sequencing. By adopting and leveraging next-generation sequencing, clinical laboratories are now performing an ever-increasing catalogue of genetic testing spanning genotyping, single genes, gene panels, exomes, genomes, transcriptomes, and epigenetic assays for genetic disorders. By virtue of increased complexity, this shift in genetic testing has been accompanied by new challenges in sequence interpretation. In this context the ACMG convened a workgroup in 2013 comprising representatives from the ACMG, the Association for Molecular Pathology (AMP), and the College of American Pathologists to revisit and revise the standards and guidelines for the interpretation of sequence variants. The group consisted of clinical laboratory directors and clinicians. This report represents expert opinion of the workgroup with input from ACMG, AMP, and College of American Pathologists stakeholders. These recommendations primarily apply to the breadth of genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. This report recommends the use of specific standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified in genes that cause Mendelian disorders. Moreover, this recommendation describes a process for classifying variants into these five categories based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data). Because of the increased complexity of analysis and interpretation of clinical genetic testing described in this report, the ACMG strongly recommends that clinical molecular genetic testing should be performed in a Clinical Laboratory Improvement Amendments–approved laboratory, with results interpreted by a board-certified clinical molecular geneticist or molecular genetic pathologist or the equivalent.

Genet Med advance online publication 5 March 2015

Key Words: ACMG laboratory guideline; clinical genetic testing; interpretation; reporting; sequence variant terminology; variant reporting

	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 *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 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			

ACMG Standard Recs
Richards et al GIM 2015
PMID:25741868

ACMG Variant Classification Rules, continued

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

2015 CSER "bakeoff"

99 germline variants
-9 classified by 9 sites
-90 classified by 2-3 sites

by ACMG and own rules

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Intra-laboratory Usual vs. ACMG Classification Comparison
9 labs x 9 variants

		Laboratory class					Total
		P	LP	VUS	LB	B	
ACMG class	P	13	0	2	0	0	15
	LP	3	18	2	0	0	23
	VUS	0	3	14	7	1	25
	LB	0	0	1	10	3	14
	B	0	0	0	0	4	4
Total		16	21	19	17	8	**81**

- 73% concordant
- 9% ACMG less pathogenic
- 19% ACMG more pathogenic
- If discordant, ACMG less certain 77% (e.g. VUS; blue boxes; 17/22)

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Intra-laboratory Usual vs. ACMG Classification Comparison: 98 variants (90 average 2.85 calls, 9 have 9 calls)

		ACMG class					
		P	LP	VUS	LB	B	Total
Lab class	P	59	12	2	0	0	73
	LP	5	58	5	0	0	68
	VUS	6	4	91	3	0	104
	LB	0	0	17	32	4	53
	B	0	0	4	5	28	37
Total		70	74	119	40	32	**335**

Benign	(i) 1 Stand-alone (BA1) *OR*
	(ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*
	(ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR
	(ii) the criteria for benign and pathogenic are contradictory

MAF > 5%

MAF > disease frequency

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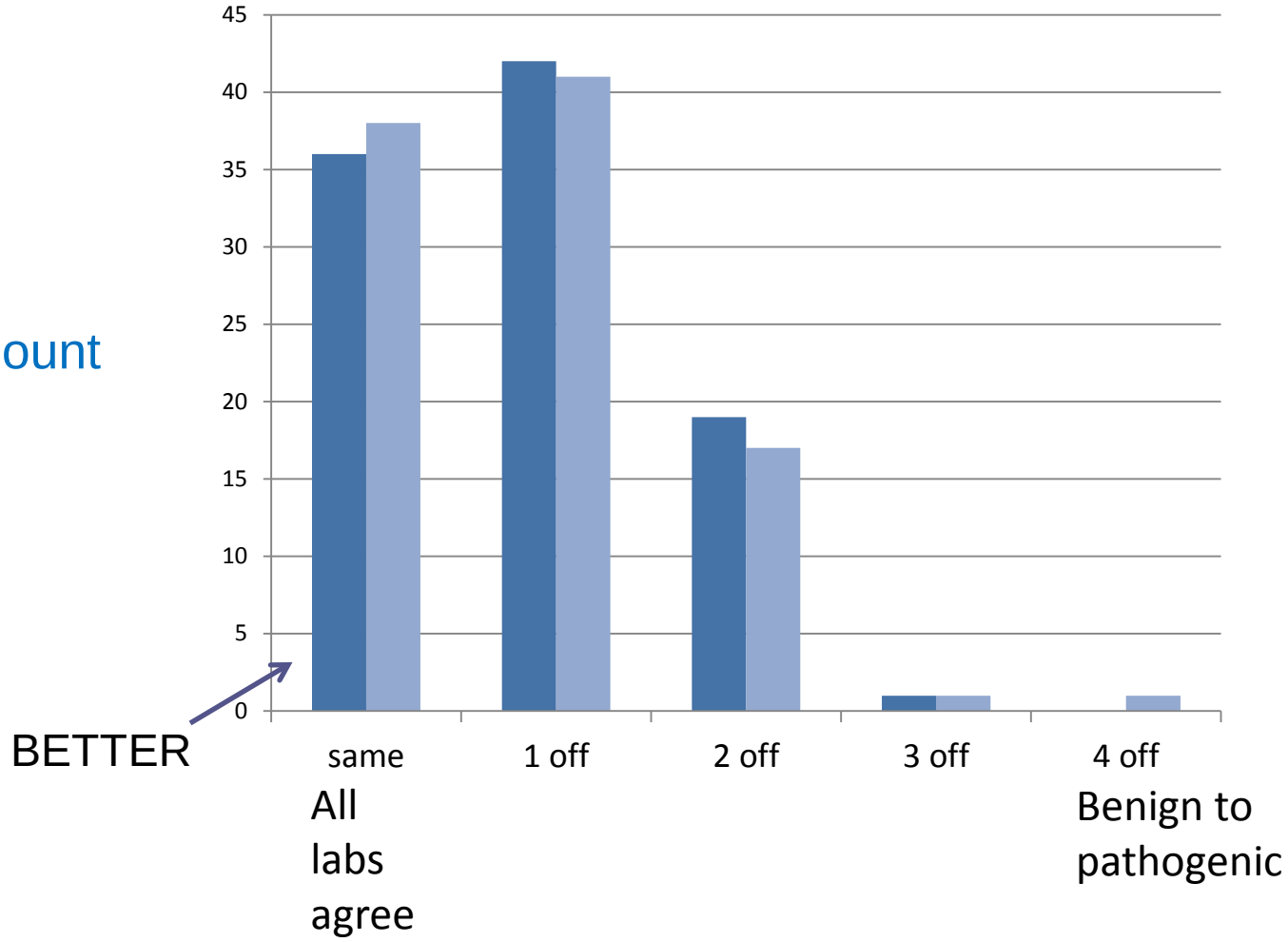
Inter-laboratory Concordance of 98 variants



P=0.9

Difference in classifications across labs

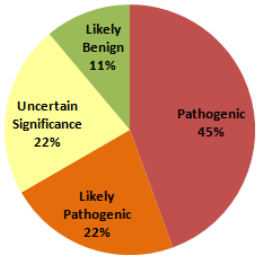
1.Pathogenic
2.Likely pathogenic
3.VUS
4.Likely benign
5.Benign

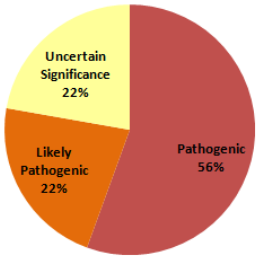
Variant with Major Disagreement: Why?

SPG7:c.1529C>T (p.Ala510Val)

- 0.4% EU chromosomes (267/66688; 0.8% people; ExAC); 3/50 people in CSER
- AR, late-onset, +/- reduced penetrance, spastic paraplegia Sanger confirmed

Laboratory classification





ACMG Classification

Time: 25 (LB/VUS) to >200 (VUS/P) minutes

AR, trans
Cosegregation
Functional evidence
MAF > disease frequency
Computational

Laboratory class	ACMG Rules	PP3	PS3	PM3	PP1	PS1	PS4	PP5	PM2	BS1	PP2	PP4	ACMG lines of evidence
Pathogenic	Pathogenic	X	X	X			X	X					PS3,PS4,PM3,PP3,PP5
Pathogenic	Pathogenic	X	X	X	X	X		X					PS1, PS3, PM3, PP1, PP3, PP5
Pathogenic	Pathogenic	X	X	X	X	X	X						PS1, PS3(moderate) ,PS4, PM3, PP1, PP3
Pathogenic	Pathogenic			X	X								PM3 (strong), PP1 (strong)
Likely Pathogenic	Likely Pathogenic	X	X	X	X		X		X				PP1, PP3, PM2, PM3, PS3(weak), PS4
Likely Pathogenic	Likely Pathogenic	X				X		X					PS1, PP3, PP5
Uncertain Significance	Pathogenic	X	X						X		X	X	PS3, PM2, PP2, PP3, PP4
Likely Benign	Uncertain Significance		X			X	X			X			PS1, PS3, PS4, BS1
Uncertain Significance	Uncertain Significance	X			X					X			PP1, PP3, BS1
		7	6	5	5	4	4	3	2	2	1	1	

Sample size to determine pathogenicity

# Cases with equal controls necessary to characterize as pathogenic		
Disease relative risk	MAF = 0.01%	MAF = 0.001%
RR=12	6,544	65,358
RR=6	16,392	163,792
RR=3	54,650	546,238
RR=1.5	490,135	4,899,864

Shirts et al.
GIM 2014
PMID:24357849

- If population-based cohort, large number to get different types of disease covered.
- Some variants will occur only in some ancestry groups.

Genomic/Phenotypic Data Commons?

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SPECIAL REPORT

The FDA and Genomic Tests — Getting Regulation Right

Barbara J. Evans, Ph.D., J.D., Wylie Burke, M.D., Ph.D., and Gail P. Jarvik, M.D., Ph.D.

The Food and Drug Administration (FDA) recently advanced two draft guidances[1,2] proposing a regulatory framework for laboratory-developed tests, a category that includes many but not all genomic tests. The FDA convened a workshop in February 2015 to discuss the oversight of next-generation sequencing.[3,4] President Barack Obama's Precision Medicine Initiative calls for the FDA to modernize its approach to genomic testing[5,6] as ment-discretion policy that shields many laboratory-developed tests from being regulated as medical devices.[1,2] The agency believes its "policy of general enforcement discretion" for laboratory-developed tests "is no longer appropriate"[1] in light of profound changes in technology and business practices. This raises a question: Are the FDA medical device regulations also out of date? These regulations rely heavily on statutory

NEJM May 2015
PMID: 26014592

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Amendola coauthors: Laura Amendola, Michael Dorschner, Peggy Robertson, Joseph Salama, Ragan Hart, Brian Shirts, Mitzi Murray[5], Mari Tokita, Carlos Gallego, Daniel Kim[2], James Bennett, David Crosslin, Jane Ranchalis, Kelly L Jones, Elisabeth Rosenthal, Ella Jarvik, Andy Itsara, Emily Turner, Daniel Herman, Jennifer Schleit, Amber Burt, Seema Jamal, Jenica Abrudan, Andrew Johnson, Laura Conlin, Matthew Dulik, Avni Santani, Danielle Metterville, Melissa Kelly, Ann Foreman, Kristy Lee, Kent Taylor, Xiuqing Guo, Kristy Crooks, Lesli Kiedrowski, Leslie Raffel, Ora Gordon, Kalotina Machini, Robert Desnick, Les Biesecker, Steven Lubitz, Surabhi Mulchandani, Greg Cooper, Steven Joffe, C. Sue Richards, Yaoping Yang, Jerome Rotter, Steve Rich, Chris O'Donnell, Jonathan Berg, Nancy Spinner, James Evans, Malia Fullerton, Kathleen Leppig, Robin Bennett, Thomas Bird, Virginia Sybert, William Grady, Holly Tabor, Jerry Kim, Michael Bamshad, Benjamin Wilfond, Arno Motulsky, C. Ronald Scott, Colin Pritchard, Tom Walsh, Wylie Burke, Wendy Raskind, Peter Byers, Fuki Hisama, Heidi Rehm, Debbie Nickerson, Gail Jarvik

CESR members involved in bakeoff: Jarvik GP, Amendola LA, McLaughlin H, Milosavljevic A, Horton C, Ghosh R, Dorschner M, Punj S, Pak C, Akkari Y, Salama J, Cooper, G, Biesecker L, Conlin LK, Biswas S, Dulik M, Ghazani A, Strande NT, Yang Y, Van Allen E, Wagle N, Green RC, Krantz I, Chinnaiyan A, Berg JS, Evans JP, Garraway L, Goddard KAB, Spinner N, Plon SE, Richards S, and Rehm HL

Barbara Evans and Wylie Burke

The whole CSER team; PIs: Sharon Plon, Will Parsons, Robert Green, Leslie Biesecker, Ian Krantz, Nancy Spinner, Levi Garraway, Pasi Janne, Richard Myers, Katrina Goddard, Ben Wilfond, Arul Chinnaiyan, Jim Evans, Gail Jarvik, Wylie Burke, Debbie Nickerson, and Peter Tarczy-Hornoch

Funding: NHGRI & NCI (including U01HG006507, U01HG006375); also 5T32GM007454 and EVS data supported by NHLBI

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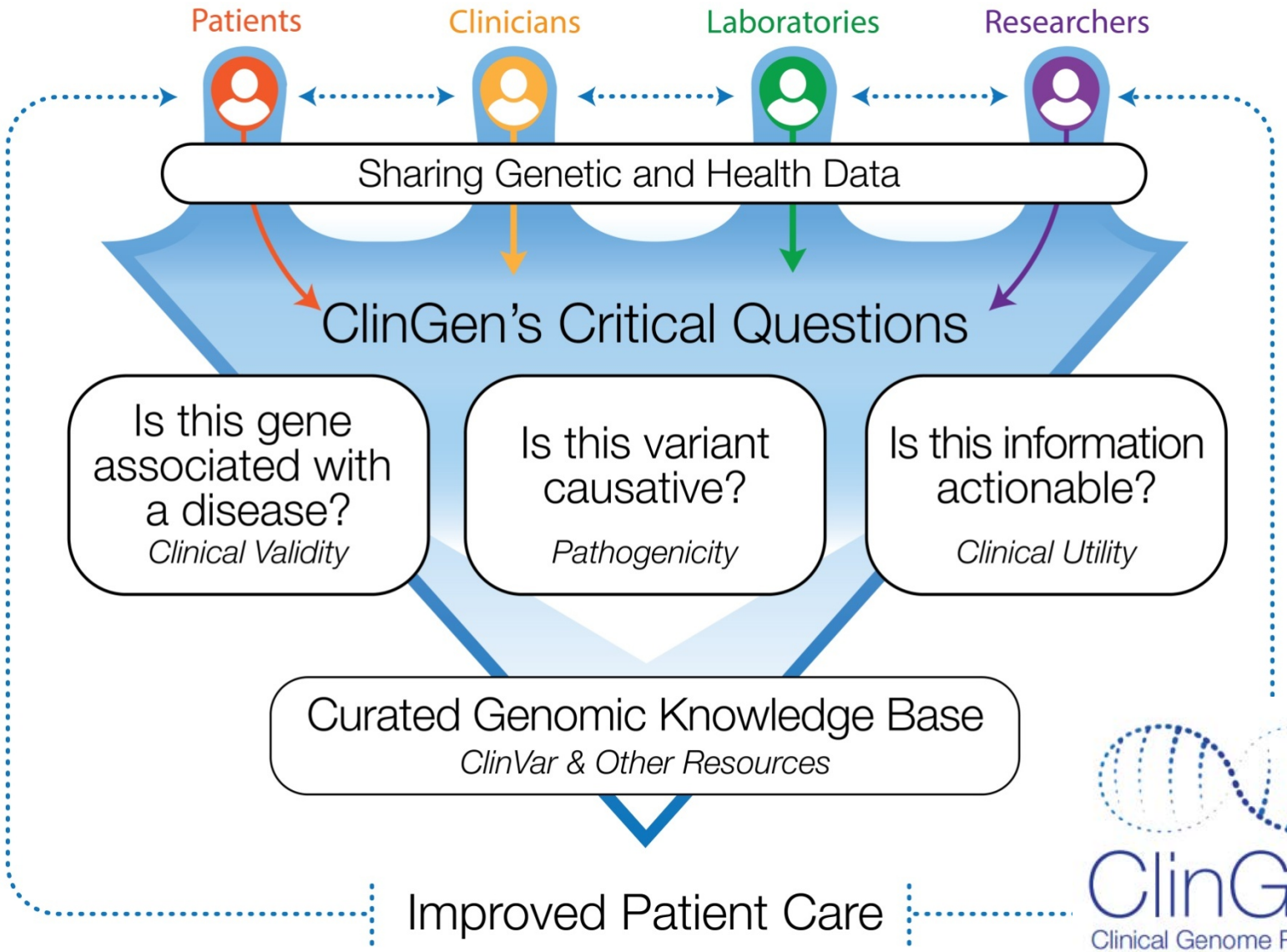
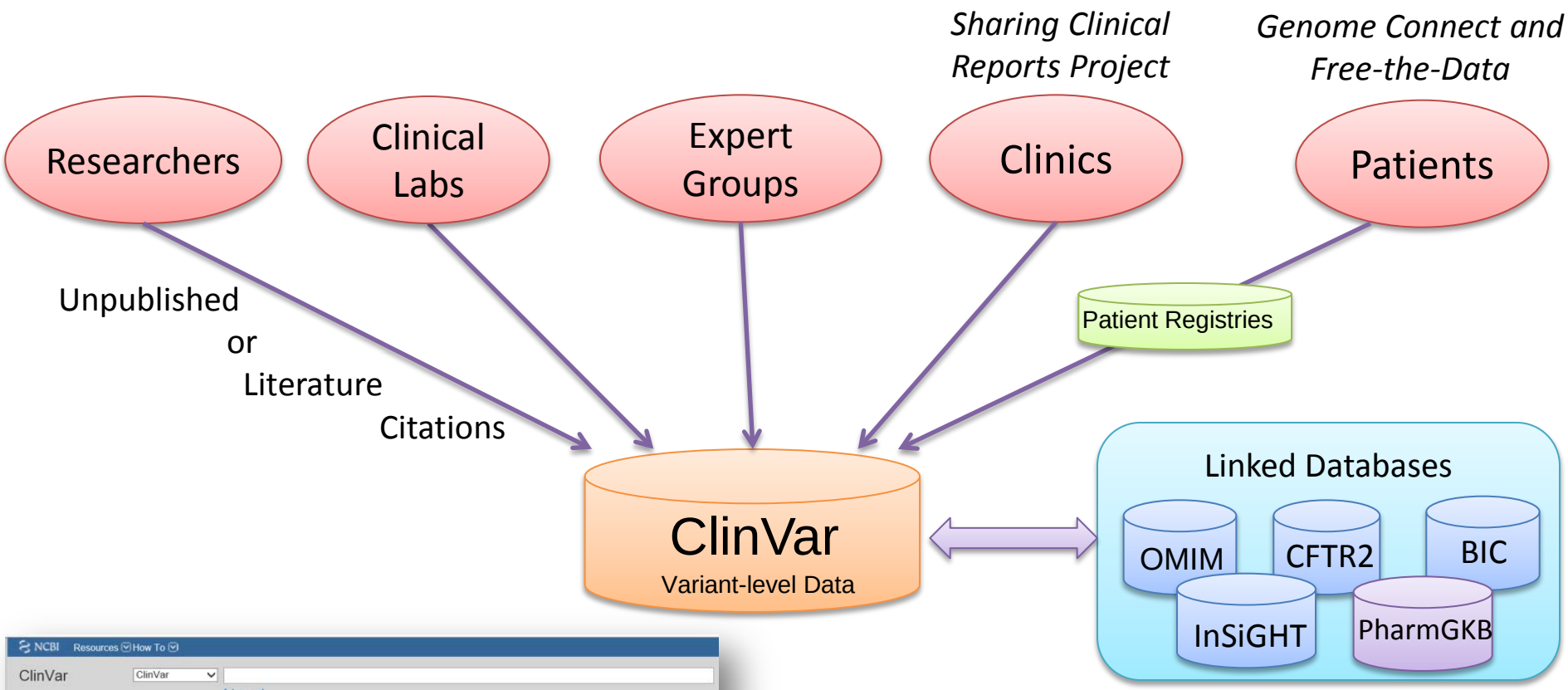
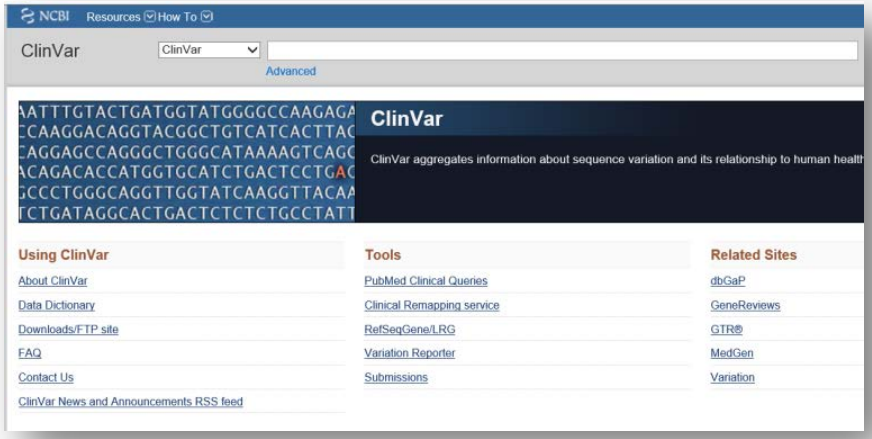
Clinical Sequencing Exploratory Research

The Clinical Genome Resource



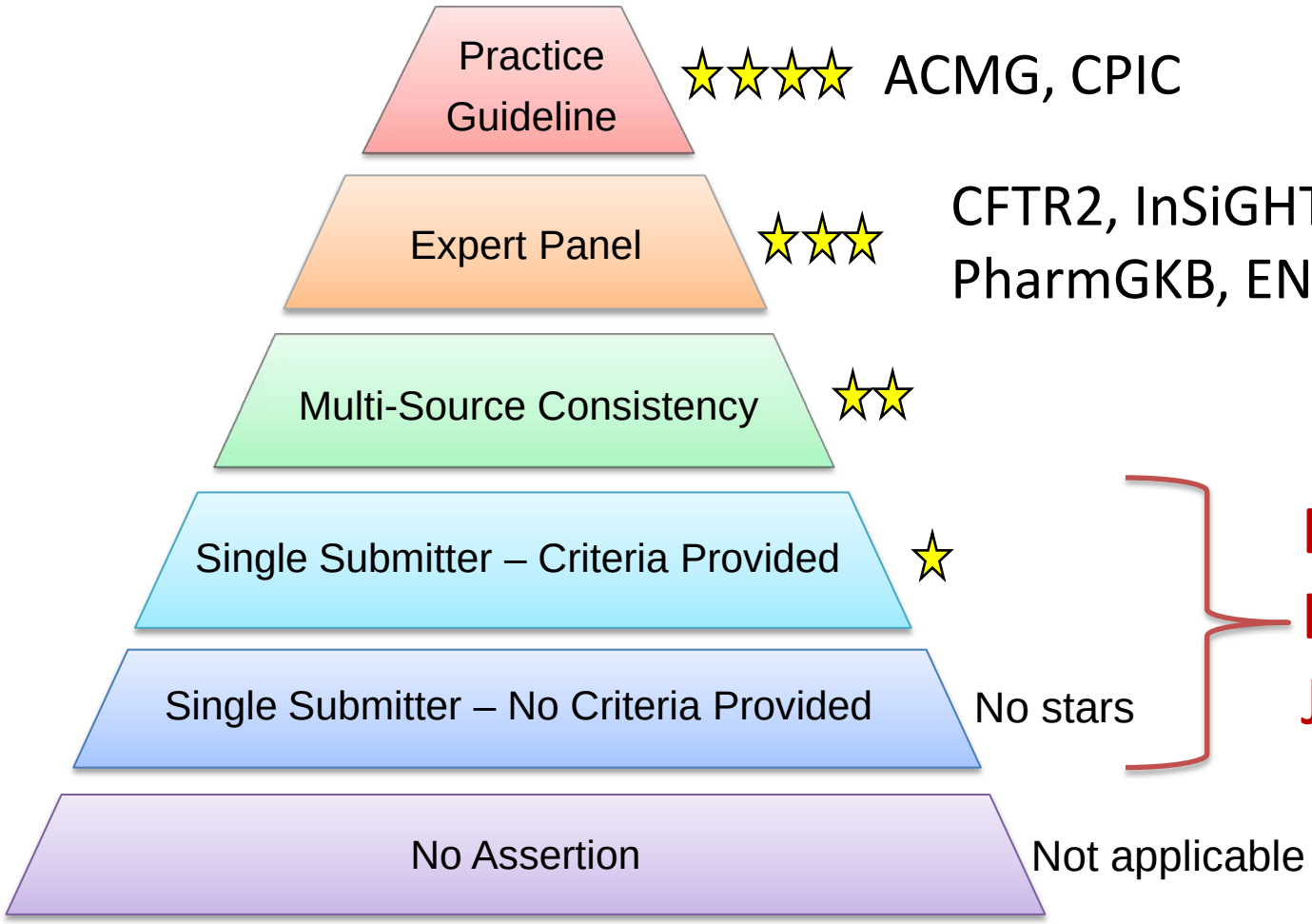
ClinVar: ClinGen's Variant Repository





>315 ClinVar submitters
>172,000 submissions
>118,000 unique interpreted variants

Assertion Levels in ClinVar

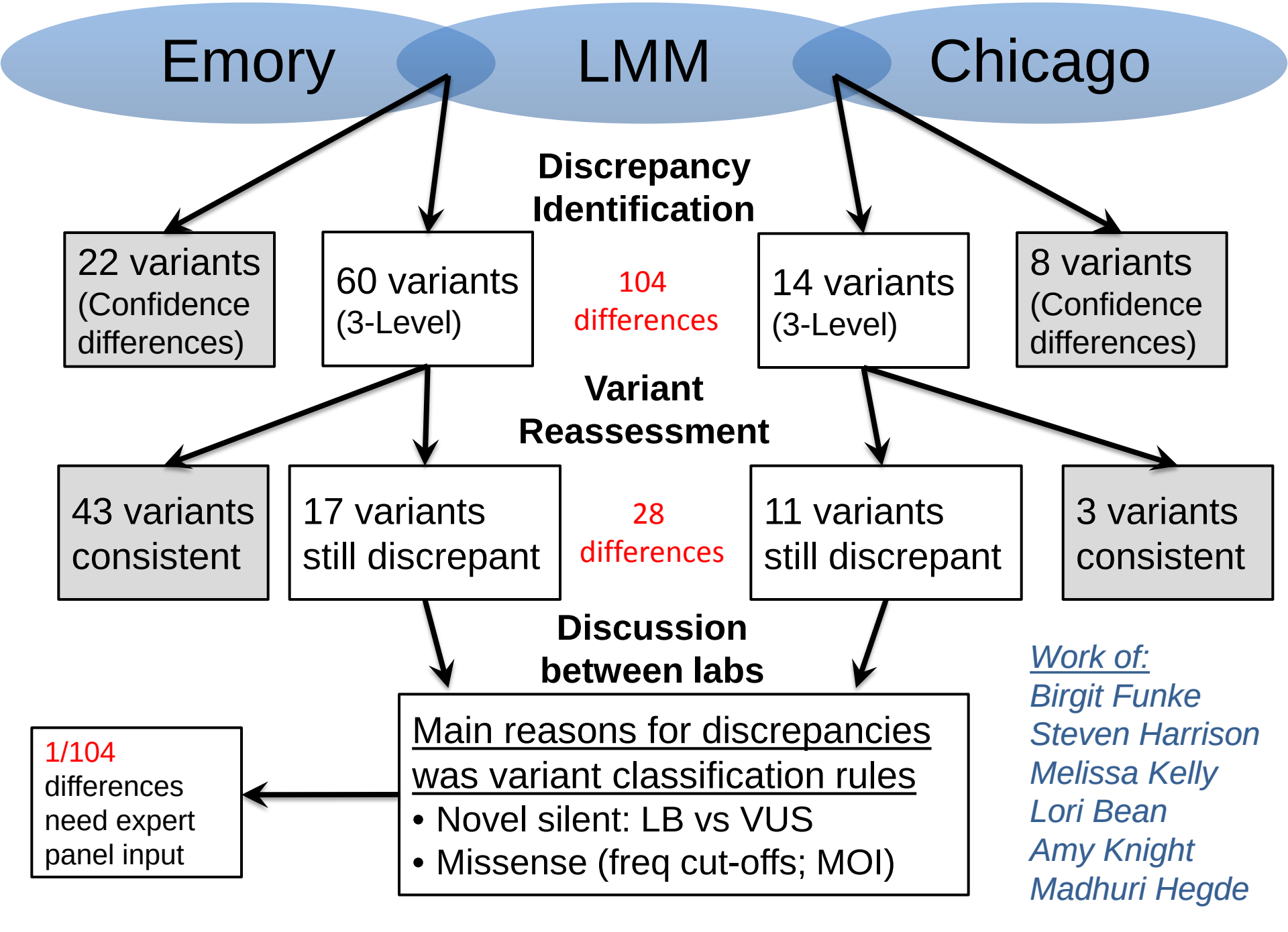


ClinVar Variant Database

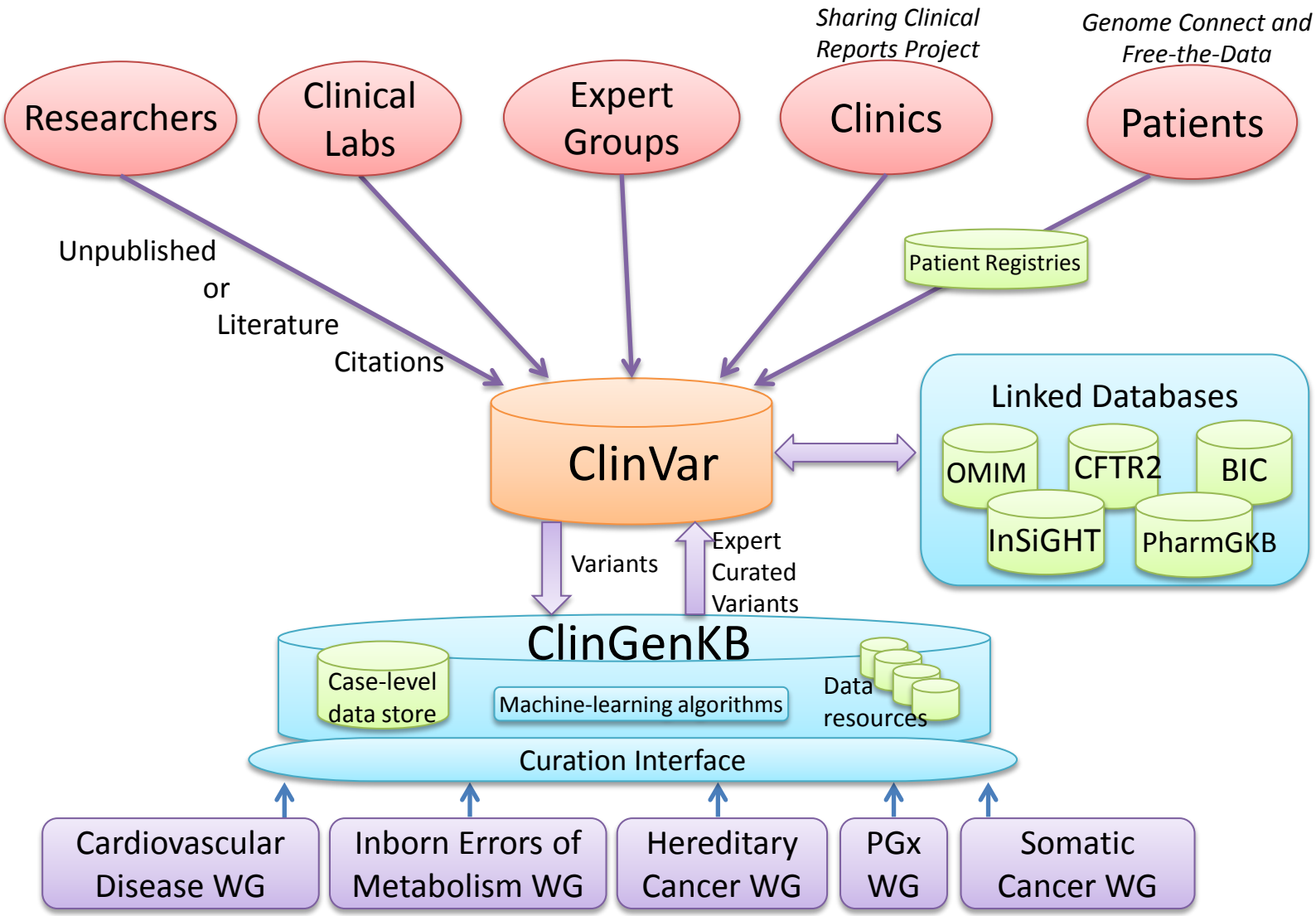
11% (12,895/118,169) of variants
have ≥2 submitters in ClinVar

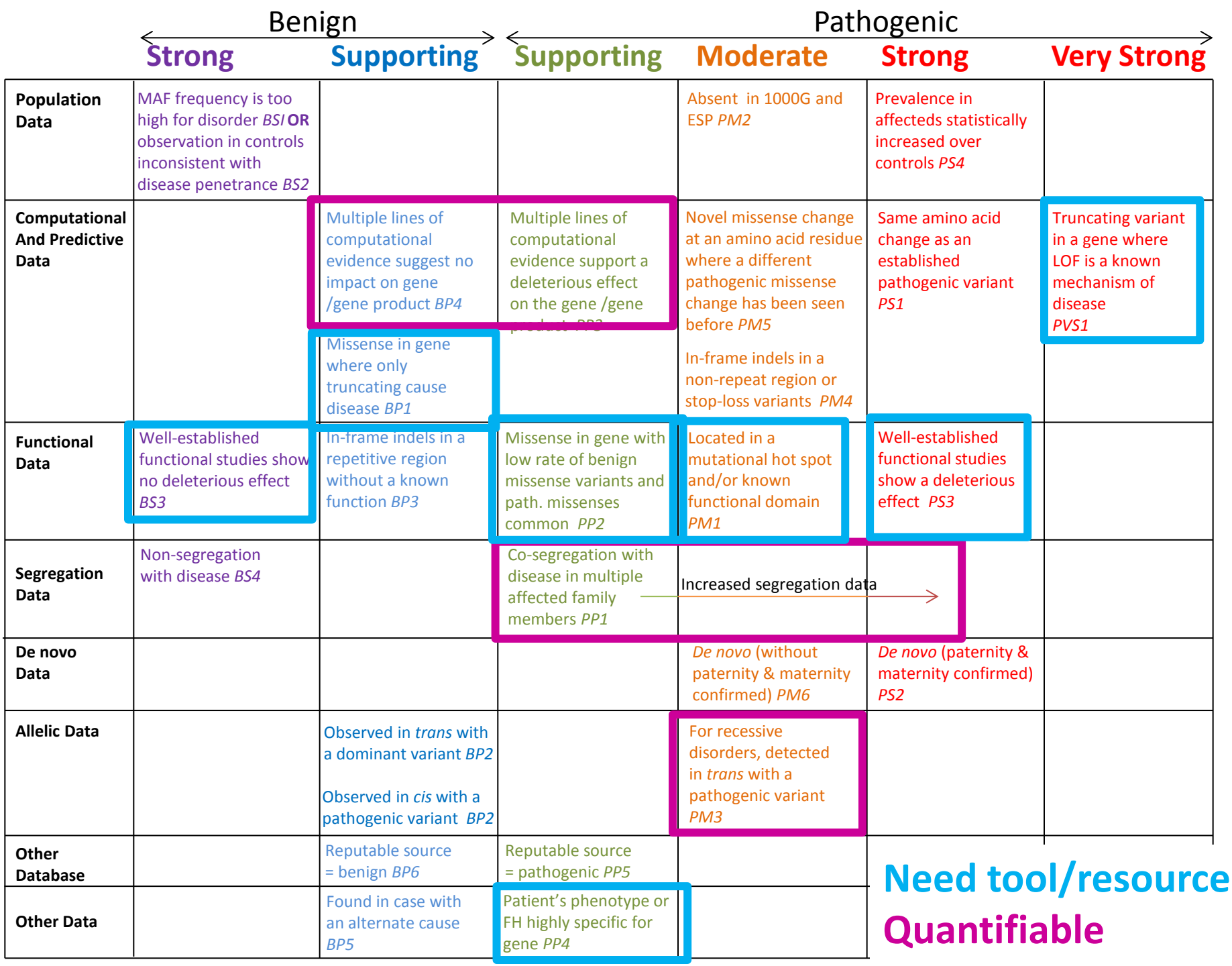
17% (2229/12,895)
are interpreted differently

ClinVar Data from May 4th, 2015


Emory
LMM
Chicago
Discrepancy Identification
22 variants (Confidence differences)
60 variants (3-Level)
104 differences
14 variants (3-Level)
8 variants (Confidence differences)
Variant Reassessment
43 variants consistent
17 variants still discrepant
28 differences
11 variants still discrepant
3 variants consistent
Discussion between labs
Main reasons for discrepancies was variant classification rules
• Novel silent: LB vs VUS
• Missense (freq cut-offs; MOI)
1/104 differences need expert panel input
Work of:
Birgit Funke
Steven Harrison
Melissa Kelly
Lori Bean
Amy Knight
Madhuri Hegde

Supporting a Curation Environment for both Crowd-Sourcing and Expert Consensus




Benign
Pathogenic
Strong
Supporting
Supporting
Moderate
Strong
Very Strong
Population Data
MAF frequency is too high for disorder BS1 OR observation in controls inconsistent with disease penetrance BS2
Absent in 1000G and ESP 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
Multiple lines of computational evidence support a deleterious effect on the gene /gene
Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5
Same amino acid change as an established pathogenic variant PS1
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Located in a mutational hot spot and/or known functional domain PM1
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Segregation Data
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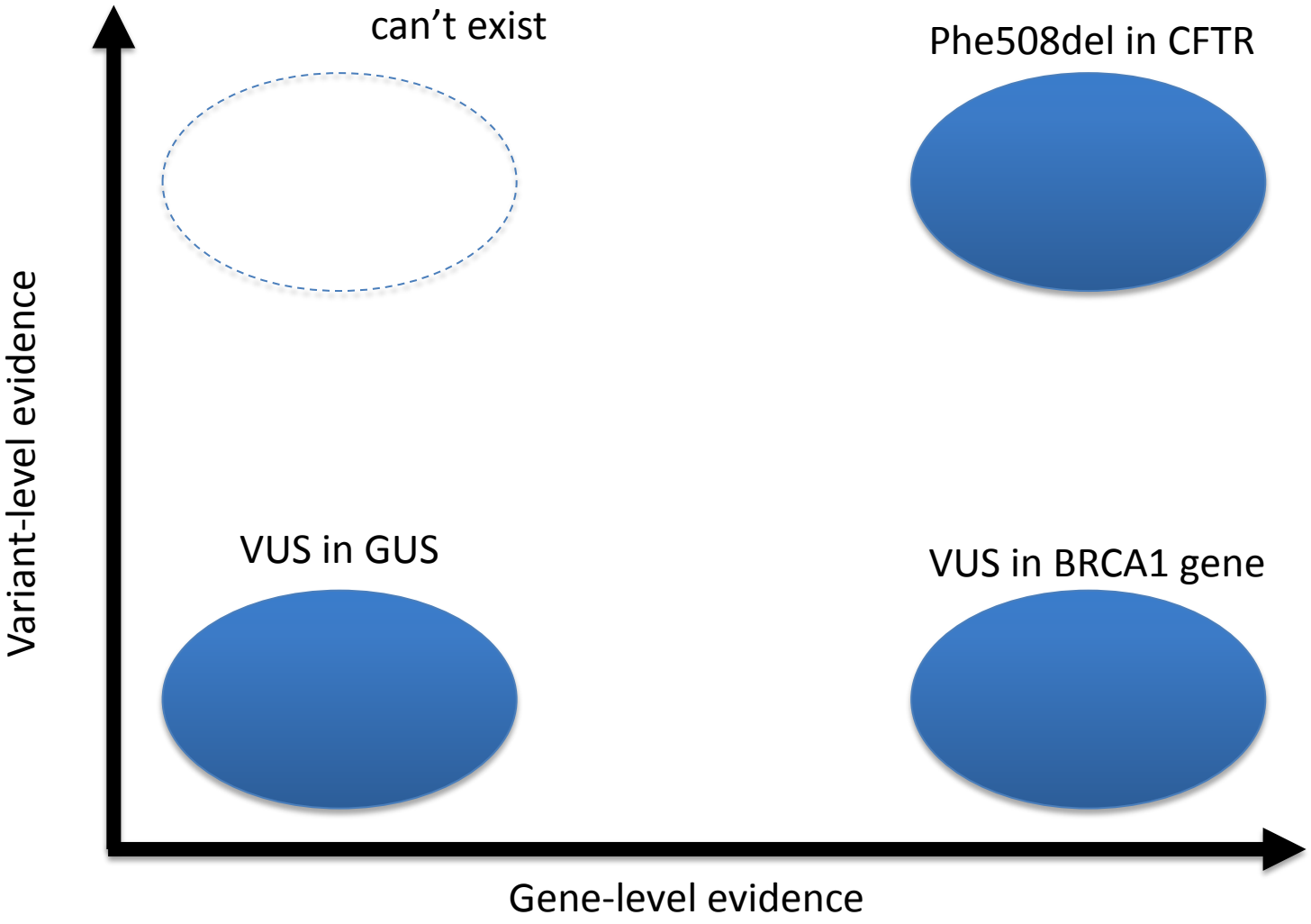
Allelic Data
Observed in trans with a dominant variant BP2
Observed in cis with a pathogenic variant BP2
For recessive disorders, detected in trans with a pathogenic variant PM3
Other Database
Reputable source = benign BP6
Reputable source = pathogenic PP5
Other Data
Found in case with an alternate cause BP5
Patient's phenotype or FH highly specific for gene PP4
Need tool/resource
Quantifiable

Major Clinical Domain WG Charges

- Define the genes with valid association to a human disease
- Define variants with valid evidence for pathogenicity and those with benign impact
- Define rules for interpreting novel variants

The two axes of implication



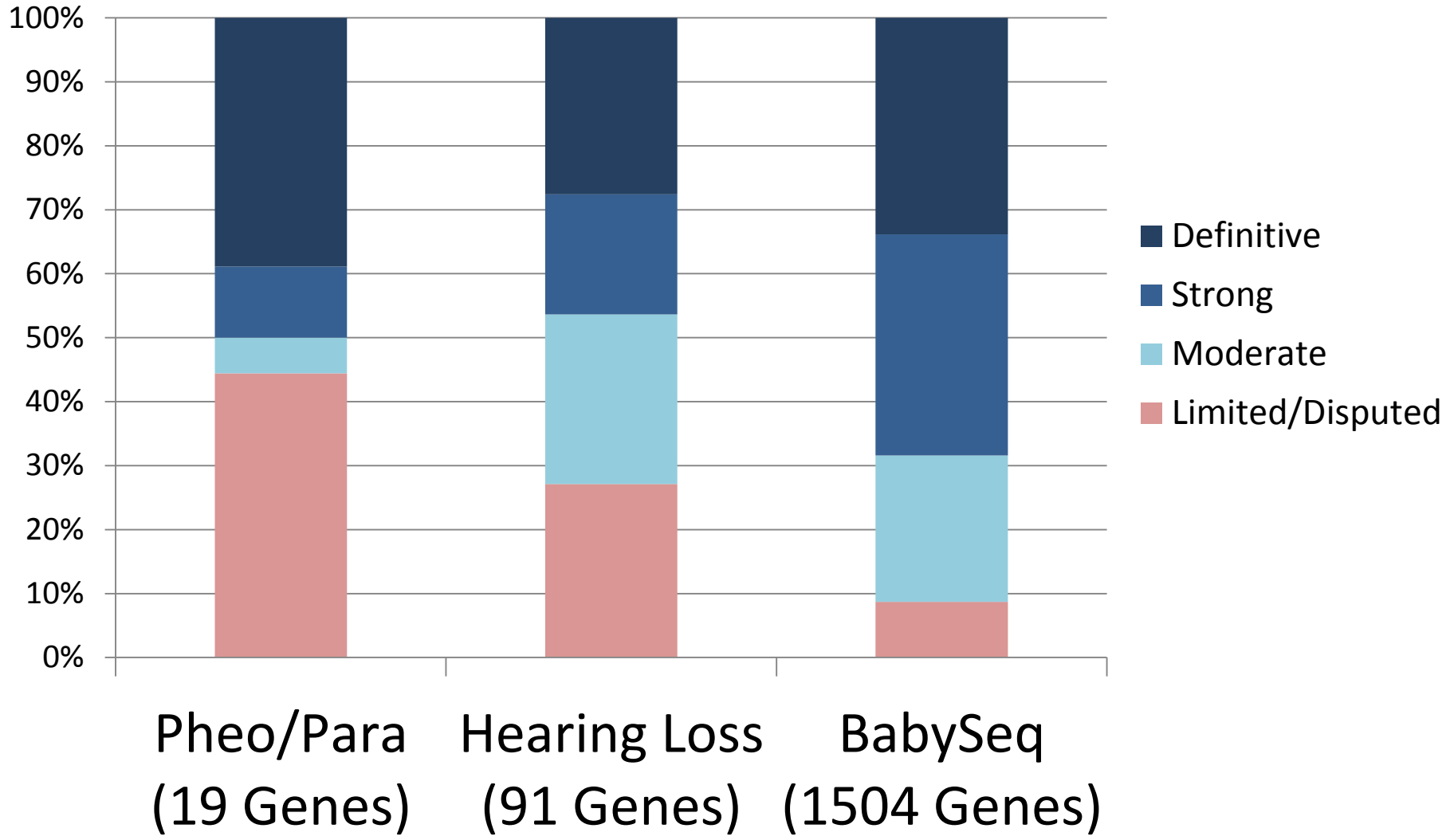
Modified from of Daniel MacArthur

Gene-Disease Validity Classification*

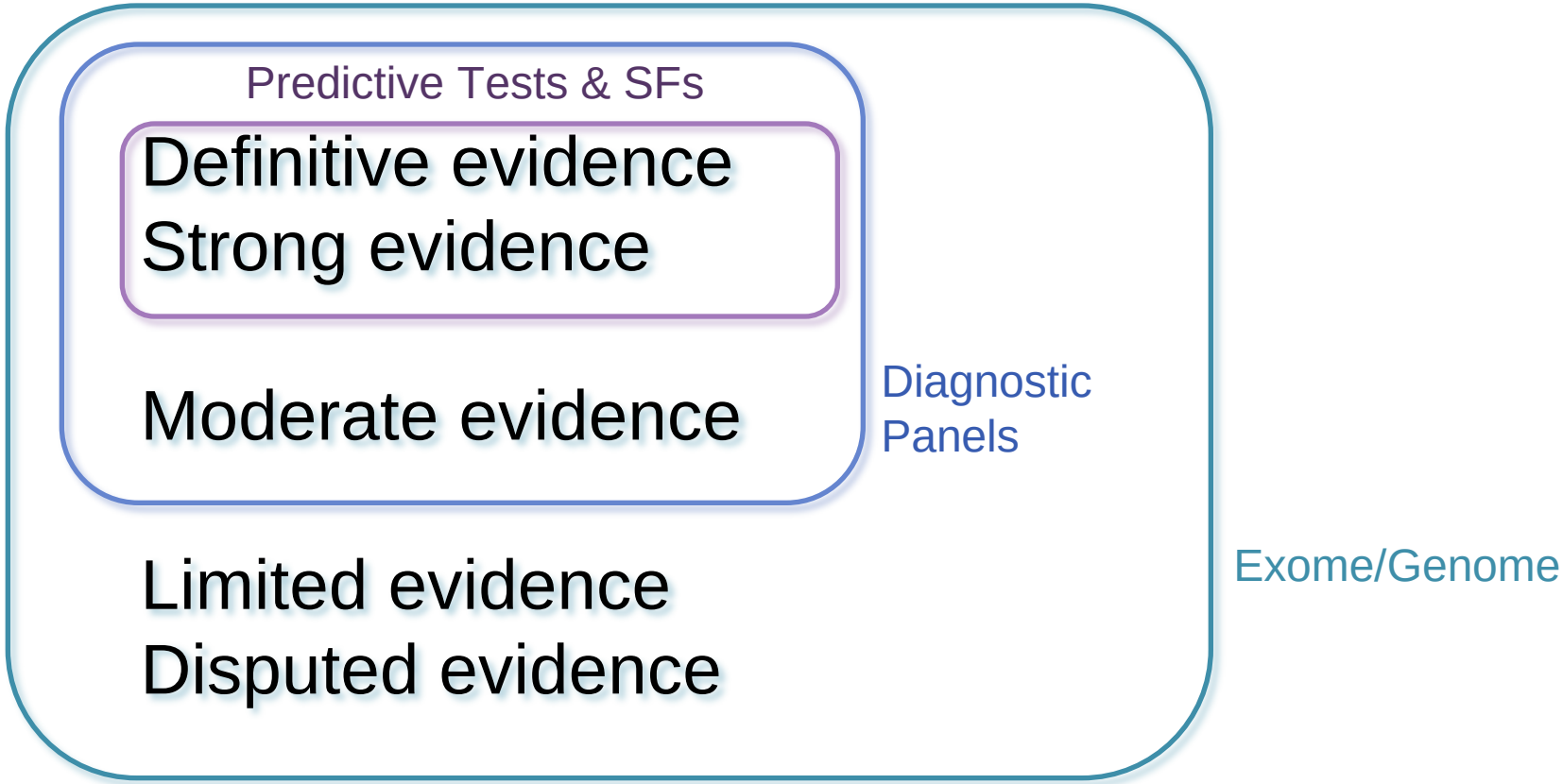
Definitive	Repeatedly demonstrated in research & clinical settings.
Strong	Excess of pathogenic variants in cases vs. controls & supporting experimental data.
Moderate	≥3 unrelated probands with pathogenic variants & supporting experimental data.
Limited	<3 probands w/ pathogenic variants.
No Evidence Reported	"Candidate" genes based on animal models or disease pathways, but no pathogenic variants reported.
Disputed	Significant evidence *refuting* a role for gene in this disease.
Evidence Against	Evidence refuting the role of the gene significantly outweighs any supporting evidence.

***Detailed criteria available online:**
http://www.clinicalgenome.org/knowledge-curation/gene-curation/

Application of ClinGen Gene-Disease Evidence Rules



Proposed Evidence Required to Include a Gene In a Clinical Test:



Genes with less evidence can be included in test design and analyzed in a research context to build evidence

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Euan Ashley
Larry Babb
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Sherri Bale
Louisa Baroudi
Les Biesecker
Chris Bizon
David Borland
Rhonda Brandon
Michael Brudno
Damien Bruno
Atul Butte
Hailin Chen
Mike Cherry

Soma Das
Johan den Dunnen
Edwin Dodson
Karen Eilbeck
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Xin Feng
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Ray Hershberger
Lucia Hindorff
Sibel Kantarci
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Melissa Kelly
Muin Khoury
Eric Klee
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Joel Krier
Danuta Krotoski
Shashi Kulkarni
Matthew Lebo
Charles Lee

Jennifer Lee
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Rong Mao
Daniel Masys
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Annie Niehaus
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Daniel Pineda-Alvaraz
Darlene Reithmaier
Erin Riggs
George Riley
Peter Robinson
Wendy Rubinstein
Shawn Rynearson
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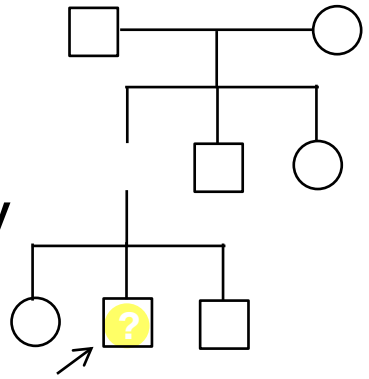
The Stakes are High in the Clinical Application of Genomics

Patients (& families) make serious decisions.

False positives lead to:

- Unnecessary surgery; years of unnecessary screening
- Premature end to diagnostic pursuit, forgoing the true answer

- False negatives lead to:
  - Forgoing necessary preventive/therapeutic modalities
- Amplified by misclassification of family members as at-risk or not
- Family planning & abortion
- The psychological damage of misinformation



Open Discussion

Summary and Recommendations

1. Critical Knowledge Gaps Impeding Genomic Medicine Implementation

- 21% of variants in ClinVar are VUSs and 17% are interpreted differently
- Case-level knowledge and other evidence is not being collected in ClinVar

2. Other Key Barriers to Implementation

- Use of inconsistent systems/implementations for evaluating variants (evidence assessment and interpretation)
- Cost and complexity of building support for variant assessment is difficult for laboratories to take on

3. Recommended Approaches to Addressing Gaps and Barriers

- Build and continue to iterate on a **tool to support variant assessment** - *ClinGen work in progress*
  - need **web-based** environment for collaborative curation with access to all evidence (Wiki-like)
  - Tool should be **open source** to allow download and integration into laboratory workflows (structured data shared back into web-based environment)
  - Tool should provide **easy access to data and support for rule usage**

- Need **publication** process to **require submission** of interpreted variants to ClinVar and supporting evidence (e.g. case-level data) into accessible databases to support curation

- Need to integrate electronic systems capturing **case-level** evidence (e.g. clinical laboratory DBs, EHRs, research study DBs) into an accessible federated network

3. Training Needs and Approaches

- Need to ensure **consistent training in variant assessment**
  - ✓ Incorporate into all training programs (medical school, graduate school in biological disciplines, postdoctoral studies in genomics, residency programs in medical genetics, fellowships in laboratory genetics, genetic counseling programs)

- Need **training of healthcare providers** on how to use genetic information of “likely” or uncertain significance and evaluate quality of source of interpretations (e.g. expert or single opinion)
  - ✓ Continuing education of healthcare providers
  - ✓ Guidelines in specific clinical disciplines

5. Bedside Back to Bench Research Questions: Facilitating a Virtuous Cycle

- Need **higher throughput approaches** to assess the impact of human variation – feed all VUSs back into research studies

- Identification of **candidate genes** from clinical WES needs to feed into research studies (e.g. matchmaker exchange)

- **Collection of clinical cases** with known genetic disorders to define targeted population for deeper studies and clinical trials

- Need return of results process to integrate back into learning system (**collect outcomes and rephenotying**)
  - Examples:
    - Unaffected family tests negative for familial variant and later develops the disease
    - Genetic results suggest specific treatment – did it work? – need to collect outcomes