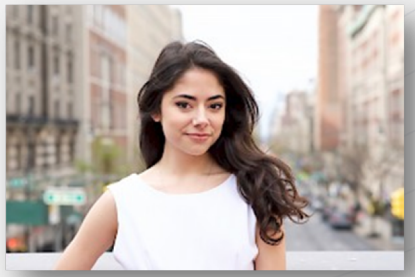
The Clinical Genome Resource (ClinGen)

Erin M. Ramos, PhD MPH & Sharon Plon, MD PhD

Lisa Brooks, Robert Fullem, Nicole Lockhart, Teri Manolio, Natalie Pino, Ken Wiley

NACHGR Open Session, February 11, 2019



Natalie Pino

Rob Fullem

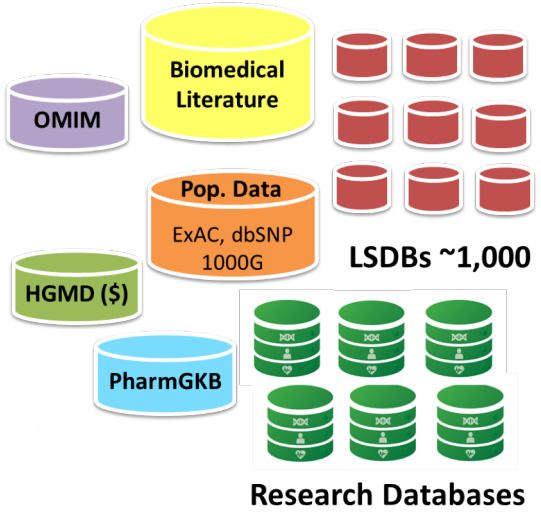
National Human Genome Research Institute

ClinGen Clinical Genome Resource

The Forefront of Genomics®

The Problem: Circa 2010

- Ability to detect DNA variants has greatly surpassed our ability to interpret their clinical impact
- ~ 20,000 genes and > 88 million known variable sites in the human genome



Often without common data standards and approaches for interpretation

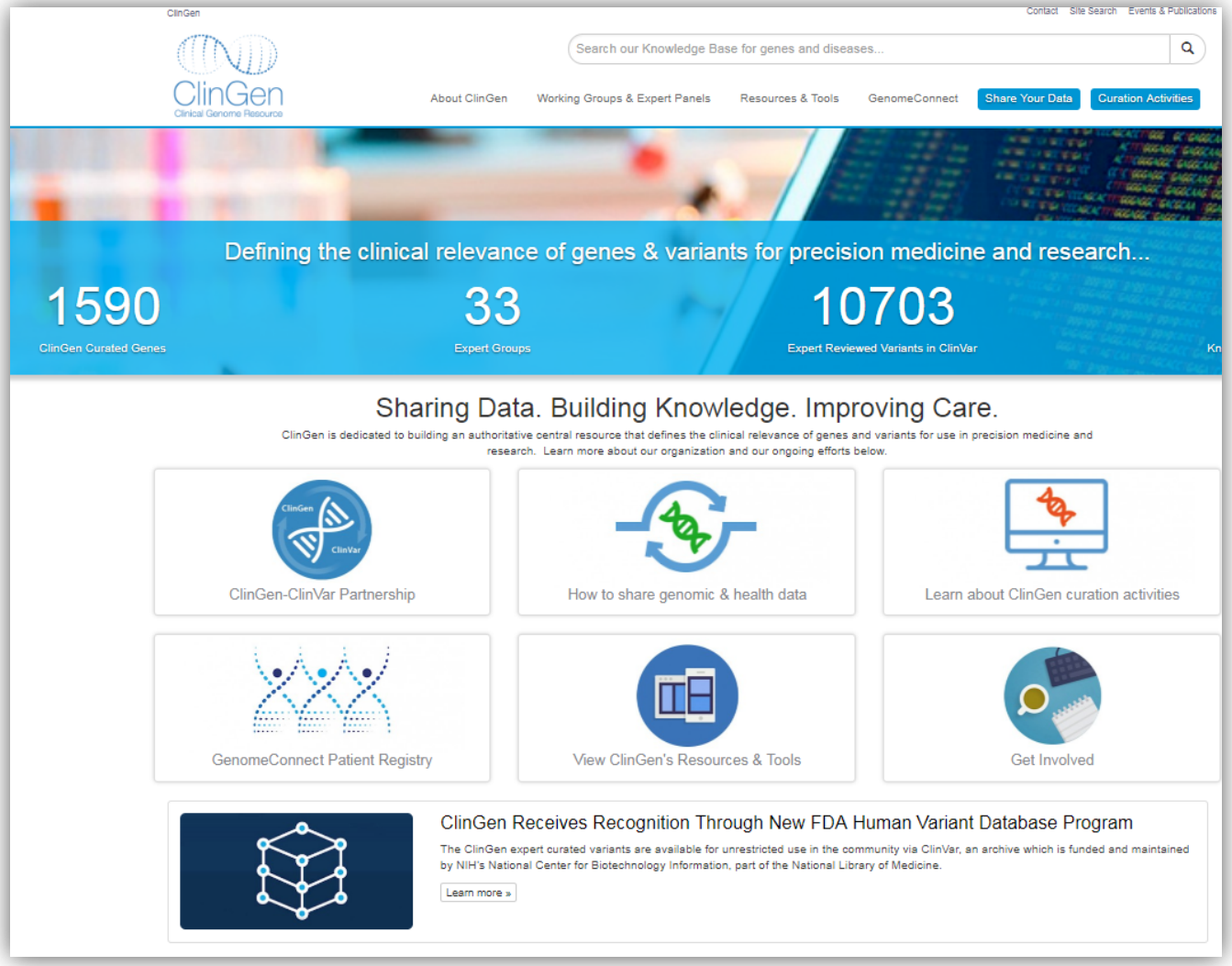
Largely absent from public domain

NIH NHGRI

The ClinGen Program

Increase data sharing and build an authoritative resource to define the clinical relevance of genes and variants for use in medicine and research.

- **Launched: Sept 2013**
  - J. Berg, K. Goddard, M. Watson, M. Williams
  - C. Bustamante, S. Plon
  - H. Rehm, C. Martin, D. Ledbetter
  - $33M, includes co-funds
- **Phase II: Sept 2017**
  - $39M
  - NICHD curation program



[www.clinicalgenome.org]

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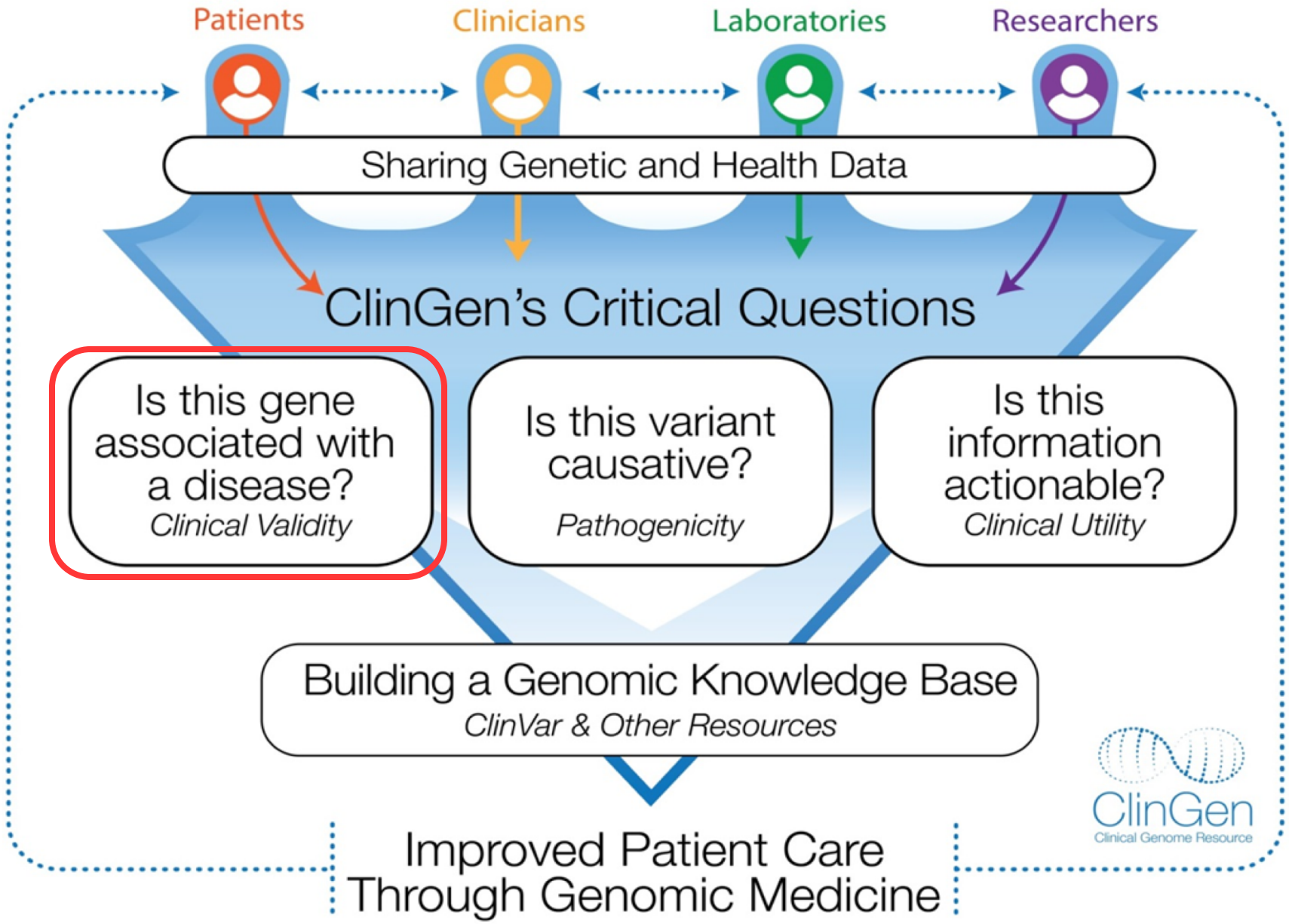
ClinGen
Clinical Genome Resource

Leadership and Coordinators


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
Improved Patient Care Through Genomic Medicine
ClinGen
Clinical Genome Resource

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ClinGen developed semi-quantitative framework to classify strength of evidence for the role of genes in disease

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,*]

Genetic Evidence: Case-level, family segregation, or case-control data

Experimental Evidence: Expression, model organism, rescue studies, etc.

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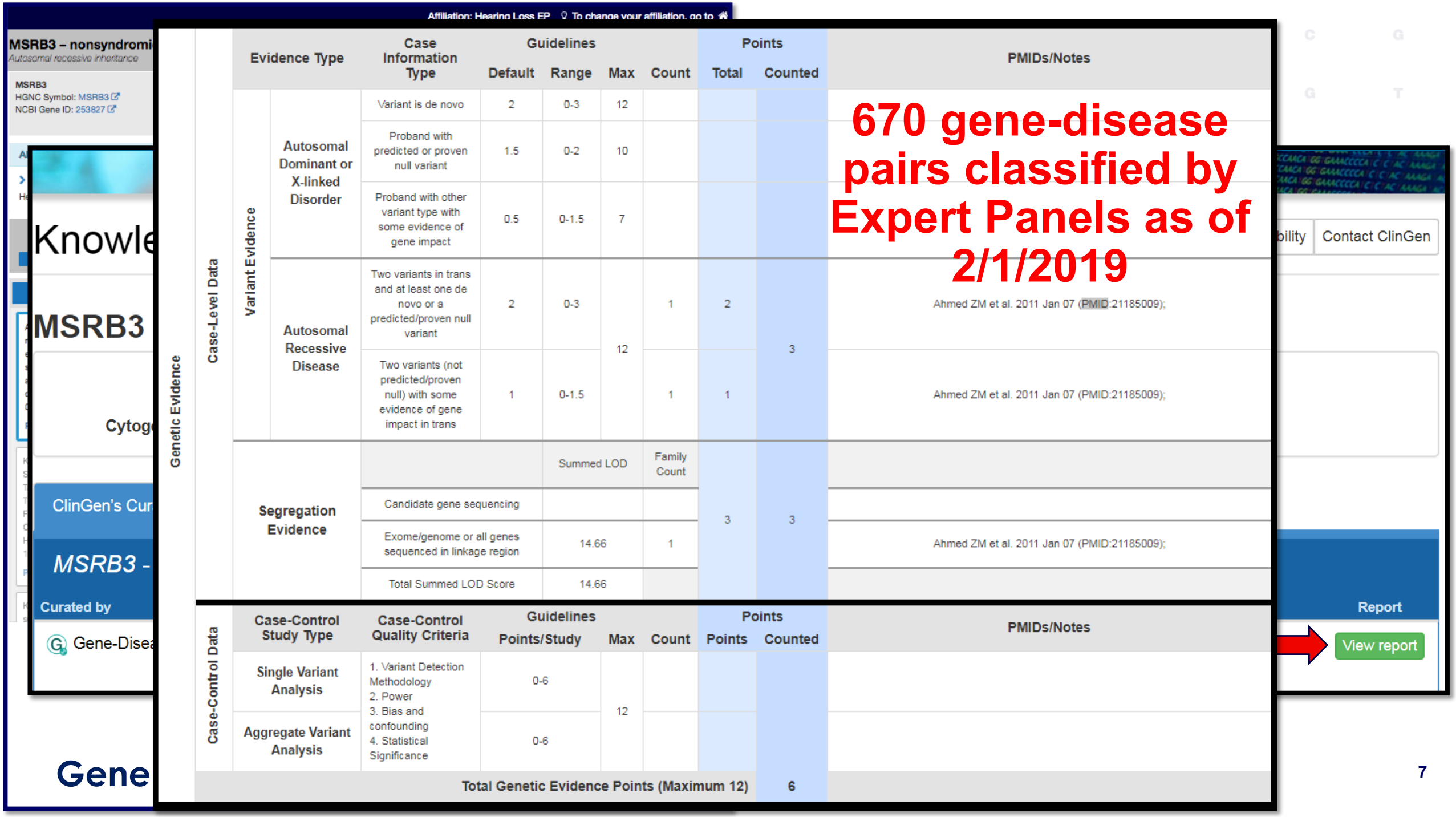
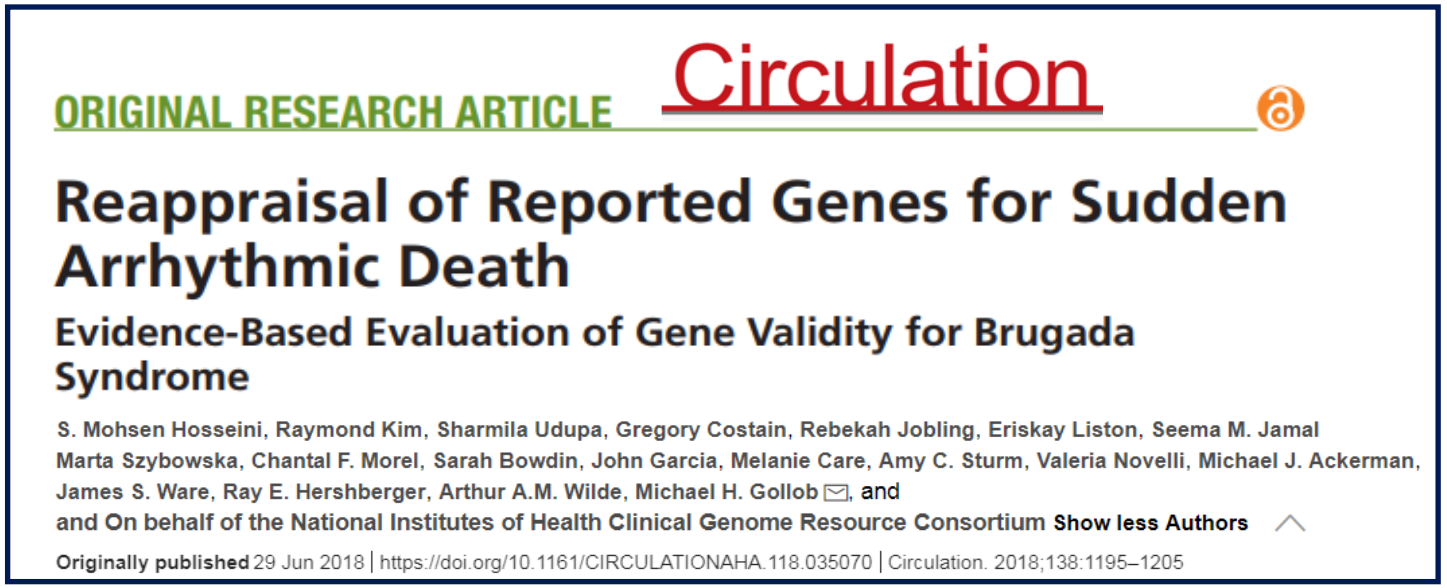

MSRB3 – nonsyndromi
Autosomal recessive inheritance
MSRB3
HGNC Symbol: MSRB3
NCBI Gene ID: 253827
Knowle
MSRB3
Cytog
ClinGen's Cur
MSRB3 -
Curated by
Gene-Disea
Gene
Affiliation: Hearing Loss EP
To change your affiliation, go to
Genetic Evidence
Case-Level Data
Variant Evidence
Evidence Type
Case Information Type
Guidelines
Default
Range
Max
Count
Points
Total
Counted
PMIDs/Notes
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
Autosomal Recessive Disease
Two variants in trans and at least one de novo or a predicted/proven null variant
2
0-3
12
1
2
3
Ahmed ZM et al. 2011 Jan 07 (PMID:21185009);
Two variants (not predicted/proven null) with some evidence of gene impact in trans
1
0-1.5
1
1
Ahmed ZM et al. 2011 Jan 07 (PMID:21185009);
Segregation Evidence
Summed LOD
Family Count
Candidate gene sequencing
Exome/genome or all genes sequenced in linkage region
14.66
1
3
3
Ahmed ZM et al. 2011 Jan 07 (PMID:21185009);
Total Summed LOD Score
14.66
Case-Control Data
Case-Control Study Type
Case-Control Quality Criteria
Guidelines
Points/Study
Max
Count
Points
Counted
PMIDs/Notes
Single Variant Analysis
1. Variant Detection Methodology
2. Power
3. Bias and confounding
4. Statistical Significance
0-6
12
Aggregate Variant Analysis
0-6
Total Genetic Evidence Points (Maximum 12)
6
670 gene-disease pairs classified by Expert Panels as of 2/1/2019
bility
Contact ClinGen
Report
View report

Select Gene Curation Expert Panel Results



ORIGINAL RESEARCH ARTICLE Circulation

Reappraisal of Reported Genes for Sudden Arrhythmic Death

Evidence-Based Evaluation of Gene Validity for Brugada Syndrome

S. Mohsen Hosseini, Raymond Kim, Sharmila Udupa, Gregory Costain, Rebekah Jobling, Eriskay Liston, Seema M. Jamal Marta Szybowska, Chantal F. Morel, Sarah Bowdin, John Garcia, Melanie Care, Amy C. Sturm, Valeria Novelli, Michael J. Ackerman, James S. Ware, Ray E. Hershberger, Arthur A.M. Wilde, Michael H. Gollob, and and On behalf of the National Institutes of Health Clinical Genome Resource Consortium Show less Authors

Originally published 29 Jun 2018 | https://doi.org/10.1161/CIRCULATIONAHA.118.035070 | Circulation. 2018;138:1195–1205

~~*ABCC9*~~ ~~*HCN4*~~ ~~*KCNJ8*~~ ~~*SCN3B*~~

~~*ANK2*~~ ~~*KCND3*~~ ~~*PKP2*~~ ~~*SCN10A*~~

~~*CACNA1C*~~ ~~*KCNE5*~~ ~~*RANGRF*~~ ~~*SLMAP*~~

~~*CACNA2D1*~~ ~~*KCNE3*~~ ~~*SCN1B*~~ *SCN5A*

~~*CACNB2*~~ ~~*KCNH2*~~ ~~*SCN2B*~~ ~~*TRPM4*~~

~~*GPD1L*~~

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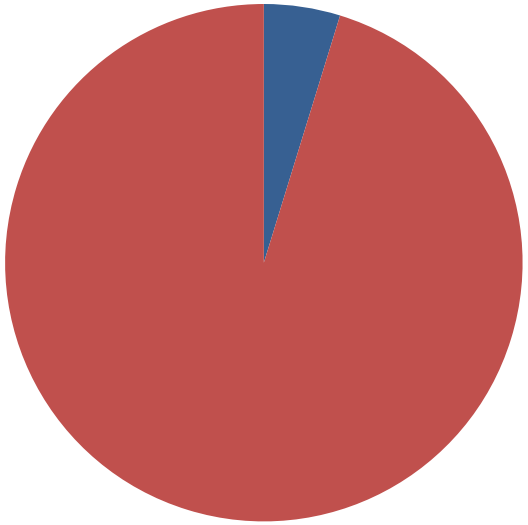
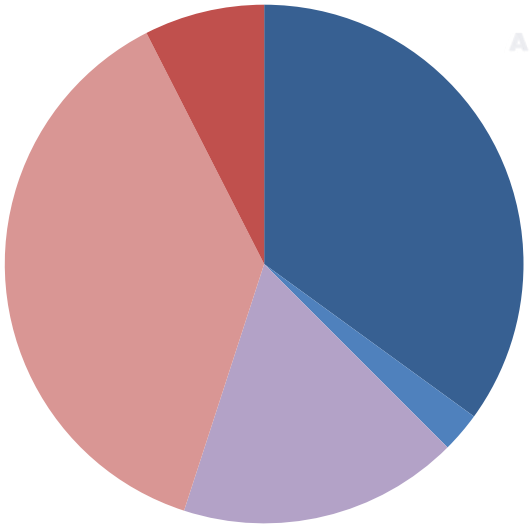
Select Gene Curation Expert Panel Results

Brugada Syndrome
21 gene-disease pairs



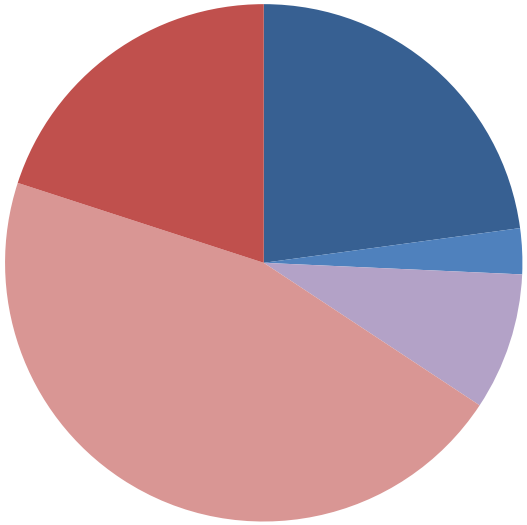
[Circulation 2018]



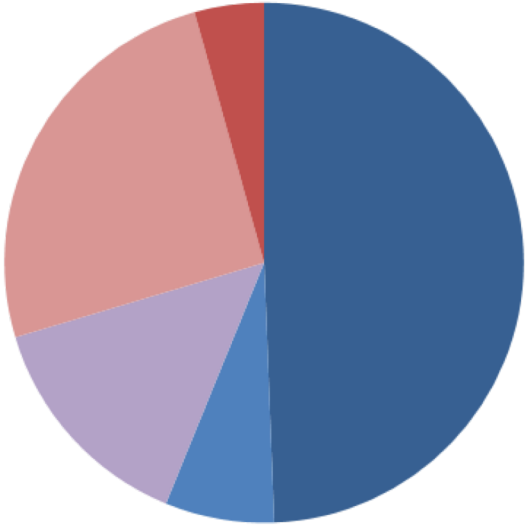
[Gen In Med 2018]

Colorectal Cancer
40 gene-disease pairs

Hypertrophic Cardiomyopathy
37 gene-disease pairs



[Circulation Gen 2019]



[Hum Mutat 2018]

Hearing Loss
164 gene-disease pairs

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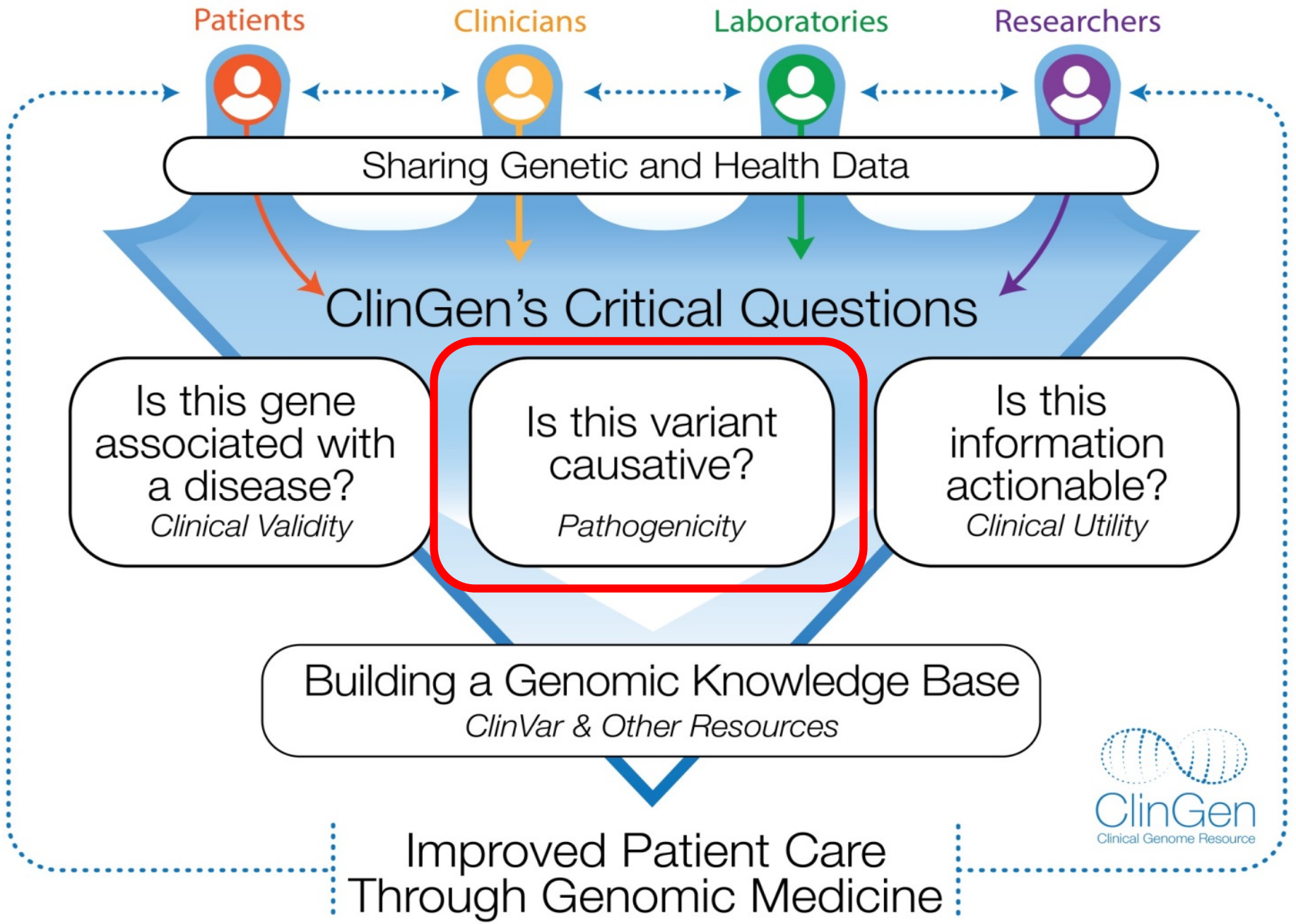
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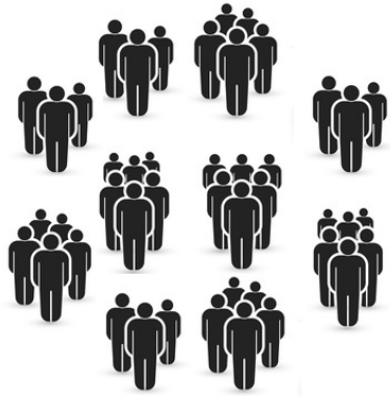
Multi-pronged effort needed for variant curation and interpretation

- Public sharing of variant interpretations via ClinVar
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven interpretation of variants (Expert Panels)
- Sequence Variants and Copy Number Variants



ClinGen

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

ClinVar

(database for ingesting and sharing variant level knowledge)

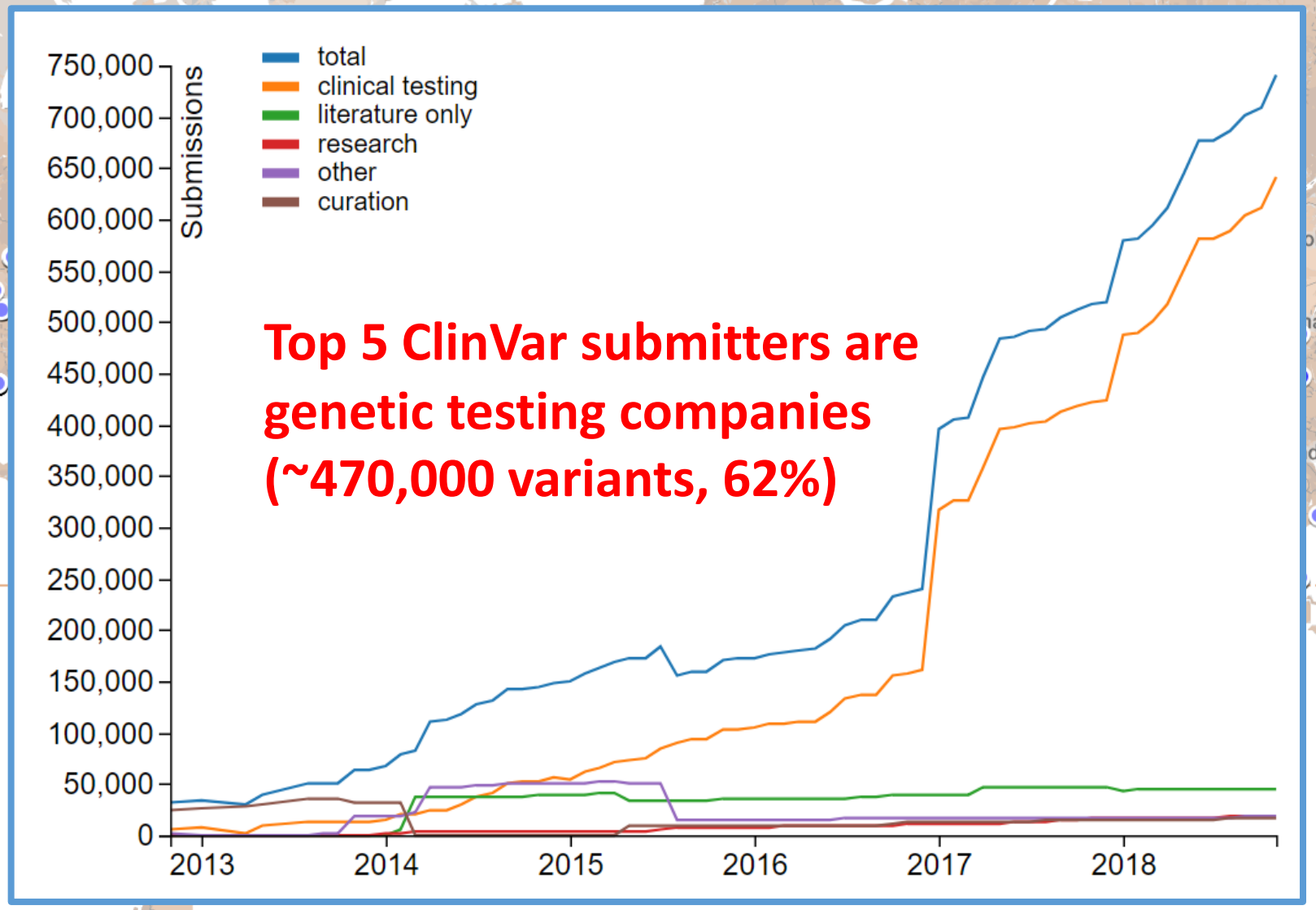
The ClinVar Database

NCBI Resources How To Sign in to NCBI

NM_004360.5(CDH1):c.3G>A (p.Met1Ile)

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name
Likely pathogenic (Nov 21, 2018)	reviewed by expert panel • ClinGen CDH1 ACMG Specifications v1	curation	Hereditary diffuse gastric cancer (Autosomal dominant inheritance) [MedGen | Orphanet | OMIM]	germline	• PubMed (3) [See all records that cite these PMIDs] • Other citation	ClinGen CDH1 Variant Curation Expert Panel FDA Recognized Database
Likely pathogenic (Jul 26, 2017)	criteria provided, single submitter • Invitae Variant Classification Sherloc (09022015)	clinical testing	Hereditary diffuse gastric cancer [MedGen | Orphanet | OMIM]	germline		Invitae
Pathogenic (Jul 11, 2017)	criteria provided, single submitter • Ambry Autosomal Dominant and X-Linked criteria (3/2017)	clinical testing	Hereditary cancer-predisposing syndrome [MedGen]	germline	• PubMed (2) [See all records that cite these PMIDs]	Ambry Genetics

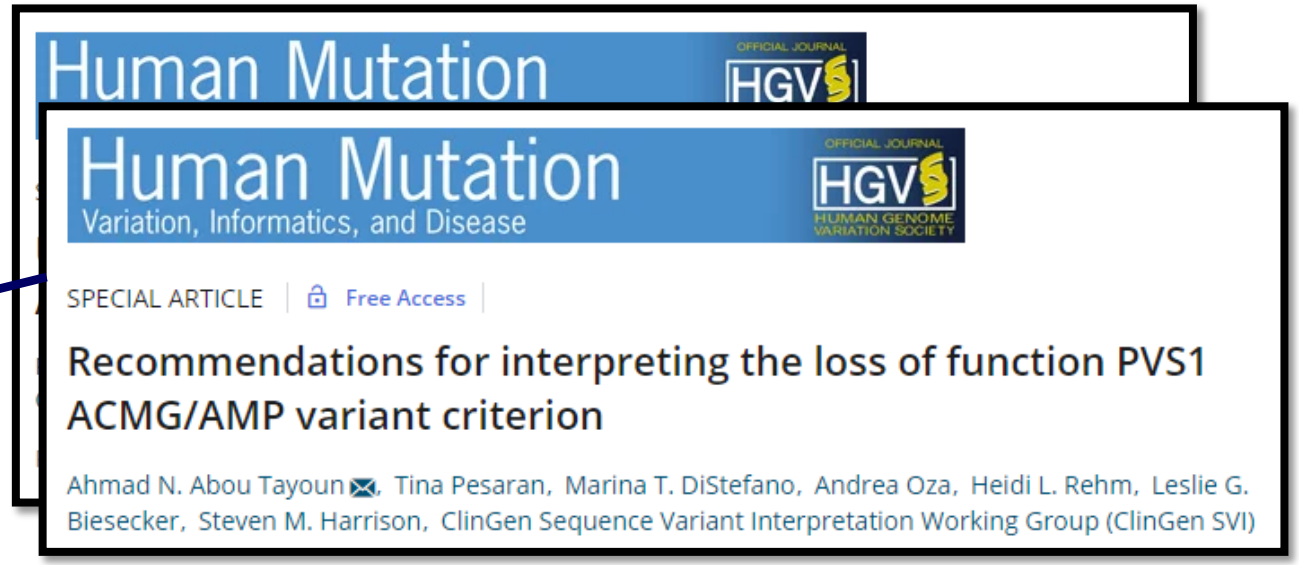
761,048 variants with interpretations submitted to ClinVar from 1,122 submitters across 67 countries



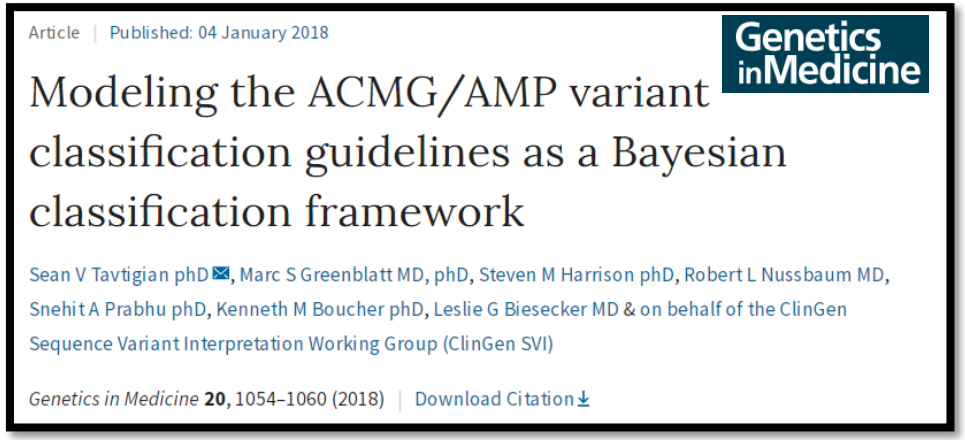
[Created by Natalie Pino, NHGRI]

Sequence Variant Interpretation WG

- Refine the ACMG/AMP guideline as they are deployed by the community



- Move towards a more quantitative framework



ACMG STANDARDS AND GUIDELINES | Genetics inMedicine May 2015

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

	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*			

Benign, Likely Benign, Uncertain Significance, Likely Pathogenic, Pathogenic

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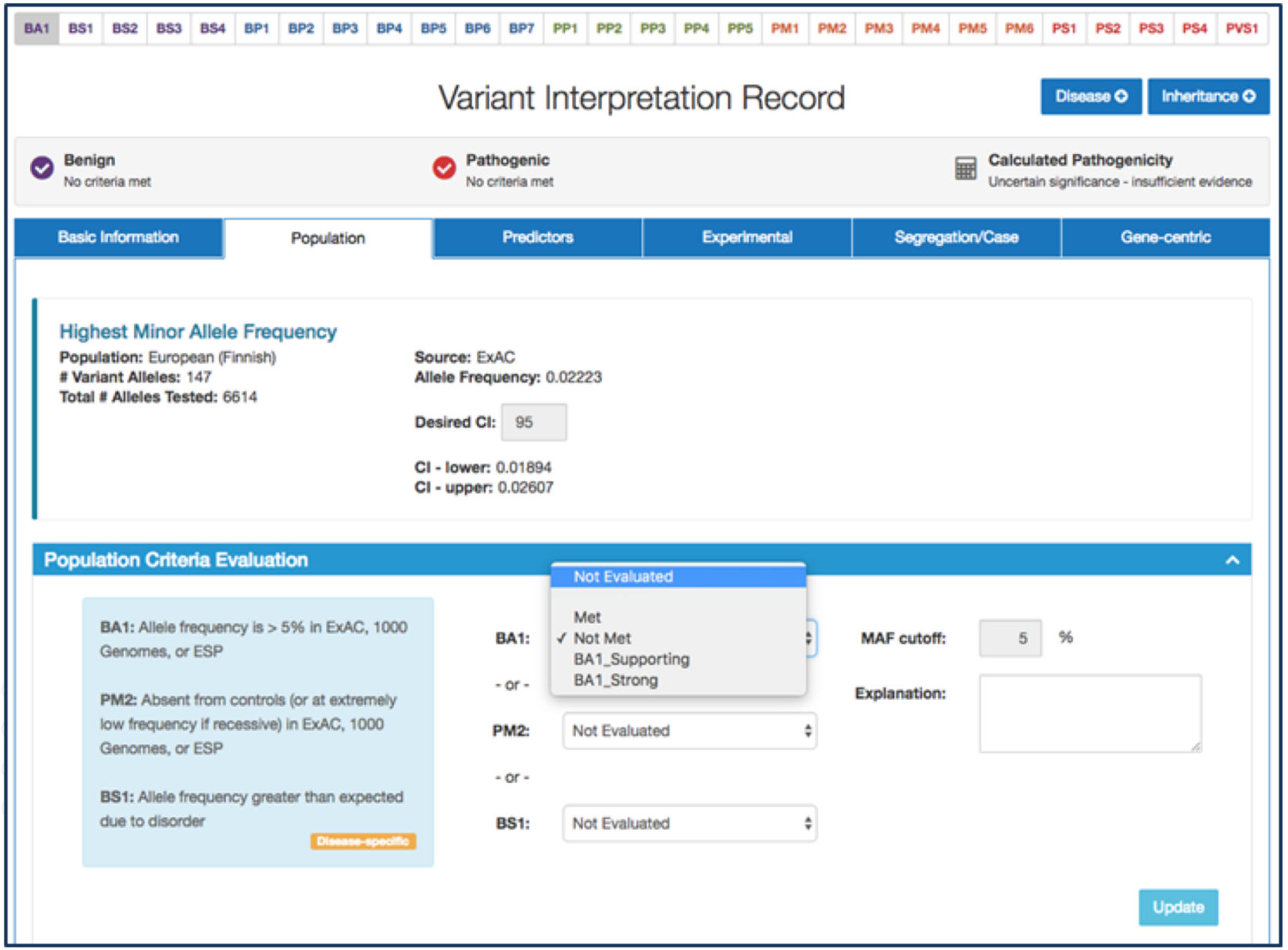
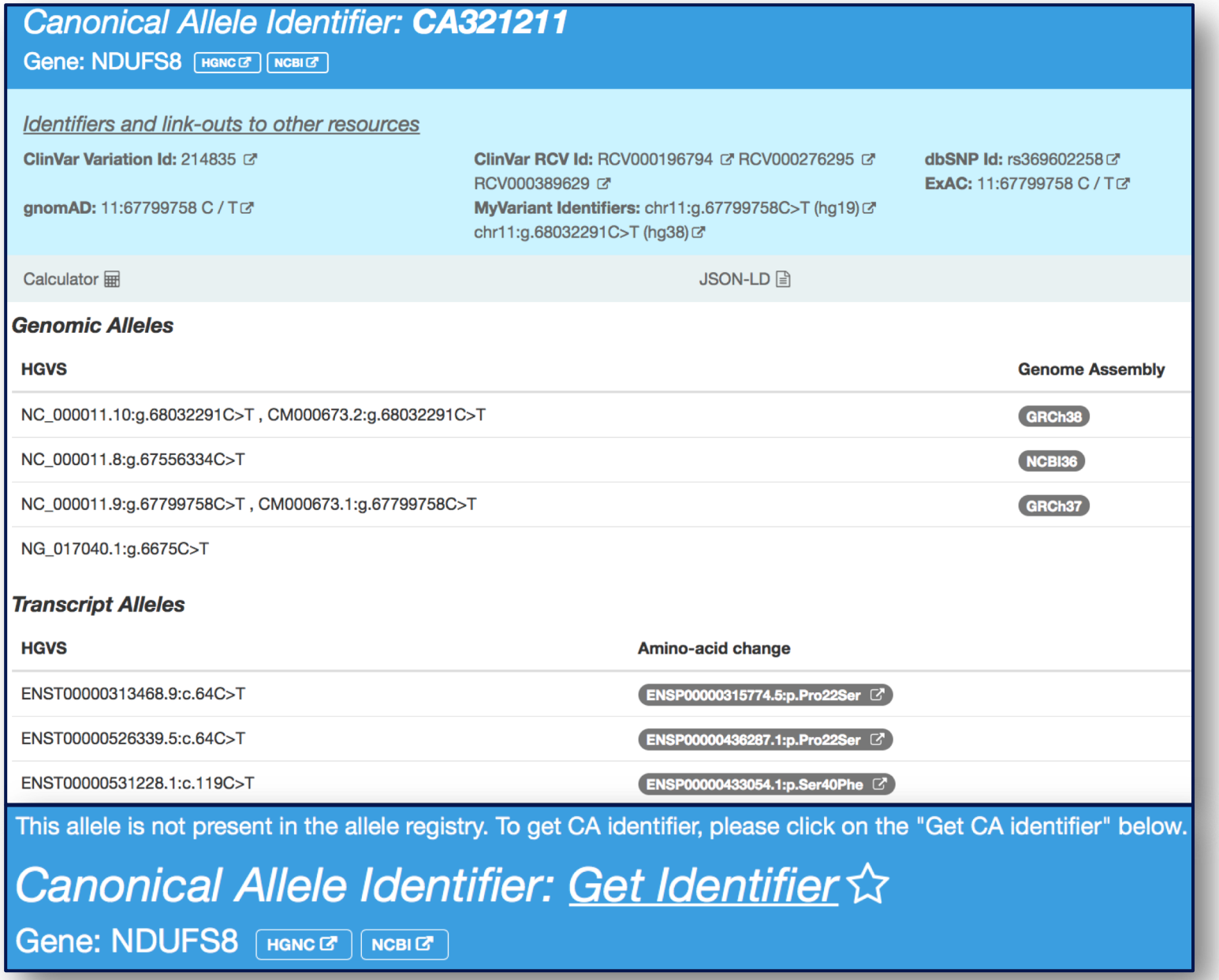
Variant Curation Interface



ClinGen Allele Registry



ClinGen Allele Registry provides identifiers (CAID) for > 910 million variants

Allows user to quickly and easily get identifiers for new variants

CIViC Clinical Interpretations of Variants in Cancer

ClinVar Clinically relevant variation

EMBL-EBI

ClinGen CAIDs used in key resources

https://reg.clinicalgenome.org

ClinGen's Variant Curation Expert Panels - Progress

Step 1: Define WG and plans	Step 2: Develop Variant Classification Rules	Step 3: Pilot Rules	Step 4: Implementation
Coagulation Factor	Creatine deficiencies	Brain Malformations	Cardio/MYH7
FBN1/Aortopathy	HHT/Vascular	Hypercholesterolemia	CDH1
HBOC/pancreatic cancer	Platelet Disorders	KCNQ1	Hearing Loss
Peroxisomal disorders	Malignant hyperthermia	Mitochondrial	PAH
Von Willebrand	Monogenic Diabetes	Myeloid Malignancies	PTEN
	Myopathies	Storage Diseases	RASopathy
	Rett-Angelman	TP53	CFTR2*
	VHL		InSIGHT*
			CFTR2*

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*Curated by other efforts

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*Curated by other efforts

ClinGen Receives FDA Recognition for Expert Curated Variants Using ClinGen Process and Tools

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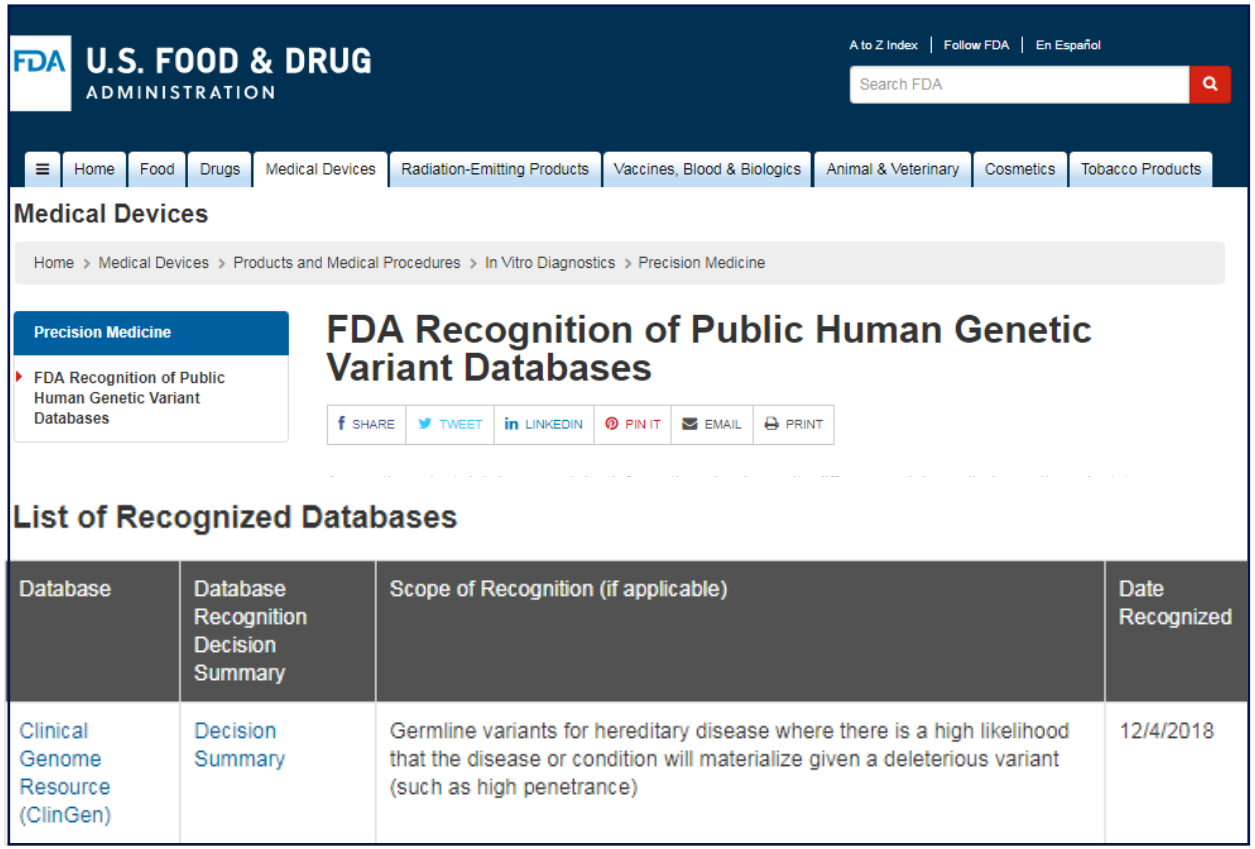
FDA Recognized Genetic Variant Database

- Data and assertions in the database are considered valid scientific evidence
- Genetic/genomic test developers can use these assertions to support clinical validity during FDA's regulatory review
- FDA hopes this program will:
  - Increase public sharing
  - Reduce regulatory burden on test developers
  - Advance the evaluation and implementation of precision medicine



Data / People / Process

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FDA Recognized Genetic Variant Database

Filters activated: Expert panel. Clear all to show 1602 items.

	Variation *Location*	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
1.	NM_000257.3(**MYH7**):c.5740G>A (p.Glu1914Lys) *GRCh37:* Chr14:23883018 *GRCh38:* Chr14:23413809	**MYH7**	Primary dilated cardiomyopathy, Dilated cardiomyopathy 1S, Myopathy, distal, 1	Likely pathogenic (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database
2.	NM_000257.3(**MYH7**):c.5736C>T (p.Ile1912=) *GRCh37:* Chr14:23883022 *GRCh38:* Chr14:23413813	**MYH7**	not specified, Hypertrophic cardiomyopathy, Cardiovascular phenotype	Benign (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database
3.	NM_000257.3(**MYH7**):c.5726G>C (p.Arg1909Pro) *GRCh37:* Chr14:23883032 *GRCh38:* Chr14:23413823	**MYH7**	Primary dilated cardiomyopathy	Likely pathogenic (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database
4.	NM_000257.3(**MYH7**):c.5704G>C (p.Glu1902Gln) *GRCh37:* Chr14:23883054 *GRCh38:* Chr14:23413845	**MYH7**	Myosin storage myopathy, Myopathy, distal, 1, not specified, Hypertrophic cardiomyopathy, Scapuloperoneal myopathy, Left ventricular noncompaction cardiomyopathy, Cardiovascular phenotype, Dilated Cardiomyopathy, Dominant	Uncertain significance (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database
5.	NM_000257.3(**MYH7**):c.5588G>A (p.Arg1863Gln) *GRCh37:* Chr14:23883283 *GRCh38:* Chr14:23414074	**MYH7**	not specified, Hypertrophic cardiomyopathy	Uncertain significance (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database
6.	NM_000257.3(**MYH7**):c.5401G>A (p.Glu1801Lys) *GRCh37:* Chr14:23884362 *GRCh38:* Chr14:23415153	**MYH7**	Primary dilated cardiomyopathy, Myopathy, distal, 1, Cardiomyopathy, not provided, Hypertrophic cardiomyopathy, Left ventricular noncompaction cardiomyopathy	Likely pathogenic (Dec 15, 2016)	**reviewed by expert panel** FDA Recognized Database

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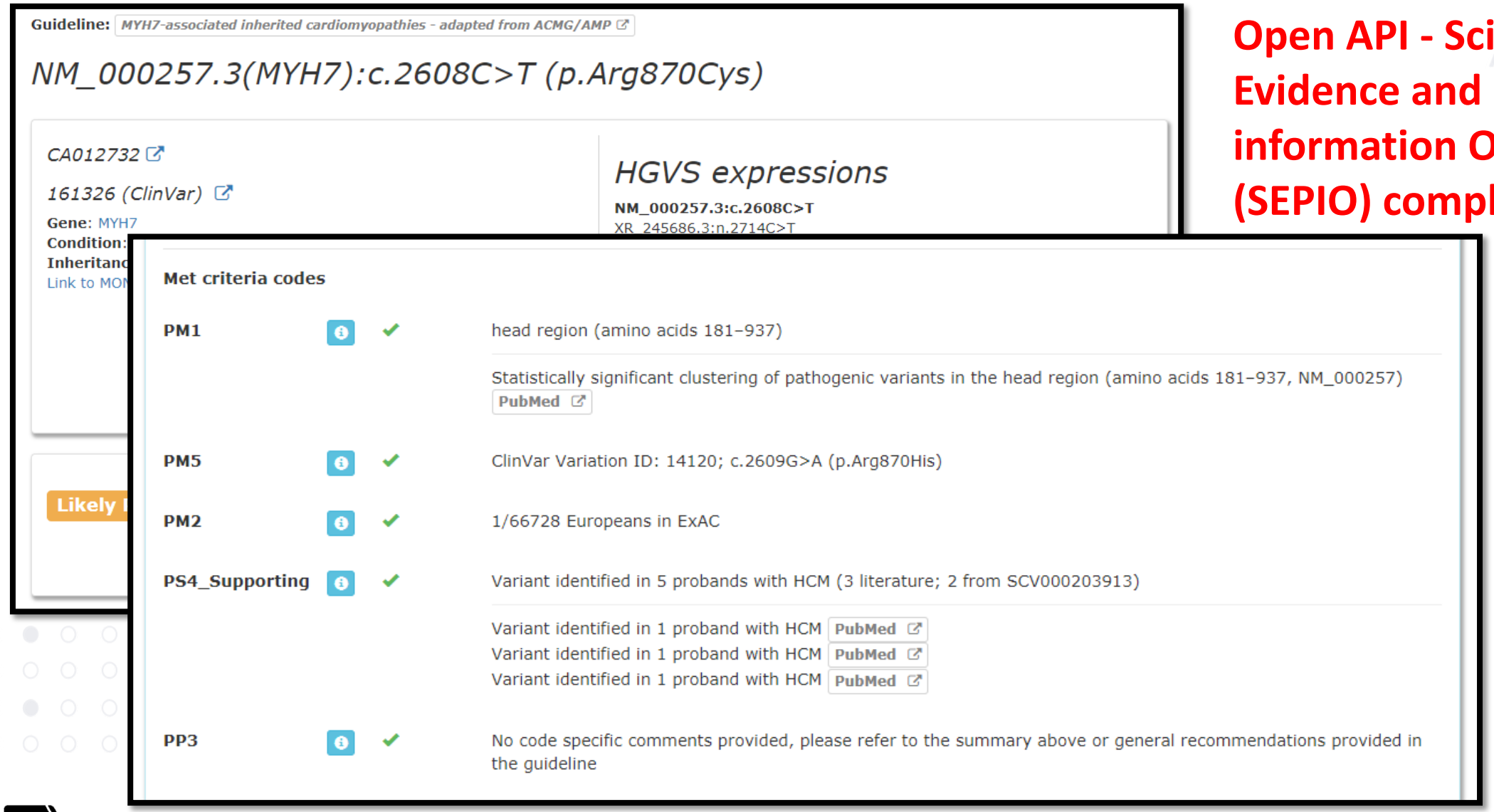
FDA program led to improvements in transparency and access



Open API - Scientific Evidence and Provenance information Ontology (SEPIO) compliant JSON-LD

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ClinGen Evidence Repository

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

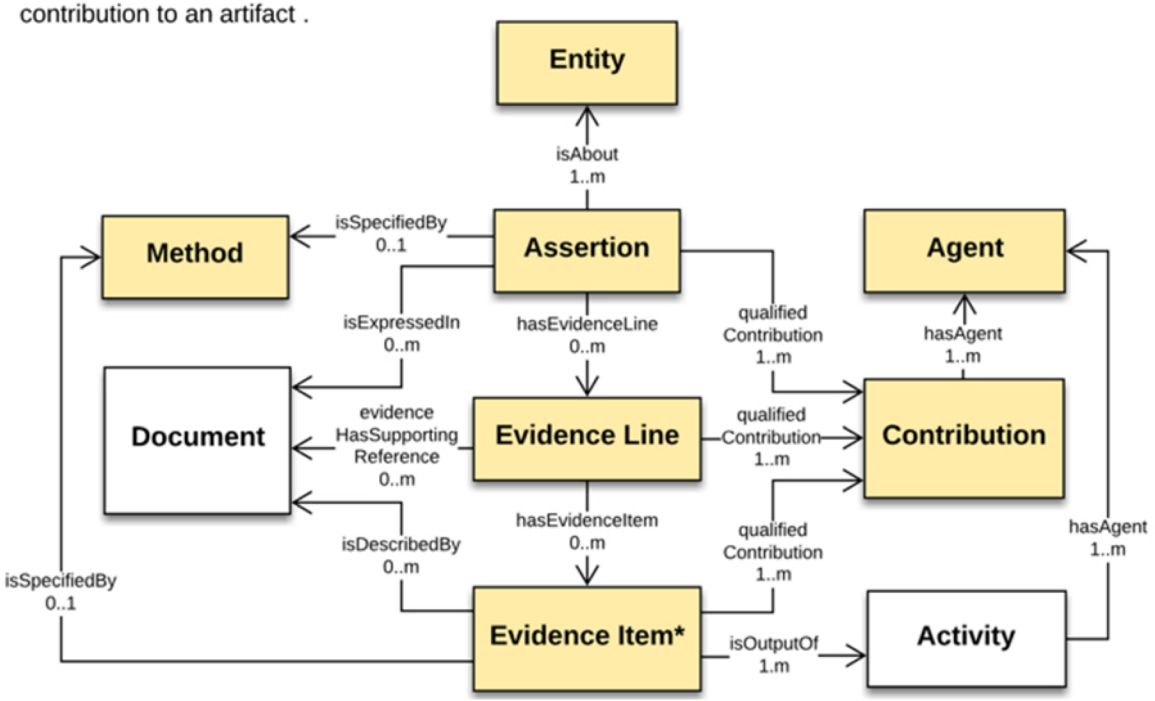
Global Alliance for Genomics & Health

Collaborate. Innovate. Accelerate.

ClinGen is a GA4GH Driver Project

- Genomic Knowledge Standards Workstream
  - Variant Modeling Collaboration
  - Interpretation Data Model (SEPIO with Monarch)
- Clinical & Phenotypic Data Capture Workstream
- Discovery Workstream
  - Variant Knowledge Sharing API

SEPIO Class Association Diagram (Qualified Contribution Model)
Associative relationships between the high-level classes in the SEPIO Data Model.
Classes in orange are the subset implemented in the ClinGen Model.
The **'qualified contribution model'** implemented by ClinGen is shown here, wherein a Contribution object is reified to capture agetns, roles, and time/place of a contribution to an artifact .



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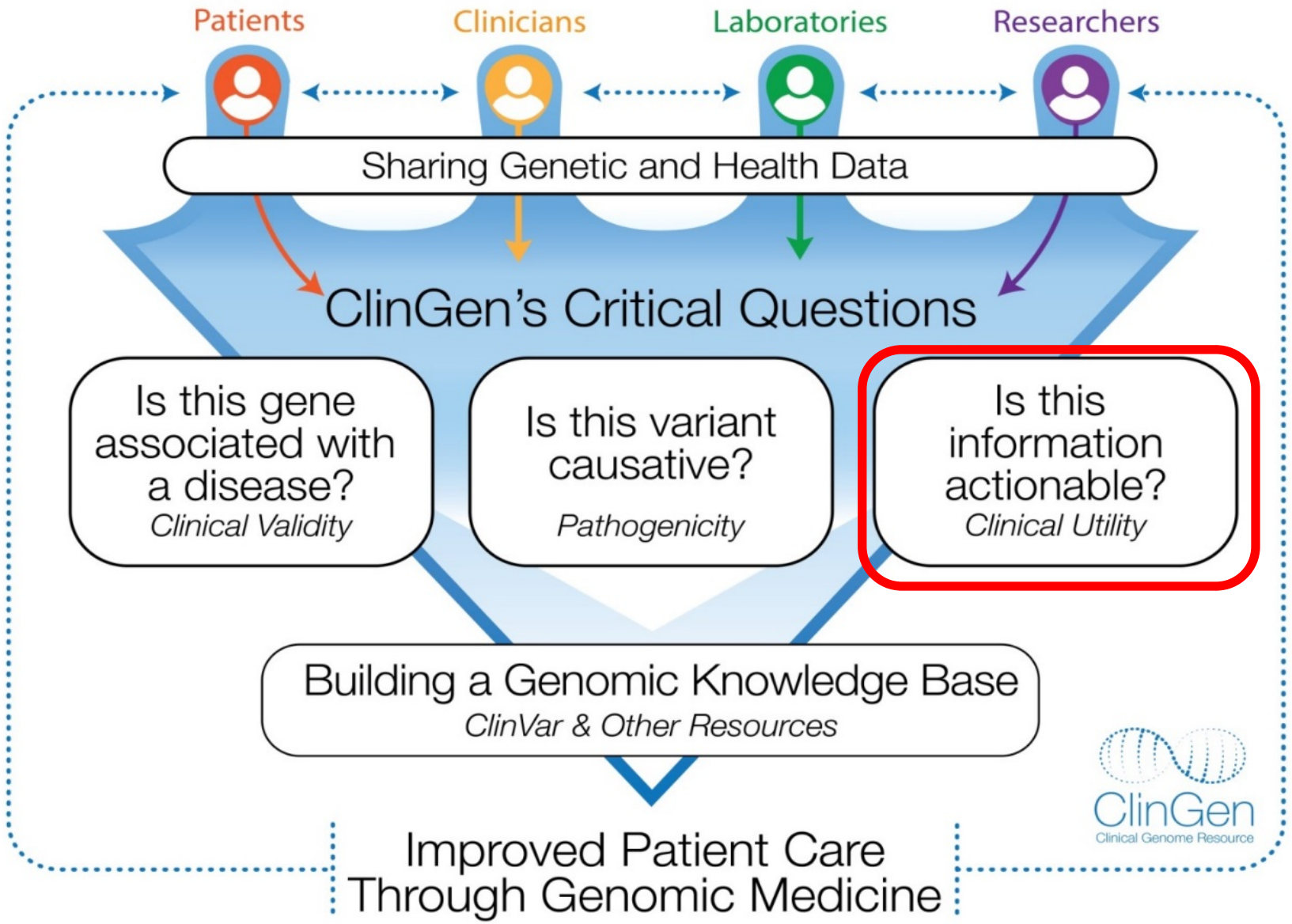
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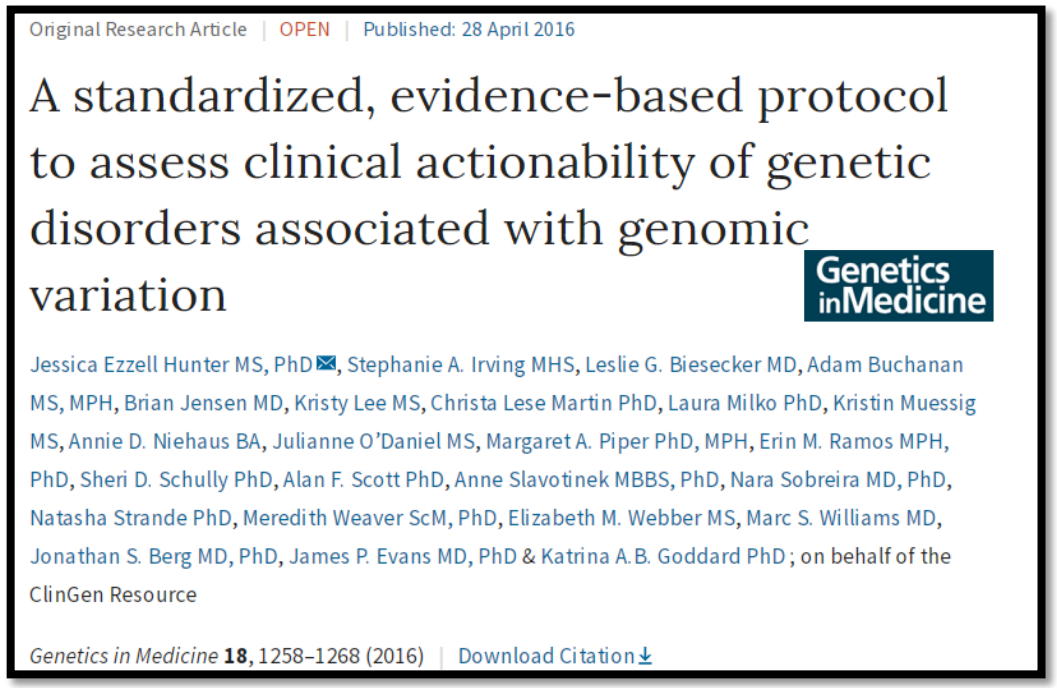
ClinGen developed a framework to provide a transparent and systematic evidence base for prioritizing genes based on their clinical actionability.



Original Research Article | OPEN | Published: 28 April 2016

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

Genetics inMedicine

Jessica Ezzell Hunter MS, PhD ✉, Stephanie A. Irving MHS, Leslie G. Biesecker MD, Adam Buchanan MS, MPH, Brian Jensen MD, Kristy Lee MS, Christa Lese Martin PhD, Laura Milko PhD, Kristin Muessig MS, Annie D. Niehaus BA, Julianne O'Daniel MS, Margaret A. Piper PhD, MPH, Erin M. Ramos MPH, PhD, Sheri D. Schully PhD, Alan F. Scott PhD, Anne Slavotinek MBBS, PhD, Nara Sobreira MD, PhD, Natasha Strande PhD, Meredith Weaver ScM, PhD, Elizabeth M. Webber MS, Marc S. Williams MD, Jonathan S. Berg MD, PhD, James P. Evans MD, PhD & Katrina A.B. Goddard PhD ; on behalf of the ClinGen Resource

Genetics in Medicine **18**, 1258–1268 (2016) | Download Citation

Clinical Actionability

- Well established clinical interventions
- Specific to the genetic disorder under consideration
- Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes

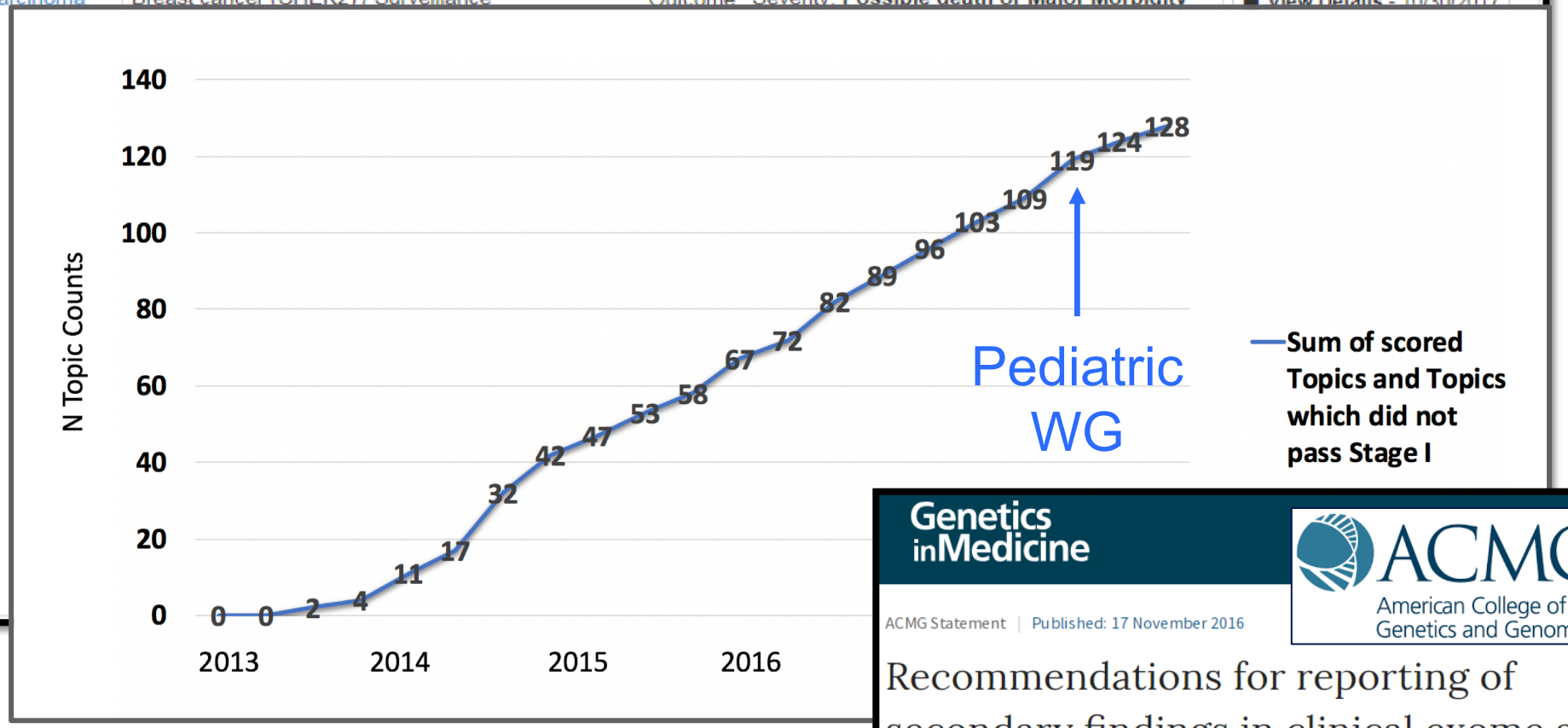
Severity

Likelihood

Effectiveness of Intervention

Nature of Intervention

Actionability Working Group Progress and Impact



ATM
CHEK2

hereditary breast carcinoma

Breast cancer (CHEK2) / Surveillance

Outcome Severity: Possible death or Major Morbidity

View Details - 10/30/2017

Genetics inMedicine

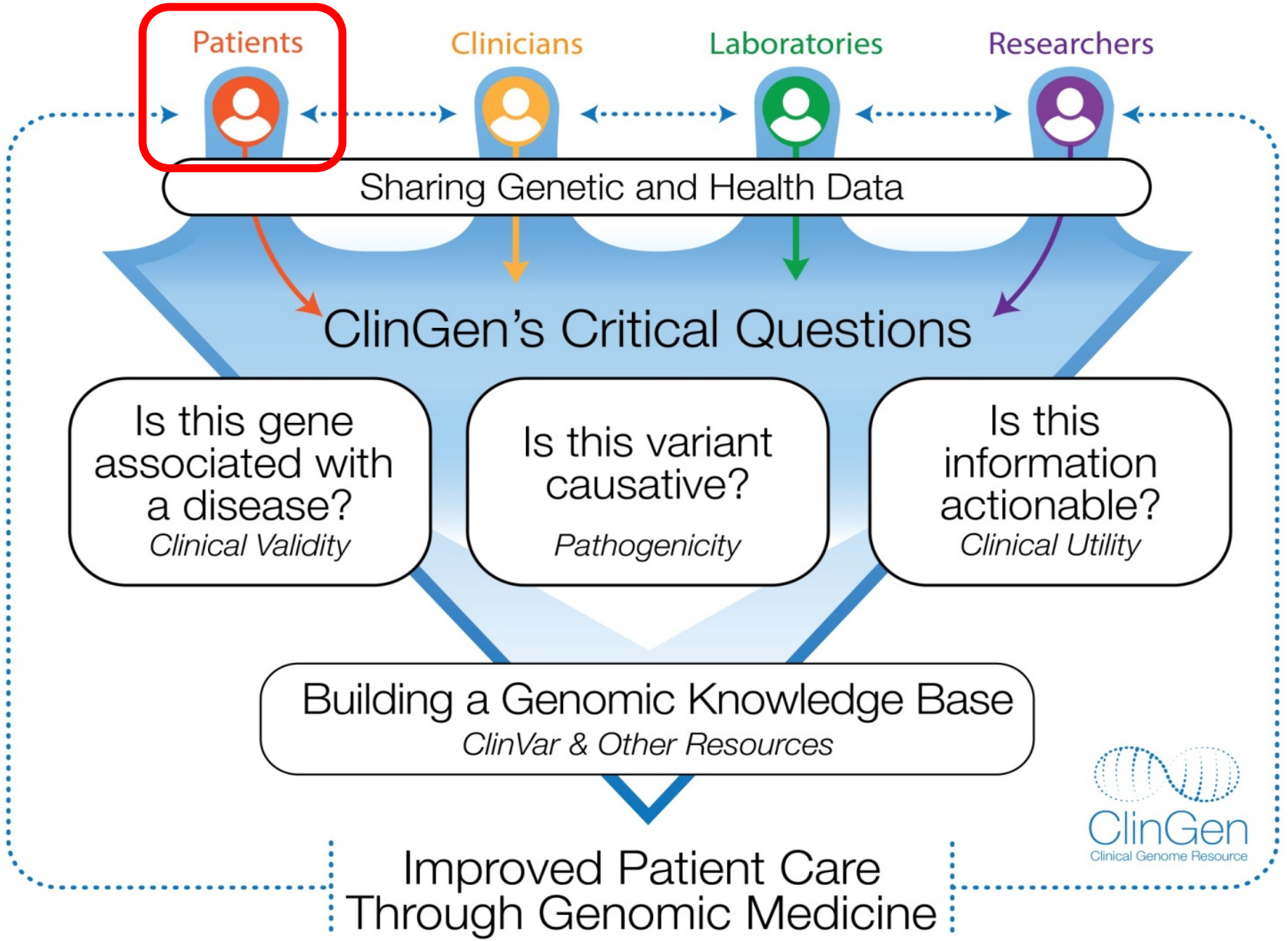
ACMG Statement | Published: 17 November 2016

ACMG American College of Medical Genetics and Genomics

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

ClinGen's Actionability Process and Results integrated into the ACMG Secondary Findings WG

NIH NHGRI

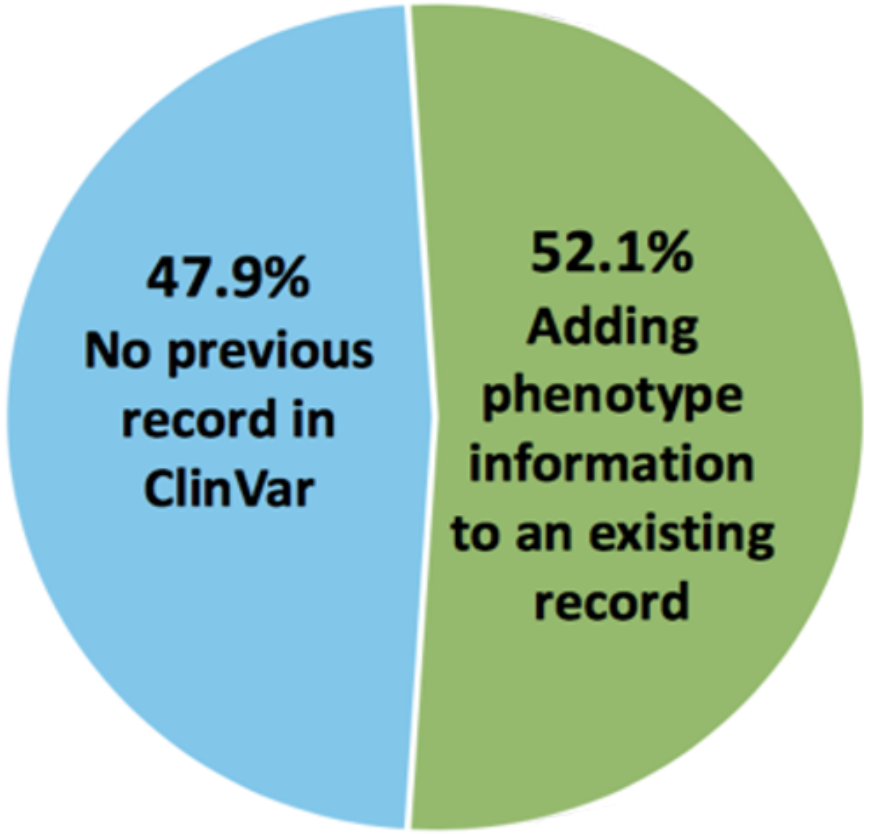

Patients
Clinicians
Laboratories
Researchers
Sharing Genetic and Health Data
ClinGen's Critical Questions
Is this gene associated with a disease?
Clinical Validity
Is this variant causative?
Pathogenicity
Is this information actionable?
Clinical Utility
Building a Genomic Knowledge Base
ClinVar & Other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

GenomeConnect

Patient portal to engage patients in data sharing:

- **Collects** patient-entered health information and genetic data extracted from genetic test reports
- **Transfers** data into secure ClinGen-hosted environment
- **Connects** patients with researchers and with other patients with the same condition

1,826 Participants
805 ClinVar submissions

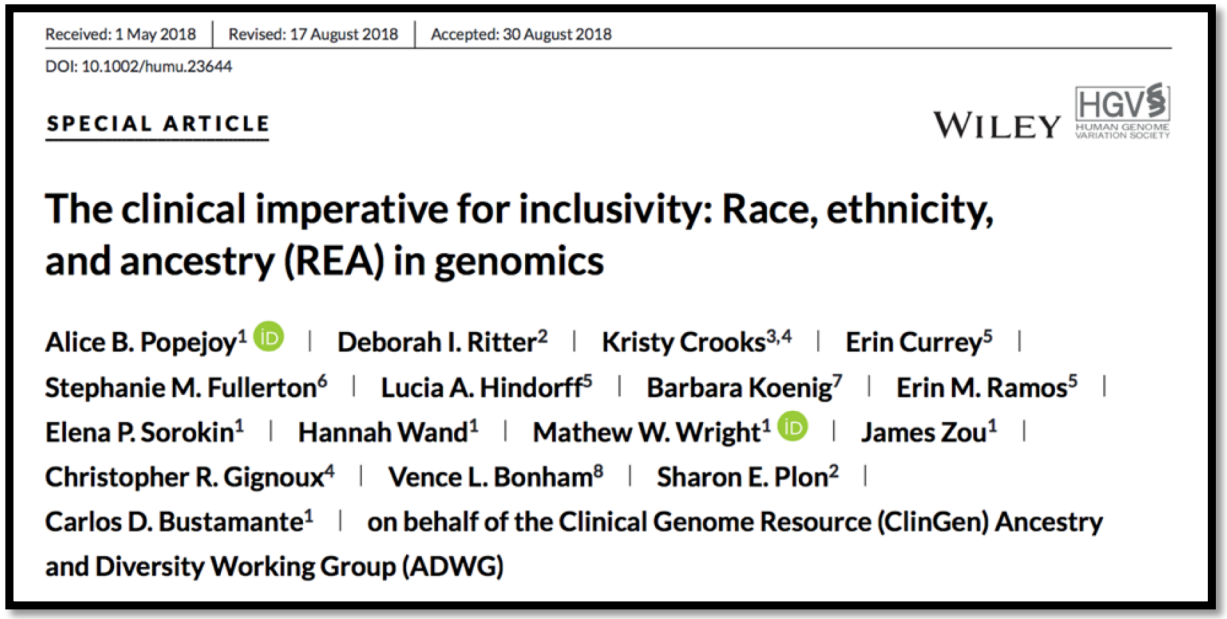


www.genomeconnect.org

NIH NHGRI

Ancestry and Diversity WG

- Exploring how race, ethnicity, and ancestry information is used in clinical genomics
- Aim to provide guidance on how to best use this information in a way that is scientifically rigorous and ethically responsible



Received: 1 May 2018 | Revised: 17 August 2018 | Accepted: 30 August 2018
DOI: 10.1002/humu.23644

SPECIAL ARTICLE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

The clinical imperative for inclusivity: Race, ethnicity, and ancestry (REA) in genomics

Alice B. Popejoy[1] | Deborah I. Ritter[2] | Kristy Crooks[3,4] | Erin Currey[5] | Stephanie M. Fullerton[6] | Lucia A. Hindorff[5] | Barbara Koenig[7] | Erin M. Ramos[5] | Elena P. Sorokin[1] | Hannah Wand[1] | Mathew W. Wright[1] | James Zou[1] | Christopher R. Gignoux[4] | Vence L. Bonham[8] | Sharon E. Plon[2] | Carlos D. Bustamante[1] | on behalf of the Clinical Genome Resource (ClinGen) Ancestry and Diversity Working Group (ADWG)

ClinGen Clinical Genome Resource

cser Clinical Sequencing Evidence-Generating Research

Survey of clinical laboratory directors, clinical geneticists, genetic counselors, researchers involved in variant interpretation and/or curation.

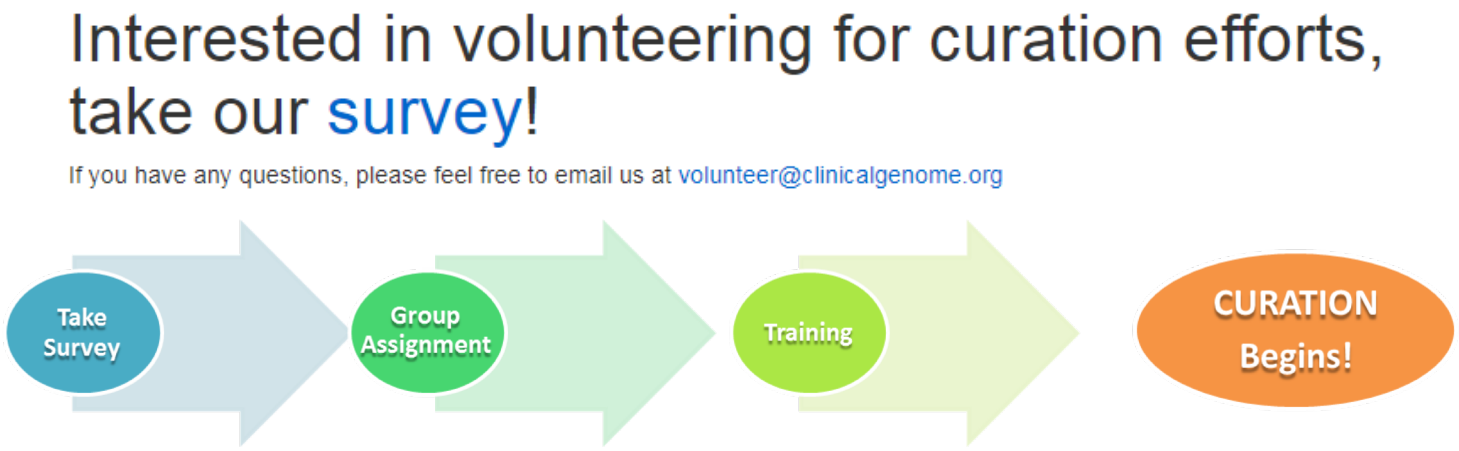
NIH NHGRI

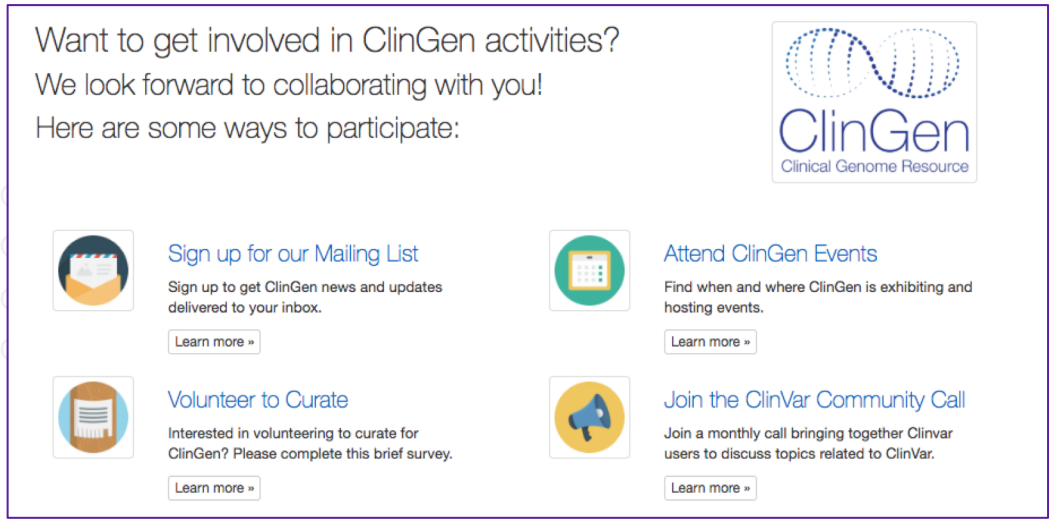
Engage and Train the Broader Community

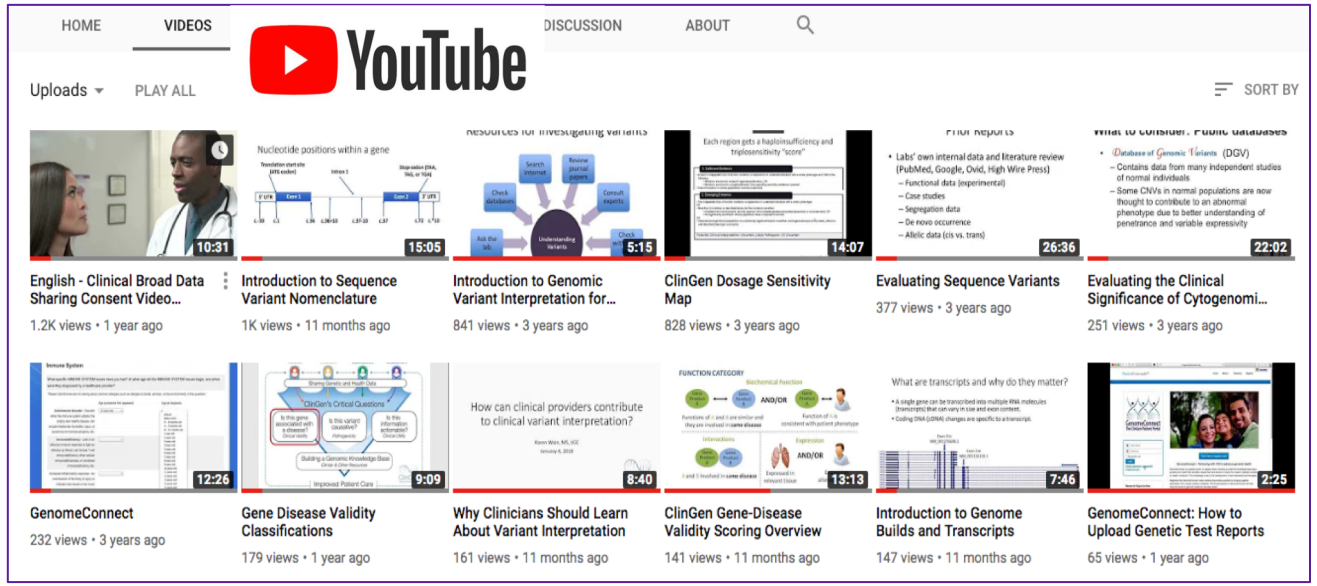
ABMGG
American Board of Medical Genetics and Genomics

Maintenance of Certification:
Improvement in Medical Practice

ClinGen – Variant Interpretation
Discrepancy Resolution Module







ClinGen Working Group and Expert Panel Membership

850 researchers & clinicians from 27 countries

[Created by Natalie Pino, Oct. 2018]

What's coming in 2019-2021

- Update ClinGen/ACMG CNV Interpretation Guideline
- Structure functional assay data for curation
- Develop clinical validity & actionability frameworks for polygenic risk scores
- Machine learning methods to improve curation efficiency
- New disease areas (e.g., Hemostasis & Thrombosis, Ophthalmology, Neuromuscular)

Curating the Clinical Genome Meeting 2019

ClinGen Clinical Genome Resource

DECIPHER

- May 29-31, Washington DC
- Topics including data sharing, variant interpretation, gene curation, population screening, sustainable partnerships

Registration Open

Early Bird Deadline
April 2019

Abstract deadline
March 2019

NIH NHGRI


The Forefront
of Genomics®

Appendix

Consent and Disclosure of Genetic Test Results (CADRe) WG

ARTICLE | Genetics inMedicine

Developing a conceptual, reproducible, rubric-based approach to consent and result disclosure for genetic testing by clinicians with minimal genetics background

Kelly E. Ormond, MS, LCGC[1], Miranda L. G. Hallquist, MSc, LGC[2], Adam H. Buchanan, MS, MPH, LGC[2], Danielle Dondanville, MS, LCGC[3], Mildred K. Cho, PhD[4], Maureen Smith, MS, LCGC[5], Myra Roche, MS, CGC[6], Kyle B. Brothers, MD, PhD[7], Curtis R. Coughlin II, MS, MBe, CGC[8], Laura Hercher, MS, CGC[9], Louanne Hudgins, MD, FACMG[10], Seema Jamal, MSc, (C)CGC[11], Howard P. Levy, MD, PhD[12], Misha Raskin, MS, CGC[2,13], Melissa Stosic, MS, CGC[14], Wendy Uhlmann, MS, CGC[15], Karen E. Wain, MS, LGC[2], Erin Currey[16] and W. Andrew Faucett, MS, LGC[2]

- Developed a conceptual rubric to define when traditional genetic counseling is recommended, versus other approaches
- Conducting a Delphi expert consensus model to define minimum components of a 'targeted discussion' consent approach
- Will test this with genetics professionals to determine if the Delphi approach resonates broadly.

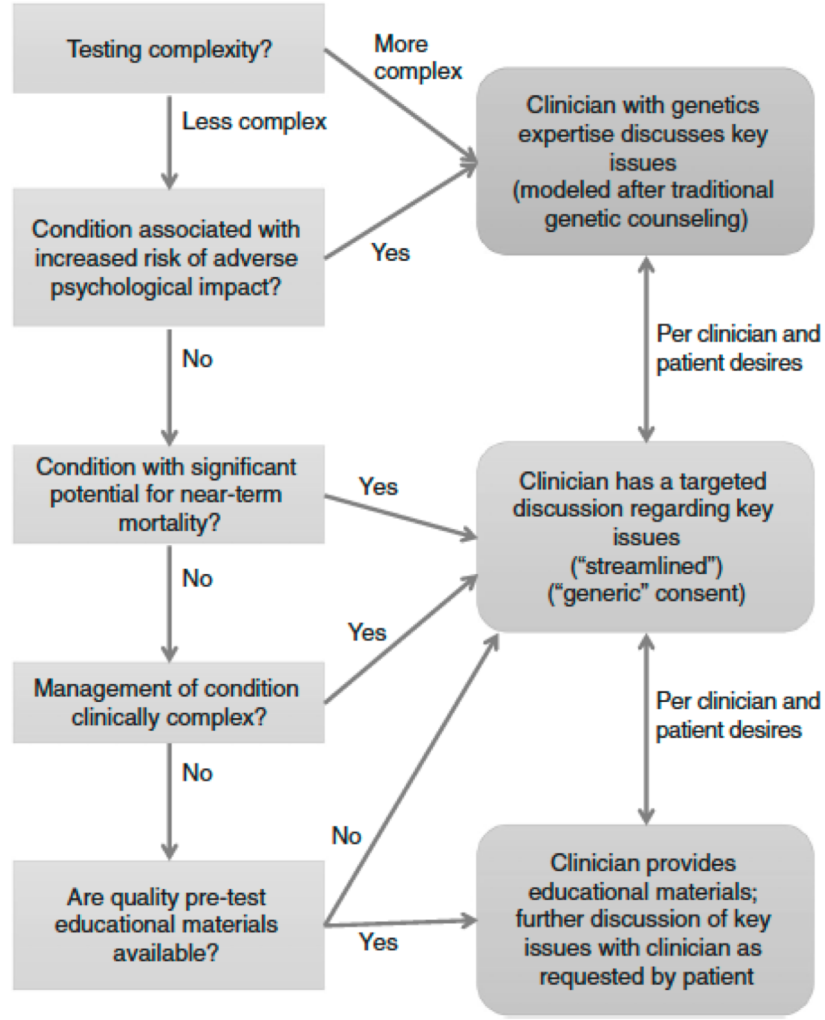


Fig. 2 Consent and Disclosure Recommendations (CADRe) Work-group ethical, legal, and social implications and medical factors (ELSIPlus) consent communication rubric. Working Definitions: Com-

ClinGen Dosage Sensitivity Map

1,457 genes and genomics regions curated

The Clinical Genome Resource (ClinGen) consortium is curating genes and regions of the genome to assess whether there is evidence to support that these genes/regions are dosage sensitive and should be targeted on a cytogenomic array.

All data are shown in GRCh37 and GRCh38 coordinates.

Search By Gene Name

Symbol:

Or click on the following examples: ZEB2, PTEN, MAPT

Go

Search By Location (GRCh37)

Location:

example: chr2:44,000,000-45,500,000, 2p21-2p16.2

Go

Genes/Regions Recently Reviewed

Gene/Region name	Haploinsufficiency score	Triplosensitivity score	Date reviewed
MOV10	Not yet evaluated	Not yet evaluated	2019-01-28
MYH10	1	0	2019-01-23
HIVEP3	1	0	2019-01-23
GNB1	1	0	2019-01-23
DIP2A	1	0	2019-01-23
PTHLH	2	1	2019-01-10
7q11.23 recurrent distal region (includes HIP1, YWHAG)	2	1	2018-12-31
17q23.1q23.2 recurrent region (includes TBX2, TBX4)	3	2	2018-11-19
ELAVL2	1	0	2018-11-28
LAMA2	30: Gene associated with autosomal recessive phenotype	0	2018-11-28
KDM6B	1	0	2018-11-28
KATNAL2	1	0	2018-11-28
GIGYF2	2	0	2018-11-28
DLG2	1	0	2018-11-28
Xp11.22 region (includes HUWE1)	0	3	2018-11-19
NR3C2	3	0	2018-11-19

Links

- ClinGen Home Page
- Help with this site
- FAQ
- Contact Us
- Pathogenic CNV regions
- Curation of the ACMG 59 Genes
- FTP

Curation Team

Joo Wook Ahn
Erica Andersen
Swaroop Aradhya
Tracy Brandt
Rachel Burnside
Oscar Cano
Yang Cao
Laura Conlin
John Herriges
Ted Higginbotham
Benjamin Hilton
Vaidehi Jobanputra
Sibel Kantarci
Hutton Kearney
Wahab Khan
Kristy Lee
Guang Li
Cindy Lorentz
Christa Martin
Con Ngo

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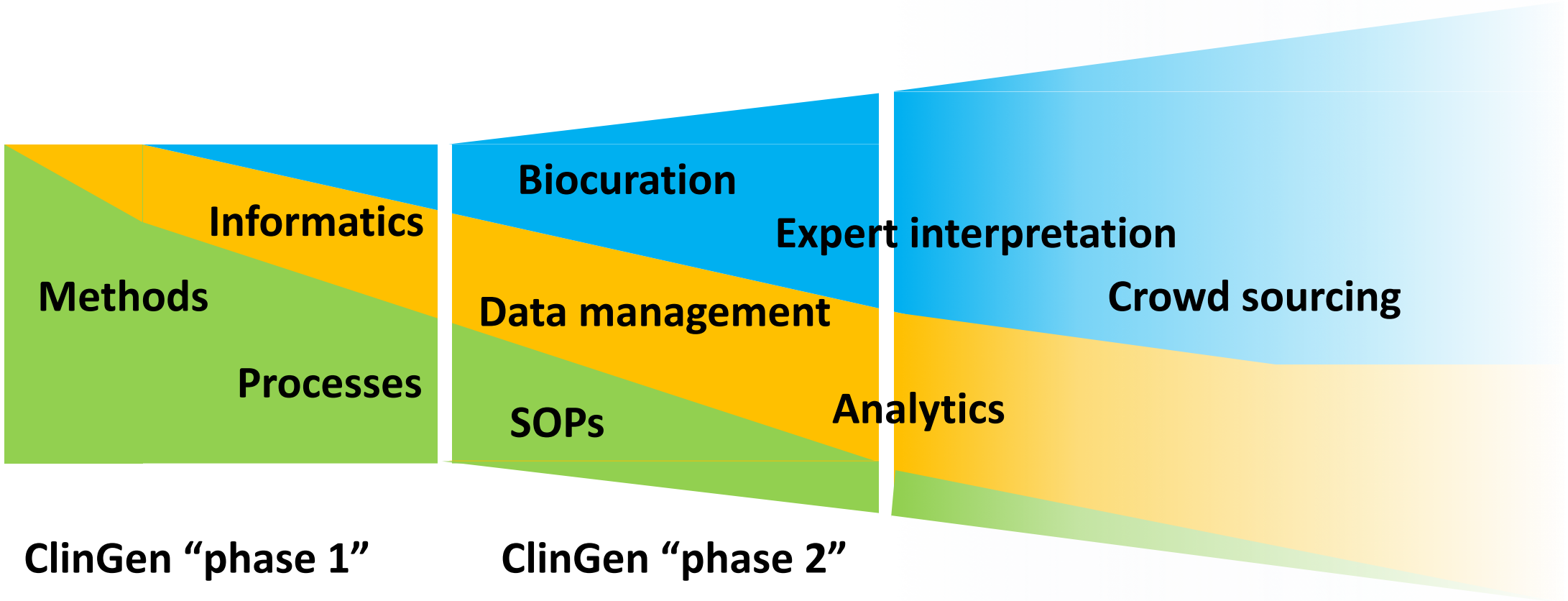

Informatics
Methods
Processes
Biocuration
Expert interpretation
Data management
Crowd sourcing
SOPs
Analytics
ClinGen “phase 1”
ClinGen “phase 2”

COMMENTARY

Competencies for the physician medical geneticist in the 21st century

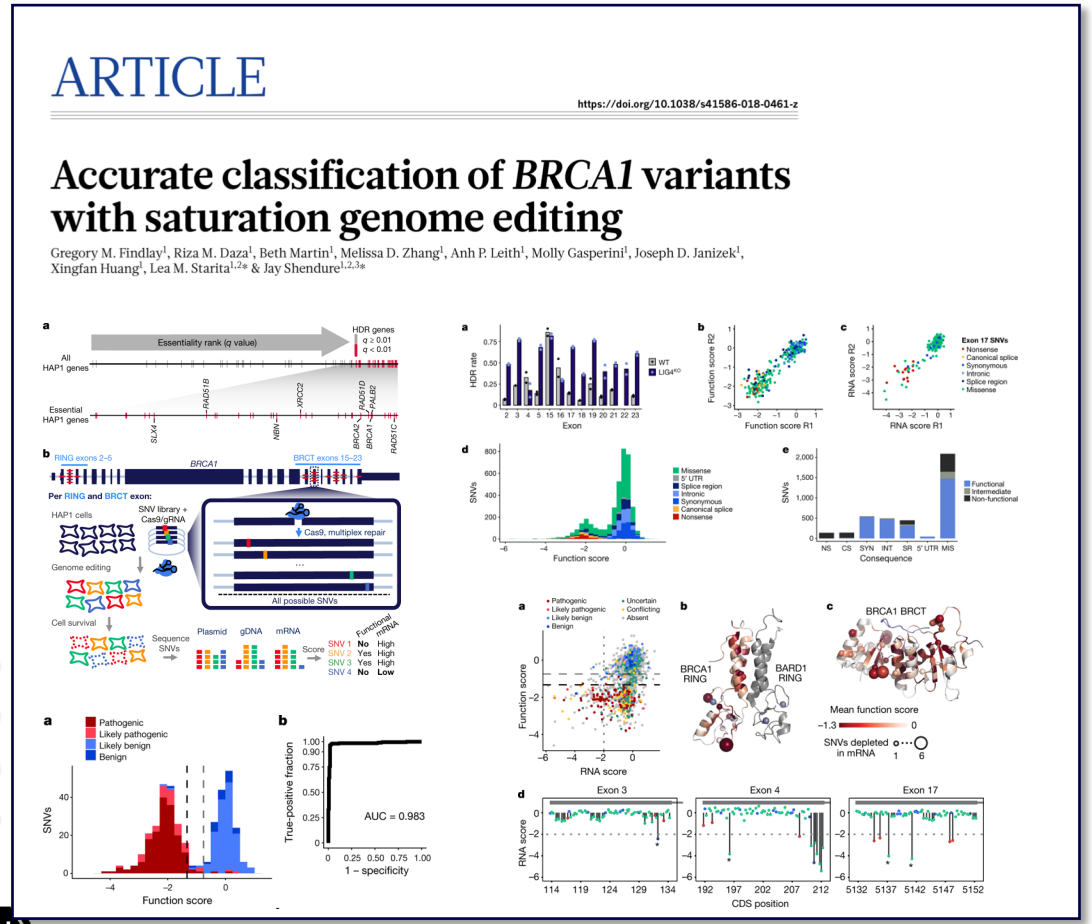
Bruce R. Korf, MD, PhD[1], Mira Irons, MD[2], and Michael S. Watson, MS, PhD[3]

Initial CDWGs	***Developing CDWGs***	***Planned CDWGs***	***Unmet need***
BIOCHEMICAL/METABOLIC	HEMATOLOGICAL	DERMATOLOGIC	CONNECTIVE TISSUE
CANCER	NEURO (*NMD*)	NEPHROLOGIC	GASTROINTESTINAL
CARDIOVASCULAR	OPHTHALMOLOGIC	PULMONARY	IMMUNOLOGICAL
DEAFNESS		SKELETAL	NEURO (*Neurodegenerative*)
NEURO (*ID/Autism*)		(*Craniosynostosis*)	PRENATAL/ REPRODUCTIVE
			PSYCHIATRIC

ENDOCRINE (*MODY*)
DYSMORPHOLOGY (*Rasopathy*)

How should functional assay evidence be structured for curation and computation?

How do we go from this…



ARTICLE

https://doi.org/10.1038/s41586-018-0461-z

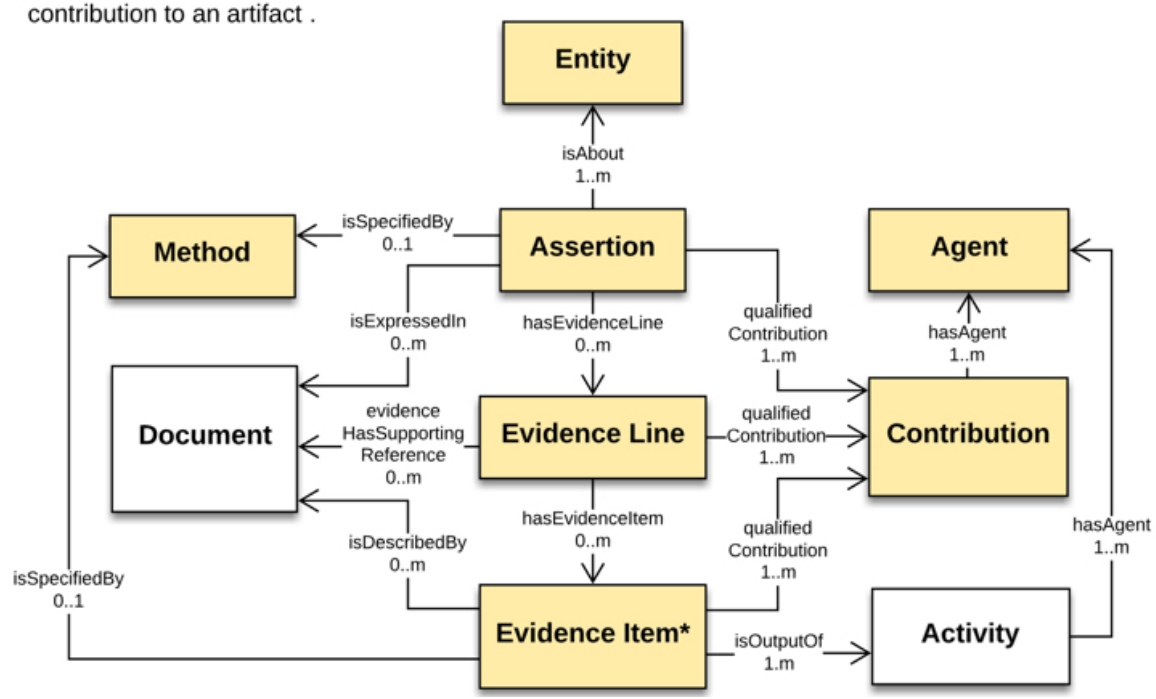
Accurate classification of *BRCA1* variants with saturation genome editing

Gregory M. Findlay[1], Riza M. Daza[1], Beth Martin[1], Melissa D. Zhang[1], Anh P. Leith[1], Molly Gasperini[1], Joseph D. Janizek[1], Xingfan Huang[1], Lea M. Starita[1,2*] & Jay Shendure[1,2,3*]

…to this?

SEPIO Class Association Diagram (Qualified Contribution Model)

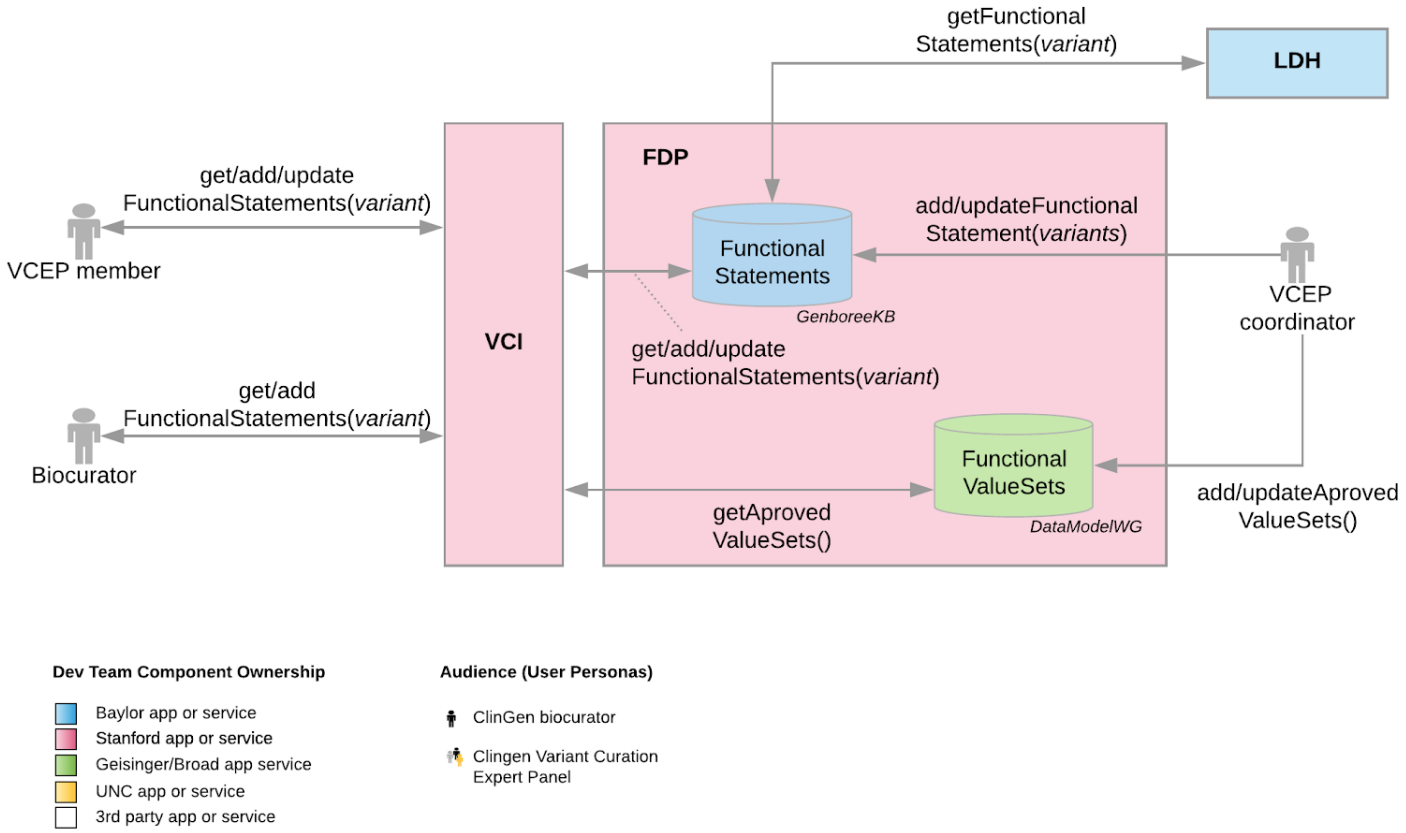
Associative relationships between the high-level classes in the SEPIO Data Model.
Classes in orange are the subset implemented in the ClinGen Model.
The **'qualified contribution model'** implemented by ClinGen is shown here, wherein a Contribution object is reified to capture agetns, roles, and time/place of a contribution to an artifact .



The goal of the Functional Data Pipeline is to accelerate the identification and curation of functional data

- Identify and curate functional datasets for aggregation/display in Variant Curation Interface (VCI)
- Design an UI component for displaying functional data in VCI
- Testing and integration of functional dataset aggregation/display in VCI

Functional Data Pipeline Architecture



ClinGen Pathogenicity Calculator: a configurable system for assessing pathogenicity of genetic variants

Recent Activity

Recently interpreted variants

1. CA534324
NM_001304360.1:c.310G>A (p.Ala104Thr)
CFAP74
Pathogenic

2. CA791502
NM_001852.3:c.1288-17C>G (p.=)
COL9A2
Pathogenic

3. CA16020684
NM_001278716.1:c.419T>C (p.Val140Ala)
FBXL4
Likely Pathogenic

Summary of interpreted variants

JADE2	0	1	0	0	0	0	0	0	0
LRRC8C	0	0	0	0	1	0	0	1	0
MEMO1	0	0	0	0	1	0	0	0	0
MYH1/MYHAS	0	0	0	0	0	0	1	0	0
NDUFS8	0	0	0	0	0	0	0	1	0
PASK	0	0	0	0	1	0	0	0	0
POLG	0	1	0	0	1	0	2	0	0

Showing 1-25 of 29 genes Show More

Variants Listing

Variants	Gene	Description	Assertion(s)/Tags	Quick Links
CA16020684	FBXL4	c.419T>C (p.Val140Ala) c.419T>C (p.Val140Ala) n.810T>C n.810T>C c.419T>C (p.Val140Ala) c.419T>C (p.Val140Ala) c.419T>C	Likely Pathogenic PM2, PM3, PP3, PP4	gnomAD ClinVarAlleles MyVariant.info (hg38) ClinVar (Variation) MyVariant.info (hg19)
CA3933439	FBXL4	c.1442T>C (p.Leu481Pro) c.1442T>C (p.Leu481Pro) n.1487T>C c.1370T>C (p.Leu457Pro) c.1370T>C c.1442T>C (p.Leu481Pro) c.1370T>C (p.Leu457Pro)	Likely Pathogenic PM2, PM3, PP3, PP4	gnomAD ClinVarAlleles MyVariant.info (hg38) ClinVar (Variation) ExAC dbSNP MyVariant.info (hg19)

[Slide provided by R. Patel, BCM]

https://calculator.clinicalgenome.org

Genome Med. 2017 Jan 12;9(1):3

Clinical Laboratories meeting ClinGen Data Sharing Requirements

- Recognize clinical labs who support data sharing and incentivize others to share as well
- Provide list of clinical labs to hospitals, healthcare providers, and insurers who wish to only order from, or reimburse, labs meeting a certain standard in data sharing and quality assurance
- **17 labs meet requirements**

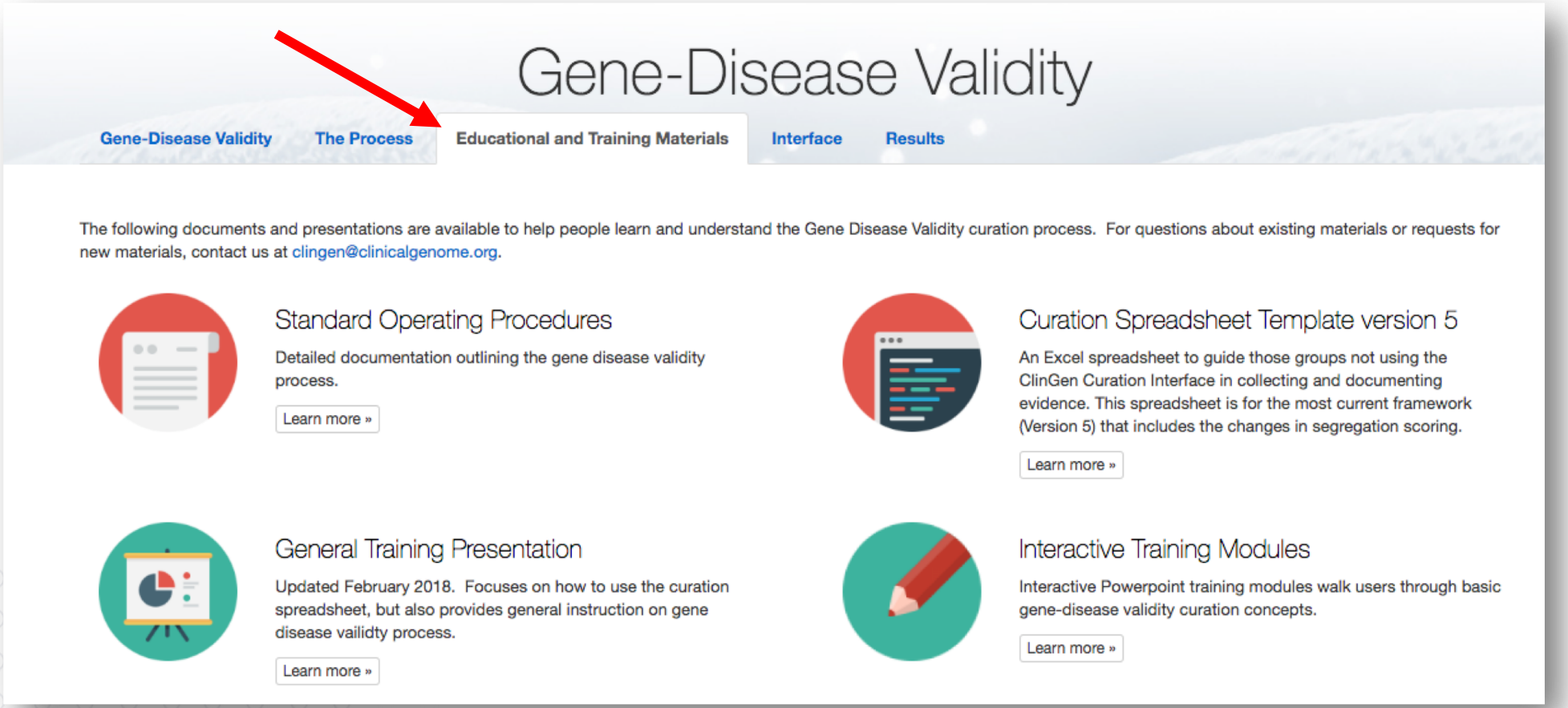
https://www.clinicalgenome.org/lablist/

Launched July 14th, 2017

NIH NHGRI

Laboratory	Meets requirements	Additional Achievements: Submitted evidence[1]	Additional Achievements: >75% from past 5 years[2]	Additional Achievements: Discrepancy resolution[3]	Additional Achievements: 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)	✓		✓	✓	
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	✓		✓	✓	✓

ClinGen's Education Working Group aims to foster community engagement through education, outreach, and resource development.



D. Azzariti, MS, CGC

E. Riggs, MS, CGC

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