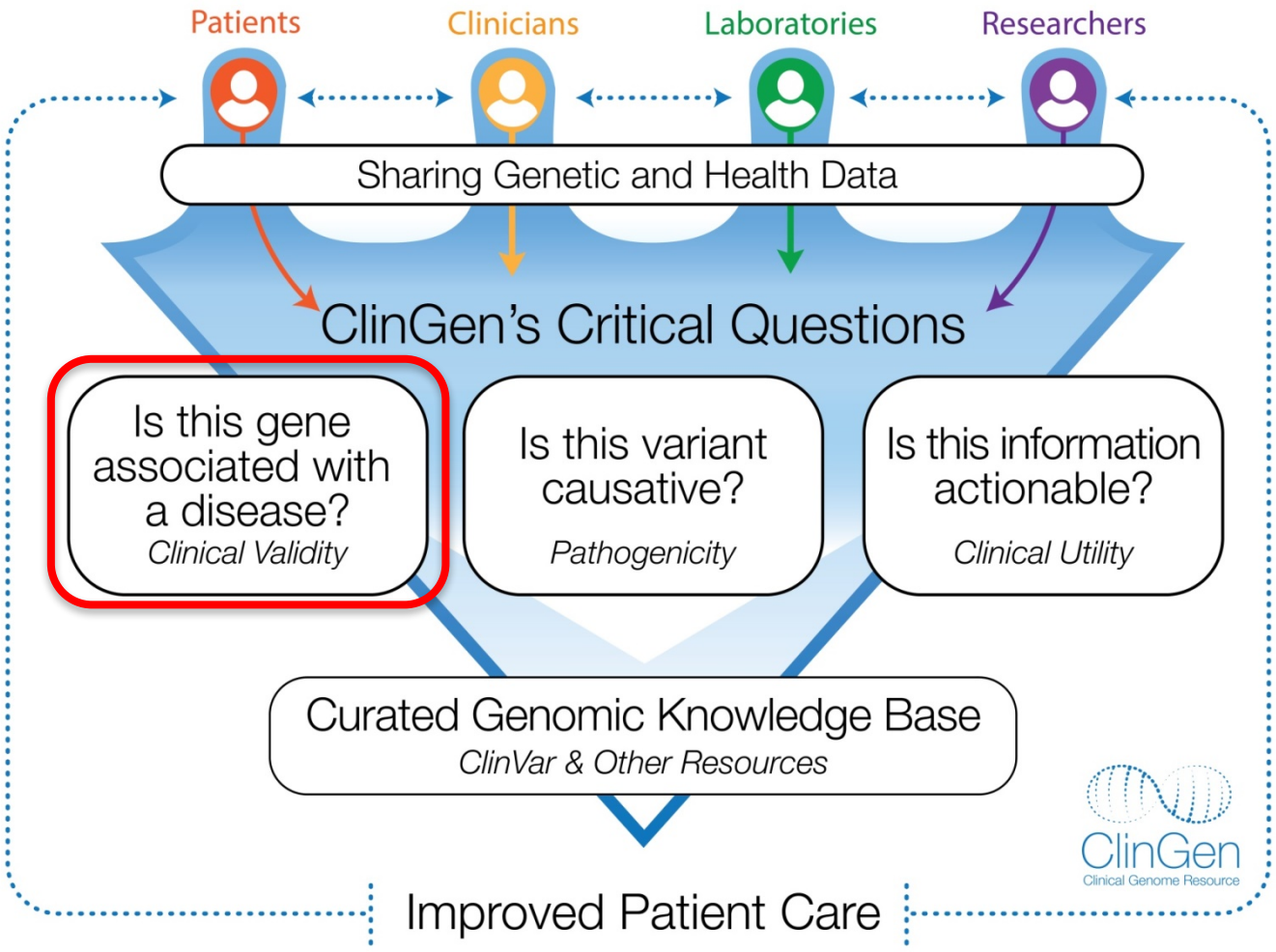
ClinGen and ClinVar: Representing PGx Information

Special thanks to Teri Klein and Mary Relling

Heidi L. Rehm, PhD, FACMG
@HeidiRehm
Director, Partners HealthCare Laboratory for Molecular Medicine
Medical Director, Broad Institute Clinical Research Sequencing Platform
Associate Professor of Pathology, Brigham and Women's Hospital and Harvard Medical School

PARTNERS HEALTHCARE | PERSONALIZED MEDICINE
BWH
HARVARD MEDICAL SCHOOL
BROAD INSTITUTE

The Clinical Genome Resource



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

www.clinicalgenome.org

>500 people from >100 institutions

Rehm et al. ClinGen - The Clinical Genome Resource. NEJM 2015

Learn About Gene-Disease Validity Curation

Gene-Disease Validity

Gene-Disease Clinical Validity Curation

The ClinGen Gene-Disease Clinical Validity curation process involves evaluating the strength of evidence supporting or refuting a claim that variation in a particular gene causes a particular disease.

The ClinGen Gene Curation working group has developed a framework to standardize the approach to determine the clinical validity for a gene-disease pair. This framework:

- Defines the criteria needed to assess clinical validity
- Describes the evidence supporting a gene-disease association in a semi-quantitative manner, and
- Allows curators to use this information to methodically classify the validity of a given gene-disease pair.

The Process

Learn how ClinGen evaluates gene-disease clinical validity.

Learn more »

Educational and Training Materials

Powerpoint slides, videos, handouts, etc. for those interested in curating gene-disease pairs using the ClinGen method.

Learn more »

Gene Curation Interface

Currently available for ClinGen biocurators and expert panels. Click here to view a demo version.

Learn more »

Gene-Disease Clinical Validity Results

Current gene-disease pairs that have been evaluated by ClinGen for clinical validity.

Learn more »

Definitive

Strong

Moderate

Limited

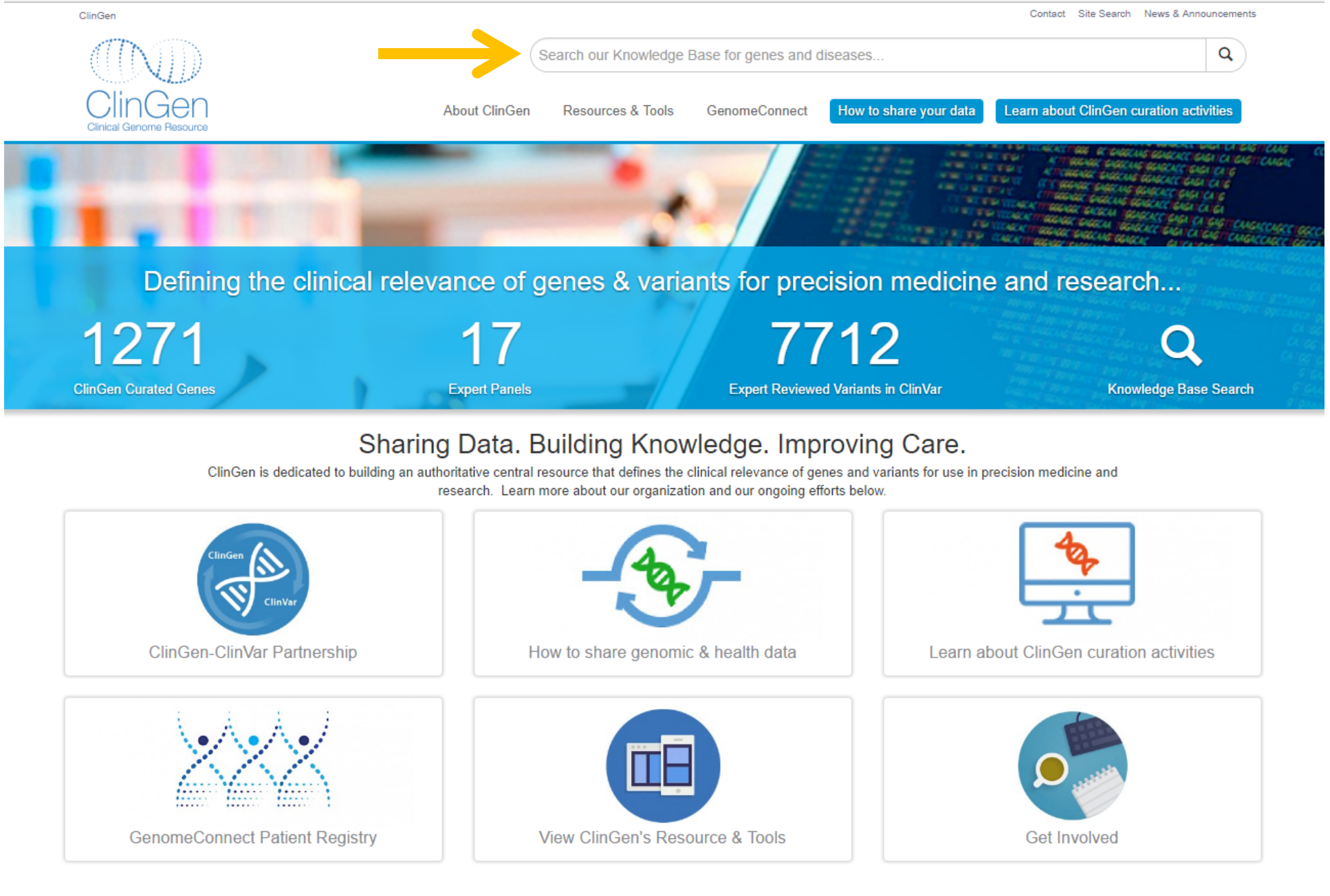
No Evidence Reported

Conflicting Evidence Reported

Disputed

Refuted

Search bar available at the top of every page



Knowledge Base Search Results

ClinGen Curated | Knowledge Base Sign-in | Sign-up

SMAD3

Sign-in to share information

Name	SMAD3	**Curated Conditions**	Aneurysm-osteoarthritis syndrome Familial thoracic aortic aneurysm and aortic dissection
HGNC ID	HGNC:6769	**External Resources**	View external resources
Cytogenetic Location	15q22.33	**ClinVar Variants**	View ClinVar Variants
Haploinsufficiency	Sufficient Evidence	**GeneReviews®**	View GeneReviews
Triplosensitivity	No Evidence		

ClinGen's Curation Summaries | External Genomic Resources | ClinVar Variants

Aneurysm-osteoarthritis syndrome

Gene-Disease Validity

Description	Date
Definitive	12/01/2016

Gene-Disease Validity

Dosage Sensitivity

Description	Date
Sufficient Evidence for Haploinsufficiency	03/14/2013

Clinical Actionability

Outcome/Intervention Pair	Description	Date
Aortic dilation progression/Beta blockers	Outcome: Severity: **Sudden Death**; Likelihood: **>40% Chance** Intervention: Effectiveness: **Highly Effective**; Intervention: **Low Risk**	03/20/2015
Clinically significant aortic aneurysm/Surveillance	Outcome: Severity: **Sudden Death**; Likelihood: **>40% Chance** Intervention: Effectiveness: **Highly Effective**; Intervention: **Low Risk**	03/20/2015

Familial thoracic aortic aneurysm and aortic dissection

Clinical Actionability

Outcome/Intervention Pair	Description	Date
Aortic dilation progression/Beta blockers	Outcome: Severity: **Sudden Death**; Likelihood: **5-39% Chance** Intervention: Effectiveness: **Highly Effective**; Intervention: **Low Risk**	05/13/2015
Clinically significant aortic aneurysm/Aortic surveillance	Outcome: Severity: **Sudden Death**; Likelihood: **5-39% Chance** Intervention: Effectiveness: **Highly Effective**; Intervention: **Low Risk**	05/13/2015

Gene-Disease Validity: Full Report

Clinical Validity Classification Summary

Gene/Disease Pair: ***BAG3* : myofibrillar myopathy 6**

HGNC: HGNC:939 | OrphaNet: ORPHA593 | OMIM: 612954

Mode of Inheritance **Autosomal dominant inheritance (HP:0000006)**

Genetic Evidence		Evidence Type		Case Information Type		Guidelines Default	Guidelines Range	Guidelines Max	Scores Points	Scores Tally	PMIDs/Notes
Case-Level Data	Variant Evidence		Autosomal Dominant or X-linked Disorder	Variant is de novo		2	0-3	12			
				Proband with predicted or proven null variant		1.5	0-2	10			
				Proband with other variant type with some evidence of gene impact		0.5	0-1.5	7	7.0	7	Selcen D et al. 2009 (PMID:19085932); Odgerel Z et al. 2010 (PMID:20605452); Semmler AL et al. 2014 (PMID:25208129); Konersman CG et al. 2015 (PMID:25728519); Kostera-Pruszczyk A et al. 2015 (PMID:26545904); D et al. 2016 (PMID:27443559); Jaffer F et al. 2012 (PMID:22734908);
			Autosomal Recessive Disease	Two variants in trans and at least one de novo or a predicted/proven null variant		2					
				Two variants (not predicted/proven null) with some evidence of gene impact in trans		1					
		Segregation Evidence		Evidence of segregation in one or more families	LOD Score Examples	3	5				
						2	4				
						1.5	3				
						1	1.5				

Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs)
Assigned Points	7	5	12	YES

CALCULATED CLASSIFICATION		
	LIMITED	1-6
	MODERATE	7-11
	STRONG	12-18
	DEFINITIVE	12-18 AND replication over time

Valid contradictory evidence (Y/N)*	NO

CALCULATED CLASSIFICATION (DATE)	DEFINITIVE	
EXPERT CURATION (DATE)	**DEFINITIVE**	12/18/2016

CYP2C19

Sign-in to share information

Name	CYP2C19	**External Resources**	View external resources
HGNC ID	HGNC:2621	**ClinVar Variants**	View ClinVar Variants
Cytogenetic Location	10q23.33	**GeneReviews®**	View GeneReviews

ClinGen's Curation Summaries | External Genomic Resources | ClinVar Variants

External Resources

PharmGKB: Gene

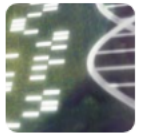
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

PharmGKB: Gene

OMIM: Gene

An Online Catalog of Human Genes and Genetic Disorders.

OMIM: Gene



GTR: Gene Tests

A voluntary registry of genetic tests and laboratories, with detailed information about the tests such as what is measured and analytic and clinical validity. GTR also is a nexus for information about genetic conditions and provides context-specific links to a variety of resources, including practice guidelines, published literature, and genetic data/information. The scope of GTR includes single gene tests for Mendelian disorders, somatic/cancer tests and pharmacogenetic tests including complex arrays, panels.

GTR: Gene Tests

Gene Reviews

An international point-of-care resource for busy clinicians, provides clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format, covering diagnosis, management, and genetic counseling for patients and their families.

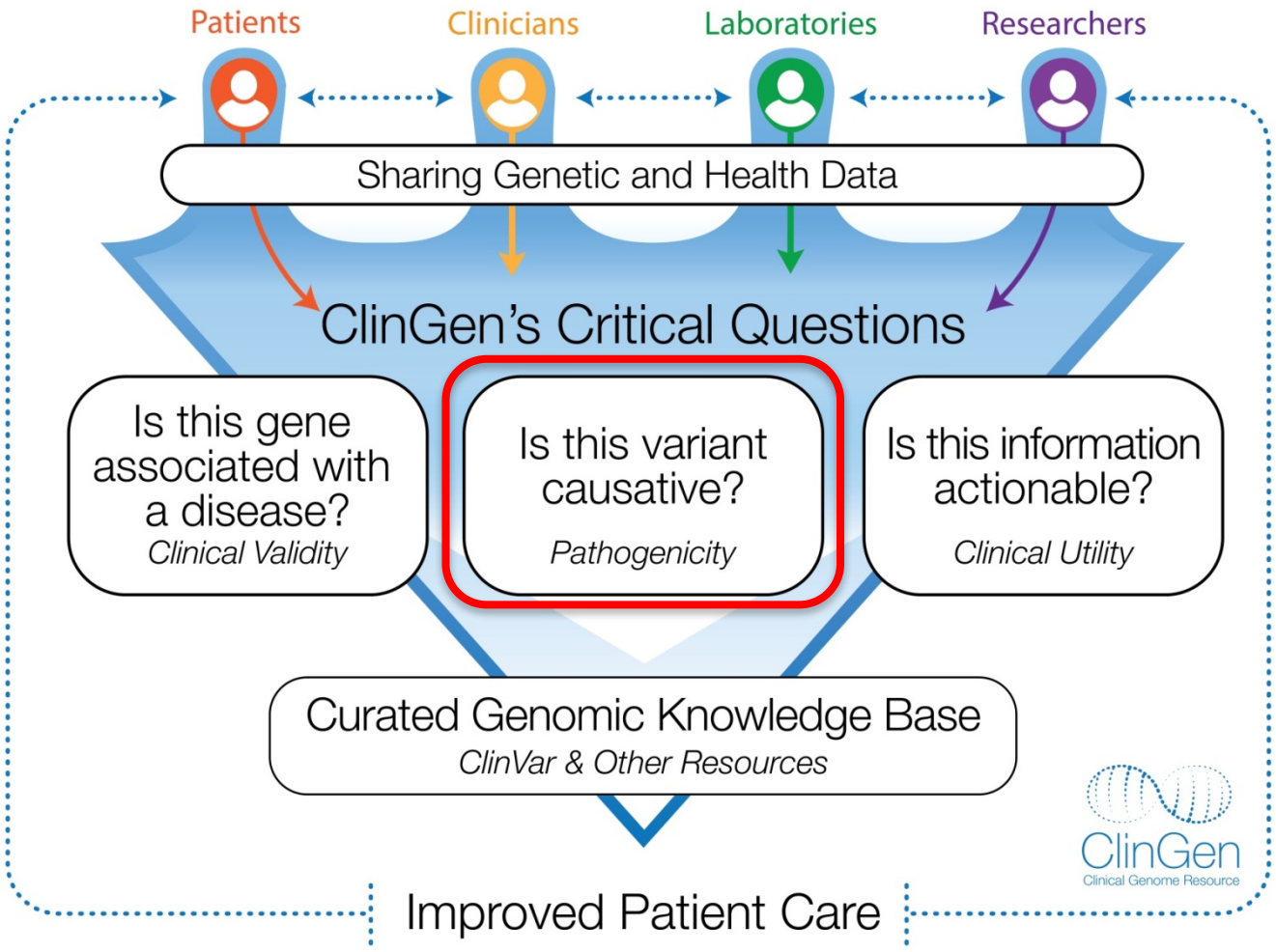
Gene Reviews

Genetic Practice Guidelines: Gene

As guidelines are identified that relate to a disorder, gene, or variation, staff at NCBI connect them to the appropriate records. This page provides an alphabetical list of the professional practice guidelines, position statements, and recommendations that have been identified.

Genetic Practice Guidelines: Gene

The Clinical Genome Resource



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

www.clinicalgenome.org

>500 people from >100 institutions

Rehm et al. ClinGen - The Clinical Genome Resource. NEJM 2015

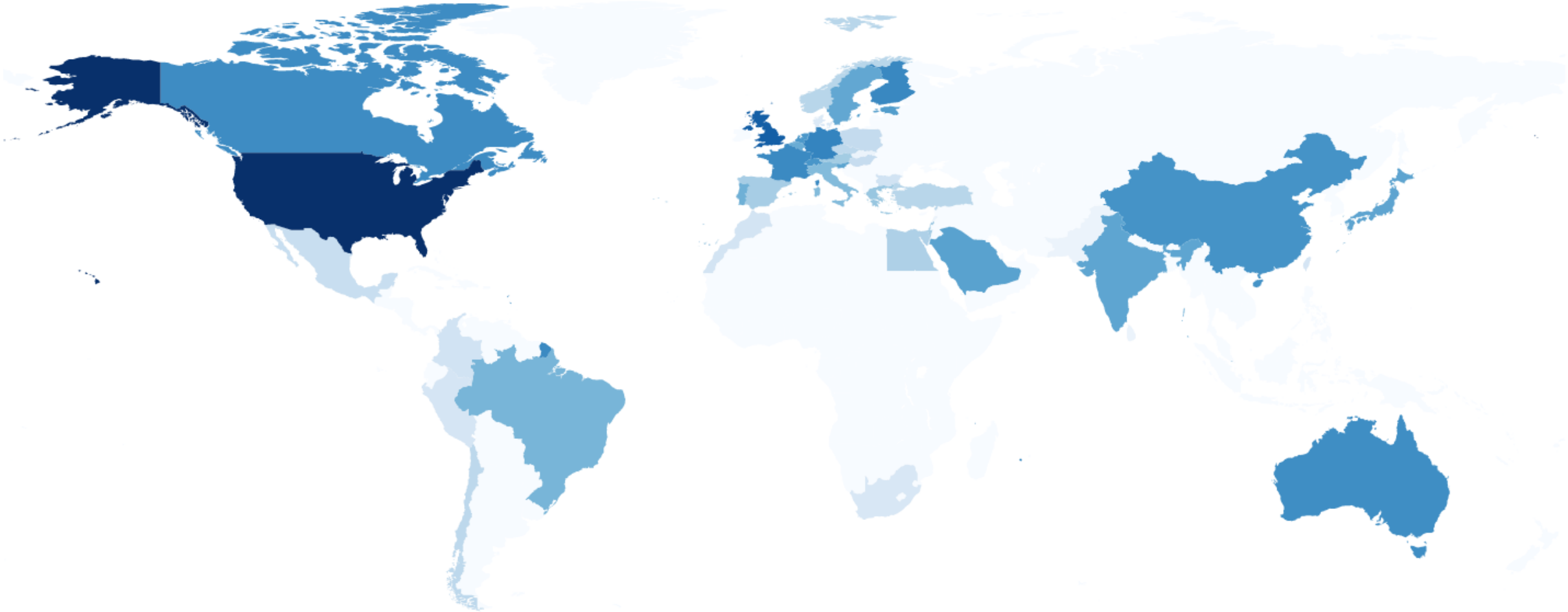
ClinGen Approaches to Variant Curation

- **Improve variant interpretation through:**
  - **Public interpretation sharing (ClinVar)**
    - Creates transparency and crowd-sources the work
  - Use of common standards (ACMG/AMP guideline)
  - Inter-laboratory conflict resolution

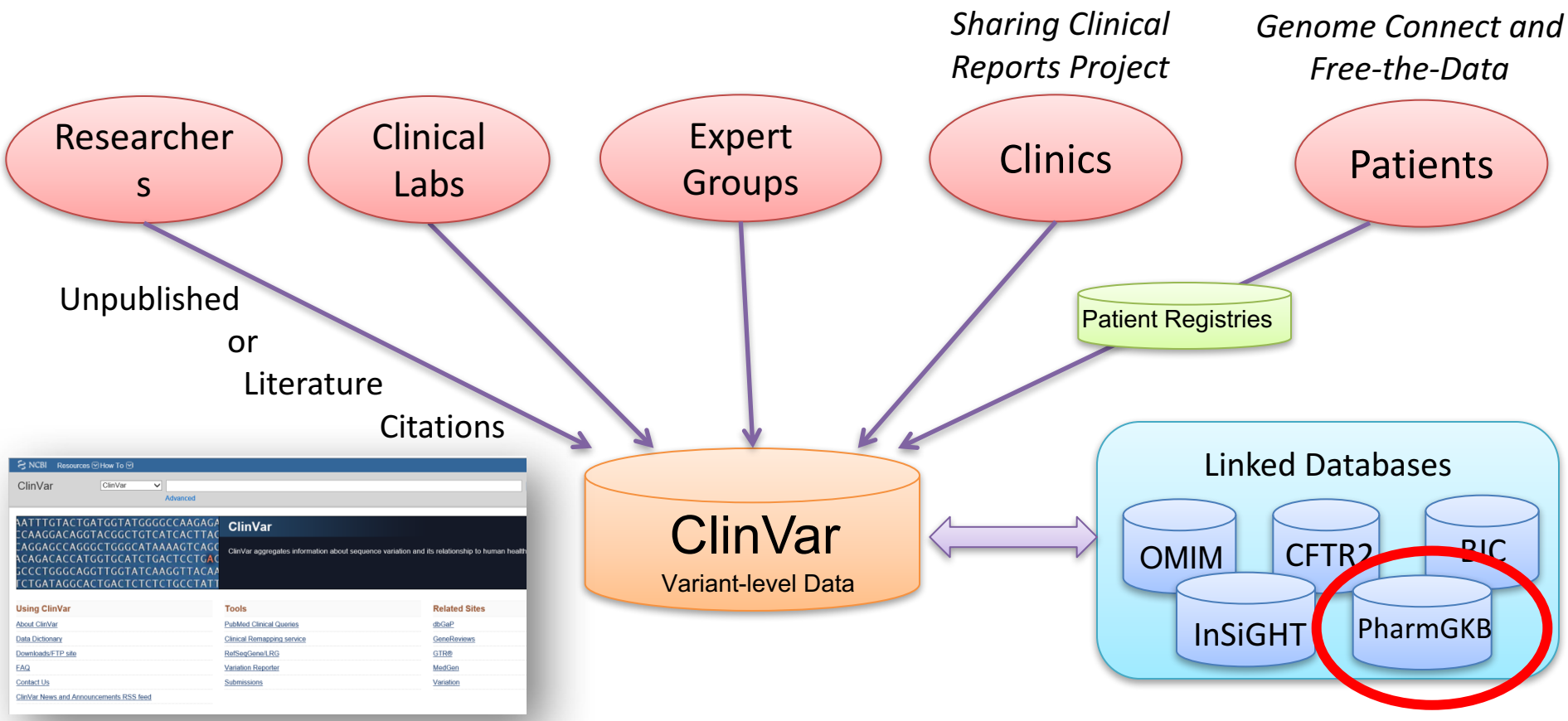
- Engage experts in systematic consensus-driven interpretation of variants

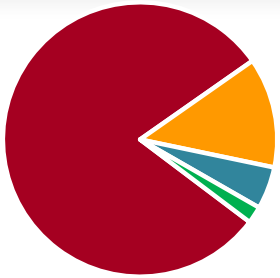
Global ClinVar Submissions

482,941 submissions on 316,353 unique variants
703 submitters from 56 countries



Aggregating Variant Interpretations in ClinVar





80% Clinical testing

13% Online resources (OMIM, GeneReviews, UniProt, LSDBs)

5% Research and other

2% ClinGen-approved Expert panels & Professional guidelines

ClinVar Variant View

NCBI Resources How To hrehm My NCBI Sign Out

ClinVar | ClinVar | Search ClinVar for gene symbols, HGVS expressions, conditions, and more | Search | Advanced | Help

Home | About | Access | Help | Submit | Statistics | FTP

NM_000769.2(CYP2C19):c.-806C>A

Variation ID: 225946
Review status: ★★★☆ reviewed by expert panel

1 Affected gene
cytochrome P450 family 2 subfamily C member 19 (CYP2C19) [Gene - OMIM - Variation Viewer]
Search ClinVar for variants within CYP2C19
Search ClinVar for variants including CYP2C19

Variant frequency in dbGaP
No dbGaP data has been submitted for this variant.

Browser views
RefSeqGene

Interpretation

Go to:

Clinical significance: drug response
Number of submission(s): 3
Condition(s):
- citalopram response - Metabolism/PK [MedGen]
- clopidogrel response - Dosage, Efficacy, Toxicity/ADR [MedGen]
- escitalopram response - Metabolism/PK [MedGen]

See supporting ClinVar records

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

PGx

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: clopidogrel response - Dosage, Efficacy, Toxicity/ADR Drug reported used for: Acute coronary syndrome [MedGen] Drug reported used for: Acute coronary syndrome;Coronary Artery Disease;Myocardial Infarction	germline	PubMed (18) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV000268179.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV000268180.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized	literature only	Condition: not provided	germline	PubMed (2) [See all	PharmGKB	SCV000268181.2

Full description for PharmGKB

PGx

PharmGKB Level of Evidence 1A: Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.

Drug-variant association: Dosage, Efficacy, Toxicity/ADR

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Drug-variant association: Metabolism/PK

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Drug-variant association: Metabolism/PK

- https://www.pharmgkb.org/clinicalAnnotation/655386913

ClinGen Approaches to Variant Curation

- Improve variant interpretation through:
  - Public interpretation sharing (ClinVar)
    - Creates transparency and crowd-sources the work
  - **Use of common standards**
    - **Terminology**
    - **Rules for variant interpretation**
  - Inter-laboratory conflict resolution

- Engage experts in systematic consensus-driven interpretation of variants

Over 45 different clinical significance terms submitted to ClinVar

pathogenic
pathogenic/likely pathogenic
Pathologic
affects
association
mut
Mutation
vlm
probable-pathogenic
probably pathogenic
likely pathogenic
suspected pathogenic

uncertain significance: likely pathogenic
unknown
unknown significance
uncertain
uncertain significance
variant of unknown significance
Vus
vous
uncertain significance: likely benign

Vlb
likely benign
suspected benign
benign/likely benign
benign
no known pathogenicity
probable-non-pathogenic
probably not pathogenic
non-pathogenic
poly

protective
risk factor
vSb
cancer

confers sensitivity
drug response
drug-response

not provided
other
Untested
moderate

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

	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 *BP4* Missense when 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	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	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 *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*			

Table 5 Rules for combining criteria to classify sequence variants

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

Pathogenic
Likely pathogenic
Uncertain significance
Likely benign
Benign

www.acmg.net

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Marilyn M. Li,*† Michael Datto,*‡ Eric J. Duncavage,*§ Shashikant Kulkarni,*¶ Neal I. Lindeman,*‖ Somak Roy,*,** Apostolia M. Tsimberidou,*†† Cindy L. Vnencak-Jones,*‡‡ Daynna J. Wolff,*§§ Anas Younes,*¶¶ and Marina N. Nikiforova*,**

the Journal of Molecular Diagnostics
jmd.amjpathol.org

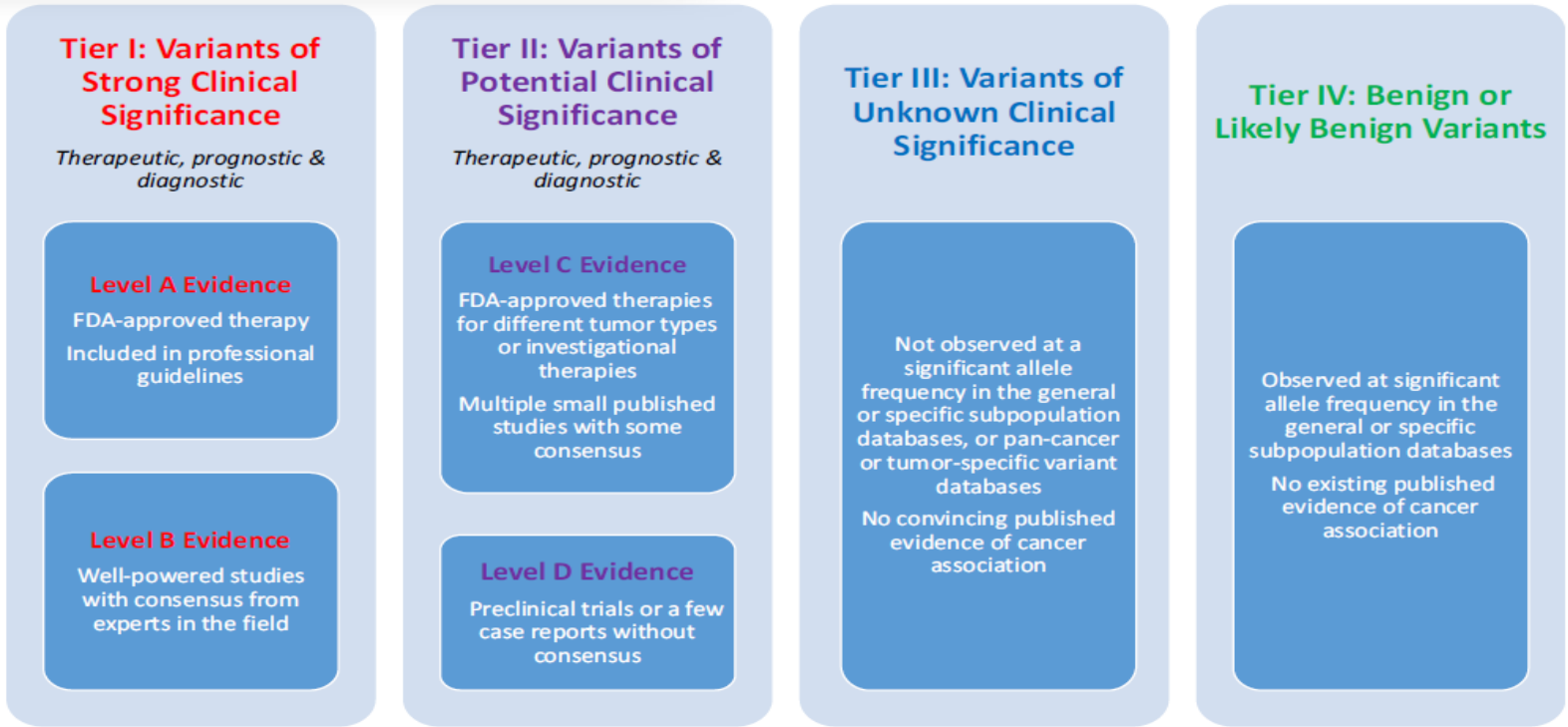


Figure 2 Evidence-based variant categorization. Somatic variants are classified into four tiers based on their level of clinical significance in cancer diagnosis, prognosis, and/or therapeutics. Variants in tier I are of strongest clinical significance, and variants in tier IV are benign or likely benign variants. FDA, Food and Drug Administration.

ELSEVIER

Table 2 Final consensus terms for allele functional status and phenotype

Term/gene category	Final term[a]	Functional definition	Gene	
Allele functional status: all genes	Increased function	Function greater than normal function	N/A	
	Normal function	Fully functional/wild-type	N/A	
	Decreased function	Function less than normal function	N/A	
	No function	Nonfunctional	N/A	
	Unknown function	No literature describing function or the allele is novel	N/A	
	Uncertain function	Literature supporting function is conflicting or weak	N/A	
Phenotype: drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultrarapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two i… than …	
	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Comb… increa…	
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*
Phenotype: transporters (SLCO1B1)	Increased function	Increased transporter function compared to normal function.	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype: high-risk genotype status (*HLA-B*)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High-risk allele not detected	No copies of high-risk allele	

[a]All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 decreased function).

Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

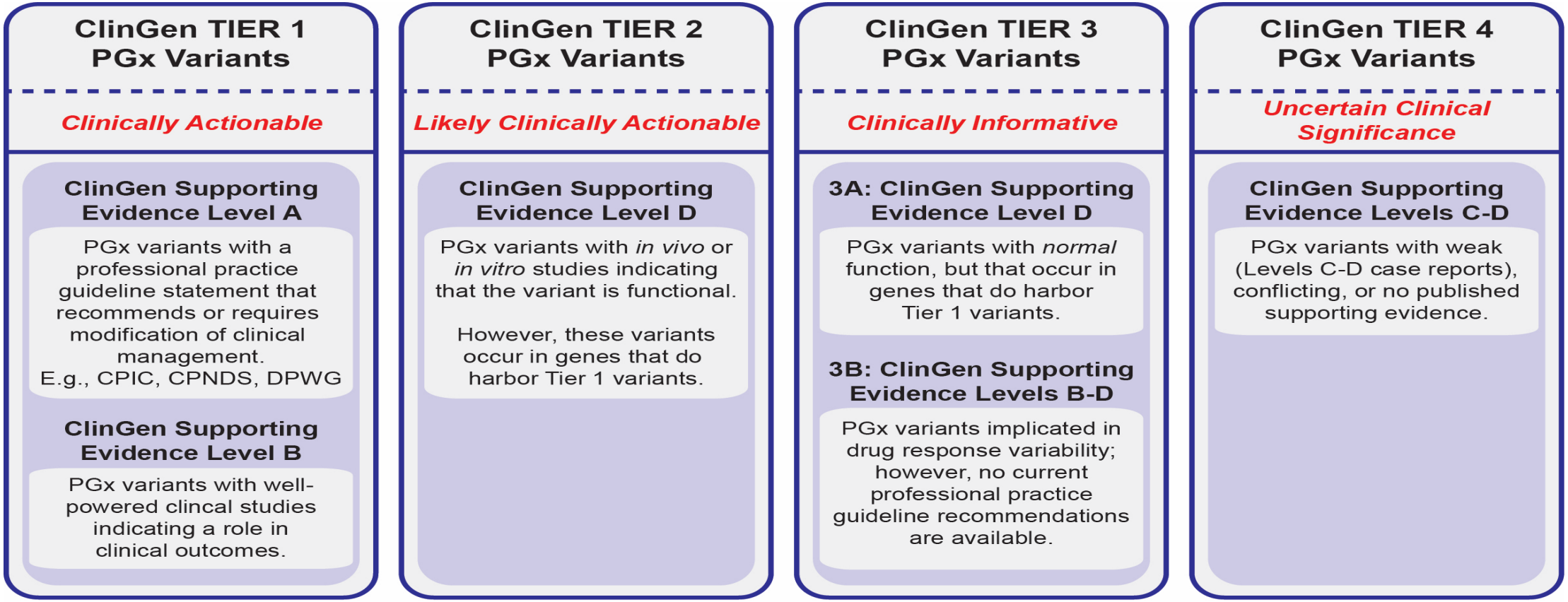
Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

Standards and Guidelines for Interpreting the Clinical Significance of Pharmacogenomic Variants

- Proposal from ClinGen PGx Working Group, in combination with ACMG Lab QA committee
- To develop a framework of tiered standard terminology and definitions that reflect clinical significance for genomic variants implicated in drug response variability (efficacy, dosing, or adverse event risk)
- To deploy this system in the ClinVar database for use by laboratories when submitting pharmacogenomic data to ClinVar, and for the interpretation of pharmacogenomic variants by clinical genetic testing laboratories
  - Will be adopted by CPIC and PharmGKB

Courtesy of Teri Klein and Mary Relling

Proposed Classification



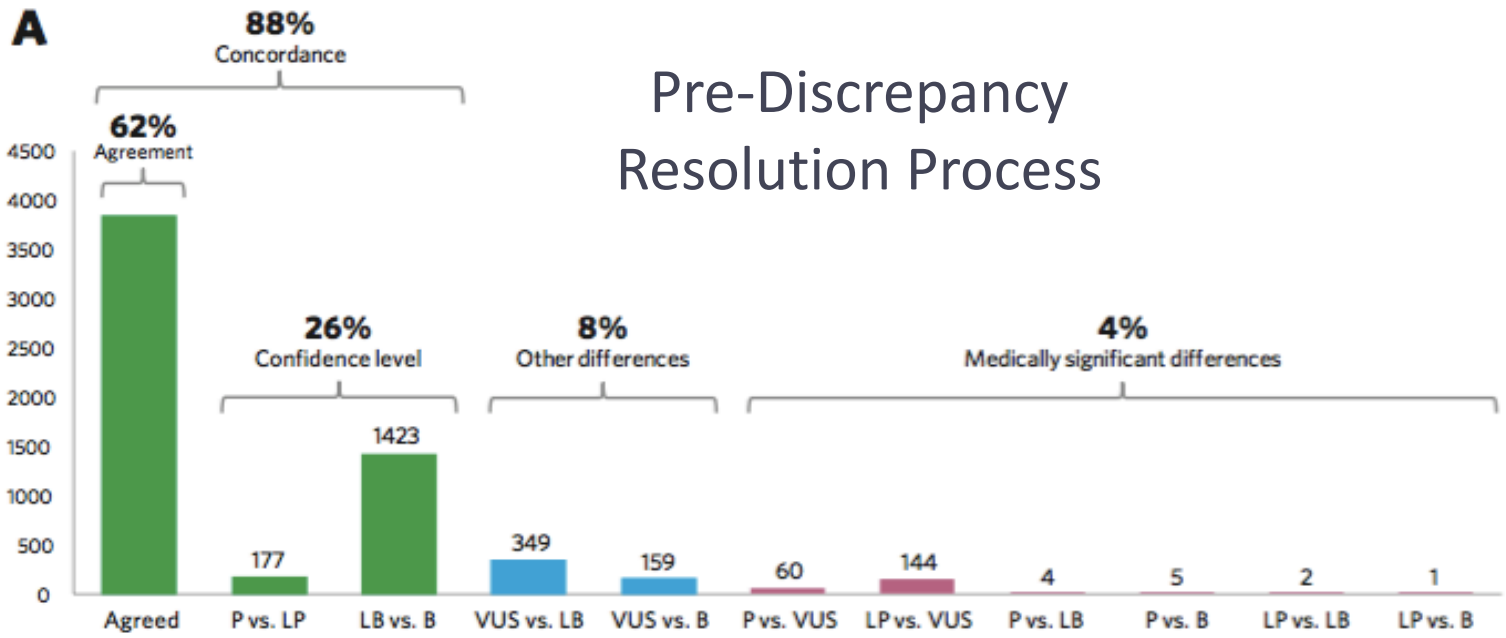
ClinGen
Clinical Genome Resource

Courtesy of Teri Klein and Mary Relling

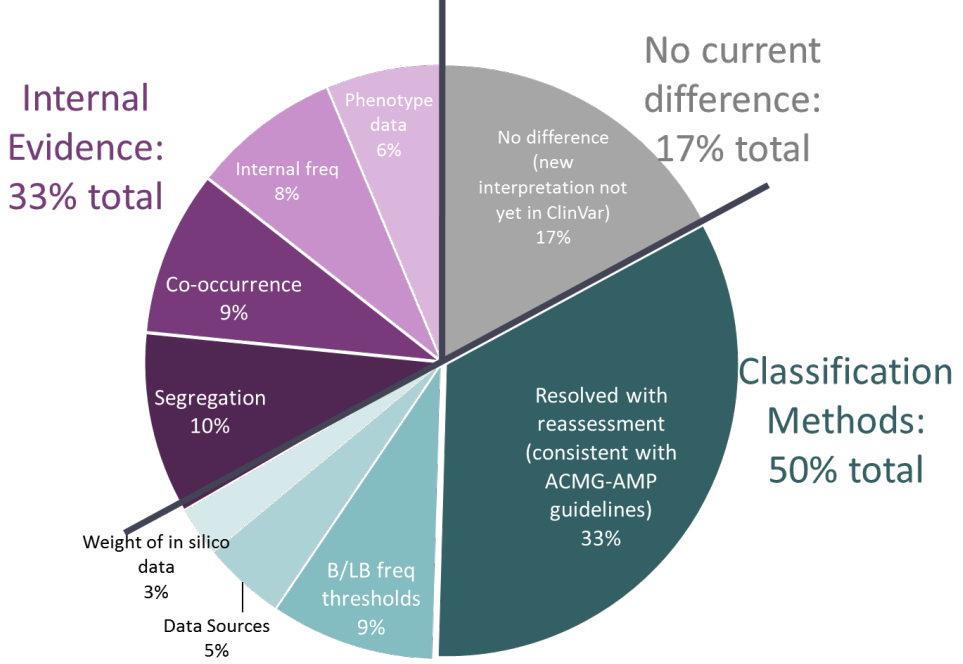
ClinGen Approaches to Variant Curation

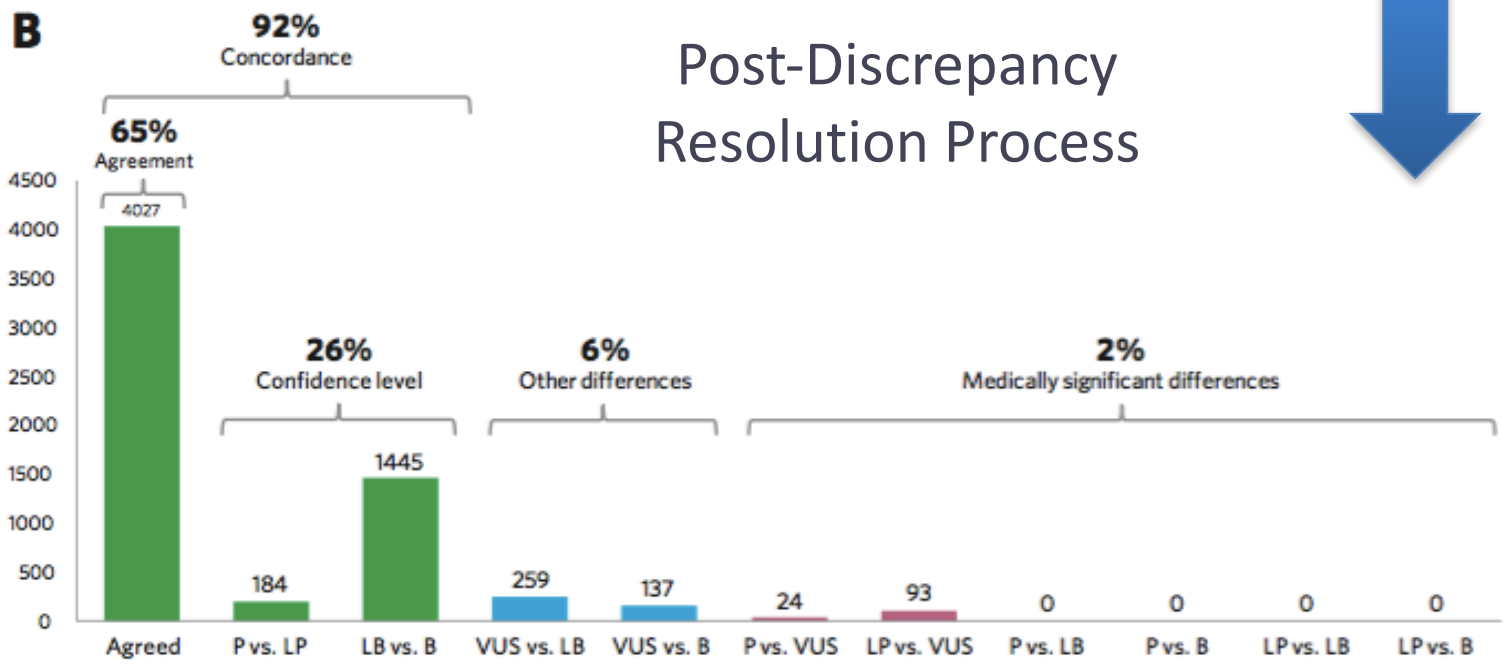
- Improve variant interpretation through:
  - Public interpretation sharing (ClinVar)
    - Creates transparency and crowd-sources the work
  - Use of common standards (ACMG/AMP guideline)
  - **Inter-laboratory conflict resolution**

- Engage experts in systematic consensus-driven interpretation of variants



Pre-Discrepancy Resolution Process





Post-Discrepancy Resolution Process

87% resolution (211/242)

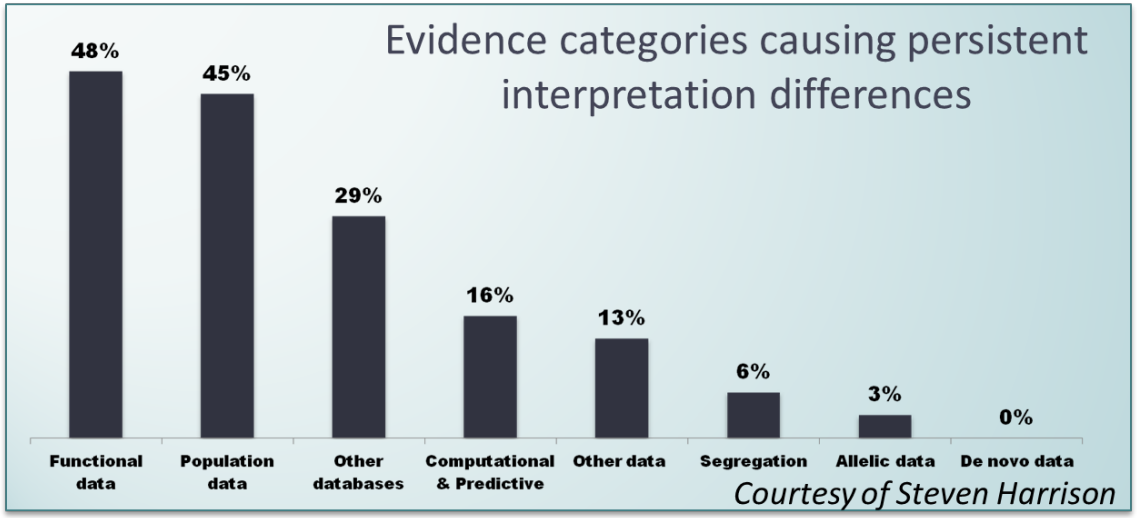
Ambry, GeneDx, Partners LMM, Univ Chicago

Harrison et al. Genet Med

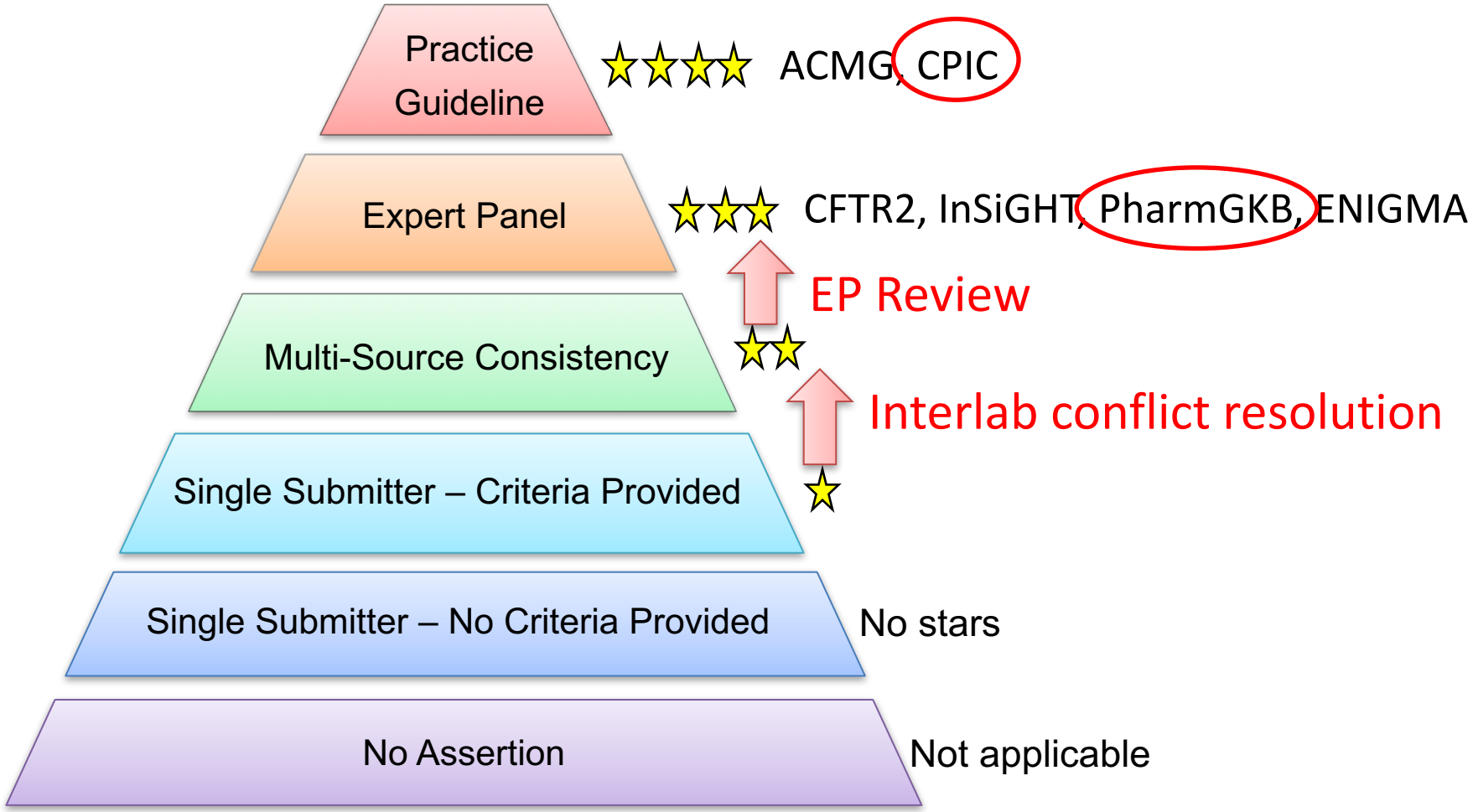
ClinGen Approaches to Variant Curation

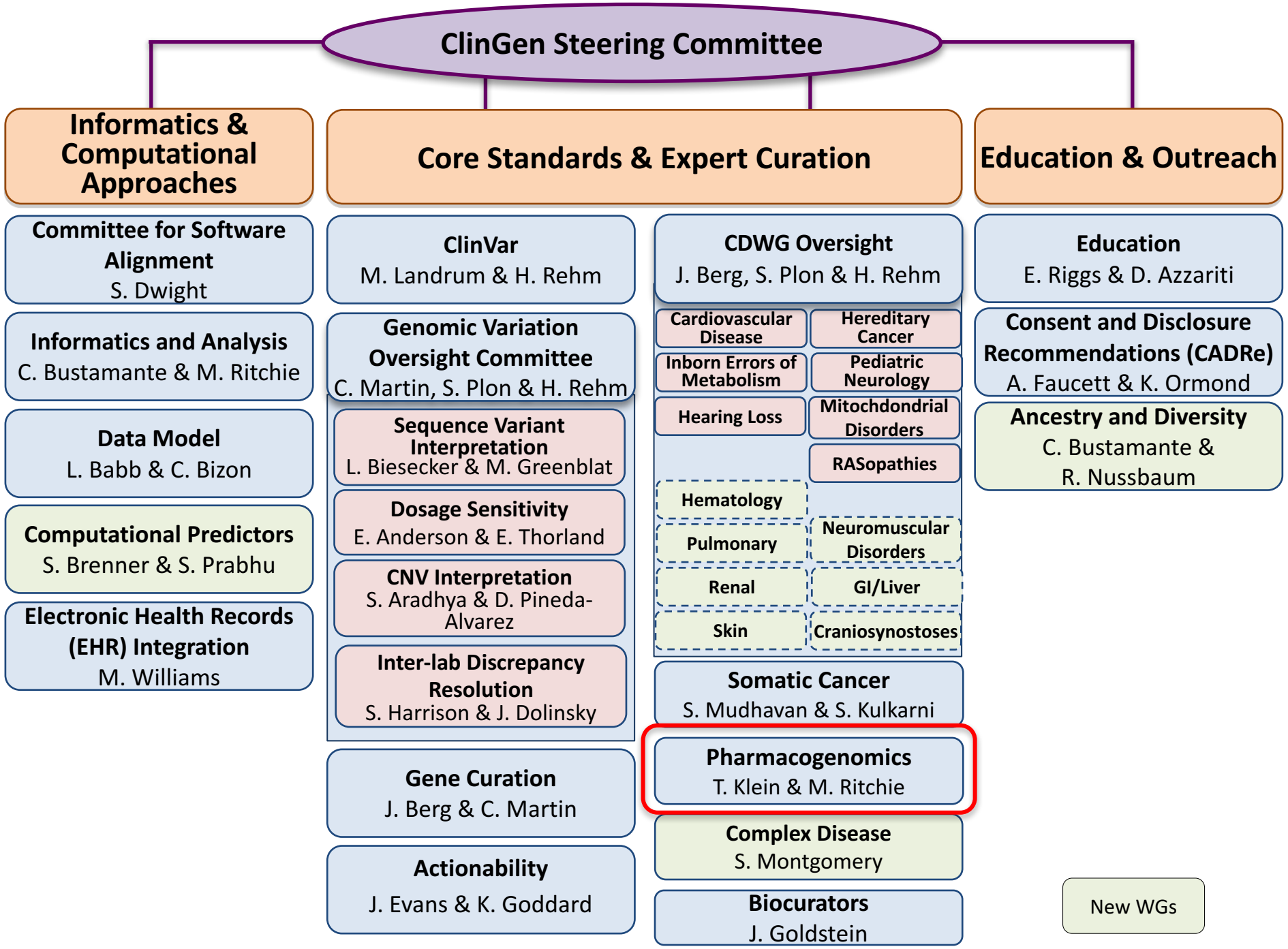
- Improve variant interpretation through:
  - Use of common standards (ACMG/AMP guideline)
  - Public interpretation sharing (ClinVar)
    - Creates transparency and crowd-sources the work
  - Inter-laboratory conflict resolution

- Engage experts in systematic consensus-driven interpretation of variants



Review Levels in ClinVar




ClinGen Steering Committee
Informatics & Computational Approaches
Core Standards & Expert Curation
Education & Outreach
Committee for Software Alignment
S. Dwight
Informatics and Analysis
C. Bustamante & M. Ritchie
Data Model
L. Babb & C. Bizon
Computational Predictors
S. Brenner & S. Prabhu
Electronic Health Records (EHR) Integration
M. Williams
ClinVar
M. Landrum & H. Rehm
Genomic Variation Oversight Committee
C. Martin, S. Plon & H. Rehm
Sequence Variant Interpretation
L. Biesecker & M. Greenblat
Dosage Sensitivity
E. Anderson & E. Thorland
CNV Interpretation
S. Aradhya & D. Pineda-Alvarez
Inter-lab Discrepancy Resolution
S. Harrison & J. Dolinsky
Gene Curation
J. Berg & C. Martin
Actionability
J. Evans & K. Goddard
CDWG Oversight
J. Berg, S. Plon & H. Rehm
Cardiovascular Disease
Hereditary Cancer
Inborn Errors of Metabolism
Pediatric Neurology
Hearing Loss
Mitochondrial Disorders
RASopathies
Hematology
Pulmonary
Neuromuscular Disorders
Renal
GI/Liver
Skin
Craniosynostoses
Somatic Cancer
S. Mudhavan & S. Kulkarni
Pharmacogenomics
T. Klein & M. Ritchie
Complex Disease
S. Montgomery
Biocurators
J. Goldstein
Education
E. Riggs & D. Azzariti
Consent and Disclosure Recommendations (CADRe)
A. Faucett & K. Ormond
Ancestry and Diversity
C. Bustamante & R. Nussbaum
New WGs

ClinGen PGx Working Group

- Membership consists of CPIC, PharmGKB leadership & ClinGen members, and, PGx experts throughout the country with different expertise
- Current Goals:
  - Provide standardized terminology to guide PGx ClinVar submissions from any source
  - Submit all dosing recommendations from CPIC and high-level PGx annotations from PharmGKB to ClinVar
  - Submit allele function information using CPIC's standardized nomenclature

Chairs
Teri E. Klein, PhD, FACMI, FACMG
Marylyn D. Ritchie, PhD

Members
Gillian Bell, PharmD
Jonathan Berg, MD, PhD
Ulrich Broeckel, MD
Joshua C. Denny, MD, MS
Cyrine-Eliana Haidar, PharmD
Howard L. McLeod, PharmD
Erin M. Ramos, MPH, PhD
Mary V. Relling, PharmD
Stuart Scott, PhD
Michelle Whirl-Carrillo, PhD
Marc S Williams, MD
Andy Rivera M. - coordinator

Courtesy of Teri Klein and Mary Relling

Challenges in Submitting PGx to ClinVar

- CPIC & PharmGKB are first groups to submit large amounts of pharmacogenomic associations to ClinVar, which typically hosts disease allele associations
- Challenges:
  - How to define haplotype, or star (*) alleles, in ClinVar
  - How to represent CPIC dosing recommendations, which are written at the genotype/diplotype level
  - Need for a template and vocabulary designed for disease associations for drugs
  - How to display links back to PharmGKB/CPIC for detailed association information

Courtesy of Teri Klein and Mary Relling

PharmGKB – 342 PGx submissions

warfarin response - Dosage
ivacaftor response - Efficacy
radiotherapy response - Toxicity/ADR
antipsychotics response - Toxicity/ADR
capecitabine response - Toxicity/ADR
fluorouracil response - Toxicity/ADR
acenocoumarol response - Dosage
anthracyclines and related substances response - Toxicity/ADR
citalopram response - Efficacy
efavirenz response - Metabolism/PK
hmg coa reductase inhibitors response - Toxicity/ADR
phenprocoumon response - Dosage
tegafur response - Toxicity/ADR
HMG CoA reductase inhibitors response - Efficacy
Platinum compounds response - Toxicity/ADR
SN-38 response - Other
Selective serotonin reuptake inhibitors response - Efficacy
aminoglycoside antibacterials response - Toxicity/ADR
antidepressants response - Efficacy
ataluren response - Efficacy
carbamazepine response - Dosage
cisplatin response - Efficacy, Toxicity/ADR
clozapine response - Toxicity/ADR
gefitinib response - Efficacy
hydrochlorothiazide response - Efficacy
irinotecan response - Toxicity/ADR
methotrexate response - Toxicity/ADR
olanzapine response - Toxicity/ADR
peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, and telaprevir response - Efficacy
pravastatin response - Efficacy
risperidone response - Toxicity/ADR
salbutamol response - Efficacy
simvastatin response - Toxicity/ADR
Platinum compounds response - Efficacy, Toxicity/ADR
Pyrimidine analogues response - Toxicity/ADR
Pyrimidine analogues response - Toxicity/ADR, Metabolism/PK
aspirin response - Efficacy
atorvastatin response - Efficacy
capecitabine response - Toxicity/ADR, Metabolism/PK
carboplatin response - Efficacy, Toxicity/ADR
cetuximab response - Efficacy
cisplatin response - Toxicity/ADR
clopidogrel response - Efficacy
clopidogrel response - Efficacy, Toxicity/ADR
erlotinib response - Efficacy
ethanol response - Toxicity/ADR
fentanyl response - Dosage
fluorouracil response - Toxicity/ADR, Metabolism/PK
metformin response - Efficacy
methadone response - Dosage
morphine response - Dosage
nevirapine response - Other
nevirapine response - Toxicity/ADR
ondansetron response - Efficacy
opioids response - Dosage
oxaliplatin response - Efficacy, Toxicity/ADR
paroxetine response - Efficacy
peginterferon alfa-2b and ribavirin response - Toxicity/ADR
peginterferon alfa-2b response - Efficacy
tegafur response - Toxicity/ADR, Metabolism/PK
trastuzumab response - Efficacy
warfarin response - Dosage, Toxicity/ADR
Ace Inhibitors, Plain response - Toxicity/ADR
Alkylating Agents, anthracyclines and related substances, fluorouracil, and Platinum compounds response - Efficacy
Antiinflammatory agents, non-steroids response - Toxicity/ADR
Bisphosphonates response - Efficacy
Drugs used in opioid dependence response - Metabolism/PK
Ivacaftor response
Tumor necrosis factor alpha (TNF-alpha) inhibitors response - Efficacy
acenocoumarol response - Dosage, Toxicity/ADR
adalimumab response - Efficacy
alfentanil response - Metabolism/PK
allopurinol response - Efficacy
amisulpride response - Toxicity/ADR
amitriptyline response - Dosage, Toxicity/ADR
amitriptyline response - Efficacy
antidepressants response - Dosage, Toxicity/ADR
antiepileptics response - Efficacy
antineoplastic agents response - Efficacy, Toxicity/ADR
aripiprazole response - Toxicity/ADR
aspirin response - Toxicity/ADR
atazanavir and ritonavir response - Toxicity/ADR
atazanavir response - Other
atorvastatin response - Toxicity/ADR
azathioprine response - Dosage, Toxicity/ADR
boceprevir response - Efficacy
budesonide response - Efficacy
buprenorphine response - Dosage
bupropion response - Efficacy
caffeine response - Toxicity/ADR
capecitabine response - Efficacy
captopril response - Efficacy
carbamazepine response - Efficacy
carboplatin response - Efficacy
carboplatin, docetaxel, erlotinib, gemcitabine, and paclitaxel response - Efficacy
celecoxib response - Dosage
celecoxib response - Toxicity/ADR
cerivastatin response - Toxicity/ADR
cetuximab response - Dosage
chlorproguanil and dapsone response - Toxicity/ADR
citalopram response - Metabolism/PK
clomipramine response - Dosage, Toxicity/ADR
clomipramine response - Efficacy
clopidogrel response - Dosage, Efficacy, Toxicity/ADR
cocaine response - Toxicity/ADR
corticosteroids response - Efficacy
cyclophosphamide and epirubicin response - Efficacy, Toxicity/ADR
cyclosporine response - Dosage, Metabolism/PK
desipramine response - Dosage, Toxicity/ADR
diclofenac response - Toxicity/ADR
digoxin response - Other
diuretics response - Efficacy
docetaxel response - Efficacy
doxepin response - Dosage, Toxicity/ADR
efavirenz response - Dosage
efavirenz response - Toxicity/ADR
escitalopram response - Metabolism/PK
etanercept response - Efficacy
ethambutol, isoniazid, pyrazinamide, and rifampin response - Toxicity/ADR
ethambutol, isoniazid, pyrazinamide, and rifampin response - Toxicity/ADR, Metabolism/PK
etoposide response - Toxicity/ADR
fentanyl response - Metabolism/PK
fluorouracil and oxaliplatin response - Efficacy
fluorouracil response - Efficacy
fluorouracil response - Efficacy, Toxicity/ADR
fluorouracil, leucovorin, and oxaliplatin response - Efficacy
fluoxetine response - Efficacy
fluticasone propionate response - Efficacy
fluticasone/salmeterol response - Efficacy
furosemide and spironolactone response - Efficacy
gemcitabine response - Other
haloperidol response - Toxicity/ADR
heroin response - Metabolism/PK
hmg coa reductase inhibitors response - Toxicity/ADR, Metabolism/PK
hormonal contraceptives for systemic use response - Toxicity/ADR
imipramine response - Dosage, Toxicity/ADR
infliximab response - Efficacy
interferon alfa-2b, recombinant and ribavirin response - Dosage, Toxicity/ADR
interferons, peginterferon alfa-2a, peginterferon alfa-2b, and ribavirin response - Efficacy
irinotecan response - Other
ivacaftor / lumacaftor response - Efficacy
lamotrigine response - Other
latanoprost response - Efficacy
leucovorin response - Toxicity/ADR
lorazepam response - Other
meperidine response - Dosage
mercaptopurine response - Dosage, Toxicity/ADR
methotrexate response - Dosage, Efficacy, Toxicity/ADR
methotrexate response - Efficacy
mirtazapine response - Efficacy
morphine response - Metabolism/PK
naloxone response - Efficacy
naltrexone response - Metabolism/PK
nicotine response - Efficacy
nicotine response - Efficacy, Toxicity/ADR
nicotine response - Metabolism/PK
nicotine response - Toxicity/ADR
nicotine response - Toxicity/ADR, Metabolism/PK
nortriptyline response - Dosage, Toxicity/ADR
opioids response - Metabolism/PK
oxazepam response - Other
oxycodone response - Dosage
paclitaxel response - Efficacy
paclitaxel response - Efficacy, Toxicity/ADR
paliperidone response - Toxicity/ADR
panitumumab response - Dosage
peginterferon alfa-2a response - Efficacy
peginterferon alfa-2a, peginterferon alfa-2b, and ribavirin response - Efficacy
peginterferon alfa-2b response - Toxicity/ADR
pentazocine response - Dosage
phenytoin response - Dosage
platinum response - Toxicity/ADR
pravastatin response - Metabolism/PK
quetiapine response - Toxicity/ADR
ribavirin response - Toxicity/ADR
risperidone response - Efficacy
rituximab response - Efficacy
rosiglitazone response - Dosage
rosuvastatin response - Efficacy
rosuvastatin response - Other
rosuvastatin response - Toxicity/ADR
salmeterol response - Efficacy
selective beta-2-adrenoreceptor agonists response - Efficacy
sildenafil response - Efficacy
sirolimus response - Dosage
sulfonamides, urea derivatives response - Efficacy
tacrolimus response - Dosage
tacrolimus response - Dosage, Metabolism/PK
tacrolimus response - Efficacy
tacrolimus response due to donor genotype - Dosage, Metabolism/PK
tamoxifen response - Efficacy, Toxicity/ADR
tenofovir response -
tramadol response - Dosage
tramadol response - Metabolism/PK
triamcinolone response - Efficacy
trimipramine response - Dosage, Toxicity/ADR
venlafaxine response - Efficacy
warfarin response - Efficacy
warfarin response - Toxicity/ADR
ziprasidone response - Toxicity/ADR

Overview of PGx Content in ClinVar today

579 assertions on 337 variants in 126 genes from 13 submitters

Submitter	Country	Submissions	Content
PharmGKB	USA	342	Many
OMIM	USA	74	Many
Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine	USA	58	EGFR, KRAS, CYP2C9, VKORC1
Albrecht-Kossel-Institute, Medical University Rostock	Germany	46	GLA, Deoxygalactonojirimycin response
Genetic Testing Lab, Ashok and Rita Patel Institute of Integrated Study and Research in Biotechnology and Allied Sciences	India	39	NPHS2, TRPC6, Prednisolone response
Genetics, Bhagwan Mahavir Medical Research Centre	India	6	EGFR, TKI Inhibitors
Center for Pediatric Genomic Medicine, Children's Mercy Hospital and Clinics	USA	5	CYP2D6
Institute of Microbiology; University Hospital and Univeristy of Lausanne	Switzerland	3	CY2B6 Efavirenz response
Center for Advanced Molecular Diagnostics, Cytogenetics Laboratory, Brigham and Women's Hospital	USA	2	RARA ATRA response
Center for Personalized Medicine, Roswell Park Cancer Institute	USA	1	GFRA2 Pazopanib response
Neurology IV Unit; Fondazione Istituto Neurologico C. Besta	Italy	1	TPMT
Oxford Haemato-Oncology Service, Oxford University Hospitals NHS Foundation Trust	New Zealand	1	BRCA2 deletion PARP Inhibitor response
Department of Genetics, Osmania University	India	1	VKORC1 Warfarin dosing

ClinVar Variant View

NCBI Resources How To hrehm My NCBI Sign Out

ClinVar | ClinVar | Search ClinVar for gene symbols, HGVS expressions, conditions, and more | Search | Advanced | Help

Home | About | Access | Help | Submit | Statistics | FTP

NM_000769.2(CYP2C19):c.-806C>A

Variation ID: 225946
Review status: ★★★☆ reviewed by expert panel

1 Affected gene
cytochrome P450 family 2 subfamily C member 19 (CYP2C19) [Gene - OMIM - Variation Viewer]
Search ClinVar for variants within CYP2C19
Search ClinVar for variants including CYP2C19

Variant frequency in dbGaP
No dbGaP data has been submitted for this variant.

Browser views
RefSeqGene

Interpretation

Go to:

Clinical significance: drug response
Number of submission(s): 3
Condition(s):
- citalopram response - Metabolism/PK [MedGen]
- clopidogrel response - Dosage, Efficacy, Toxicity/ADR [MedGen]
- escitalopram response - Metabolism/PK [MedGen]

See supporting ClinVar records

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

PGx

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: clopidogrel response - Dosage, Efficacy, Toxicity/ADR Drug reported used for: Acute coronary syndrome [MedGen] Drug reported used for: Acute coronary syndrome;Coronary Artery Disease;Myocardial Infarction	germline	PubMed (18) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV000268179.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: not provided	germline	PubMed (2) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV000268180.2
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized	literature only	Condition: not provided	germline	PubMed (2) [See all	PharmGKB	SCV000268181.2

Full description for PharmGKB

PGx

PharmGKB Level of Evidence 1A: Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.

Drug-variant association: Dosage, Efficacy, Toxicity/ADR

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Drug-variant association: Metabolism/PK

PharmGKB Level of Evidence 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Drug-variant association: Metabolism/PK

- https://www.pharmgkb.org/clinicalAnnotation/655386913

NM_000492.3(CFTR):c.1647T>G (p.Ser549Arg)

Variation ID: 40190

Review status: ★★★☆ reviewed by expert panel

Assertion and evidence details

Go to:

Clinical assertions | Summary evidence | Supporting observations

Germline

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Pathogenic (Mar 28, 2013)	reviewed by expert panel • Submitter's publication	literature only	Cystic fibrosis [MedGen | Orphanet | OMIM]	germline	• PubMed (1) [See all records that cite this PMID] • Other citation	CFTR2 - CFTR2	SCV000087508.3
Pathogenic (Nov 27, 2015)	criteria provided, single submitter • Counsyl Autosomal and X-linked Recessive Disease Classification criteria (2015)	clinical testing	Cystic fibrosis [MedGen | Orphanet | OMIM]	unknown		Counsyl	SCV000485210.1

PGx

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response	reviewed by expert panel • Pharmacogenomics knowledge for personalized medicine	literature only	Condition: ivacaftor response - Efficacy Drug reported used for: Cystic fibrosis [MedGen | Orphanet | OMIM]	germline	PubMed (1) [See all records that cite this PMID] • Other citation	PharmGKB	SCV000268176.2

Representing variants with pathogenicity for Mendelian disease and responsiveness to therapy

NM_005228.4(EGFR):c.2573T>G (p.Leu858Arg)

Variation ID: 16609

Review status: ★ ★ ★ ☆ reviewed by expert panel

Clinical assertions | Summary evidence | Supporting observations

Somatic

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Pathogenic (Jul 14, 2015)	no assertion criteria provided	literature only	Non-small cell lung cancer [MeSH | MedGen]	somatic	PubMed (21) [See all records that cite these PMIDs] Other citation	Database of Curated Mutations (DoCM) Study description	SCV000504239.1
Likely pathogenic (May 31, 2016)	no assertion criteria provided	literature only	Adenocarcinoma of lung [MeSH | MedGen]	somatic	PubMed (1) [See all records that cite this PMID] Other citation	Database of Curated Mutations (DoCM) Study description	SCV000504240.1

PGx

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
drug response	reviewed by expert panel Pharmacogenomics knowledge for personalized medicine	literature only	Condition: gefitinib response - Efficacy Drug reported used for: Carcinoma, Non-Small-Cell Lung [MedGen]	germline	PubMed (24) [See all records that cite these PMIDs] Other citation	PharmGKB	SCV000268169.2

Representing somatic variants with cancer risk and responsiveness to therapy

Update on CPIC submissions to ClinVar

- New excel template was designed for CPIC submissions
  - Ideally pulled by NCBI via API
- CYP2C19 guidelines is the test case, and then to submit the guidelines on a gene-by-gene basis
  - Submission included haplotype (* allele) function as defined by CPIC using CPIC's standardized nomenclature, and HGVS definition
  - Also includes all diplotype combinations with metabolizer status, drug association, CPIC guidance and recommendation strength

Courtesy of Teri Klein and Mary Relling

ClinGen Acknowledgements

ClinGen Steering Committee

Jonathan Berg, UNC
Carlos Bustamante, Stanford
Mike Cherry, Stanford
James Evans, UNC
Andy Faucett, Geisinger
Katrina Goddard, Kaiser Permanente
David Ledbetter, Geisinger
Christa Lese Martin, Geisinger

Aleks Milosavljevic, Baylor
Kelly Ormond, Stanford
Sharon Plon, Baylor
Heidi Rehm, Harvard
Michael Watson, ACMG
Kirk Wilhelmsen, UNC
Marc Williams, Geisinger

Lisa Brooks, NHGRI
Andy Freedman, NCI
Danuta Krotoski, NICHD
Melissa Landrum, NCBI
Erin Ramos, NHGRI
Steve Sherry, NCBI

Program Coordinators:
Danielle Azzariti, Erin Currey, Colette Fletcher-Hoppe, Miranda Hallquist, Jules Koenig, Kristy Lee, Laura Milko, Andy Rivera, Cody Sam, Meredith Weaver

ClinGen Working Groups (WG) and WG Chairs

Clinical Domain WGs

Hereditary Cancer : Ken Offit, Sharon Plon

Somatic Cancer: Shashi Kulkarni, Subha Madhavan

Cardiovascular: Euan Ashley, Birgit Funke, Ray Hershberger

Inborn Errors of Metabolism: Rong Mao, Robert Steiner, Bill Craigen

Pharmacogenomics: Teri Klein, Marilyn Ritchie

Pediatric Neurology: Michael Friez, Heather Mefford, Scott Myers

Data Model WG
Larry Babb, Chris Bizon

Informatics WG
Carlos Bustamante

Actionability WG
Katrina Goddard, Jim Evans

Phenotyping WG
David Miller

Education, Engagement, Access WG
Erin Rooney Riggs, Danielle Azzariti

Gene Curation WG
Jonathan Berg, Christa Martin

Genomic Variant WG
Christa Martin, Sharon Plon, Heidi Rehm

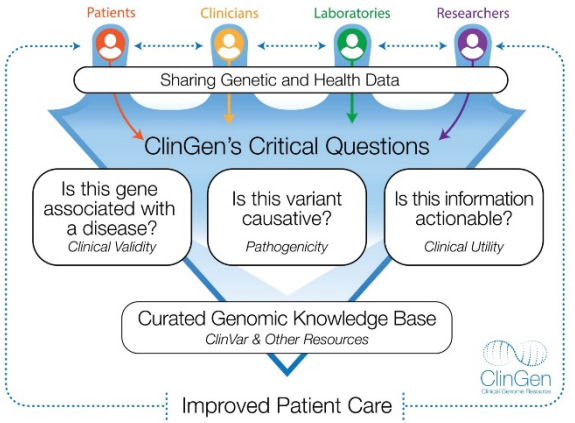
Electronic Health Record WG
Marc Williams

Consent and Disclosure Recommendations (CADRe) WG
Andy Faucett, Kelly Ormond

ClinGen
Clinical Genome Resource

www.clinicalgenome.org

>500 people from >100 institutions



Curating the Clinical Genome 2017

A scientific conference co-sponsored by ClinGen and DECIPHER to advance genomic medicine through global data sharing and curation

Who should attend? Clinical molecular and cytogenetic lab directors, researchers, clinicians, genetic counselors, bioinformaticians, genomic application developers and genetic standards & guideline developers

Session topics:

- Curating Gene-Disease Relationships
- Evolving Guidelines/Resources to Support Variant Assessment
- Genomic Data Sharing
- Matchmaking Phenotypes, Genes and Variants
- New Frontiers for Clinical Genomics

Scientific Program Committee:

- Helen Firth, DM (Cambridge University Hospitals)
- Christa Lese Martin, PhD (Geisinger Health System)
- Sharon Plon, MD, PhD (Baylor College of Medicine)
- Erin Ramos PhD, MPH (National Human Genome Research Institute)
- Heidi Rehm, PhD (Harvard Medical School)
- Joris Vermeesch, PhD (University of Leuven)
- Michael Watson, PhD (American College of Medical Genetics and Genomics)
- Marc Williams, MD (Geisinger Health System)
- Caroline Wright, PhD (Wellcome Trust Sanger Institute)

www.clinicalgenome.org/meeting

ClinGen
Clinical Genome Resource

DECIPHER

June 28-30, 2017
Washington Marriott Georgetown
1221 22nd Street NW, Washington, DC, 20037

Learn more at www.clinicalgenome.org/meeting/

Early Bird Registration Deadline: March 31, 2017
Abstract Deadline: April 28, 2017