Deciphering the Genome: Community Driven Approaches

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Harvard Medical School

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Disclosures

- Employee of BWH/Partners Healthcare which offers genomic services and receives royalties from sales of GeneInsight software
- Employee of the Broad Institute which offers fee-for-service molecular diagnostics
- NIH funding
  - ClinGen
  - MedSeq (CSER Consortium)
  - BabySeq (NSIGHT Consortium)
  - eMERGE
  - Center for Mendelian Genomics

MEDSEQ™

Robert Green

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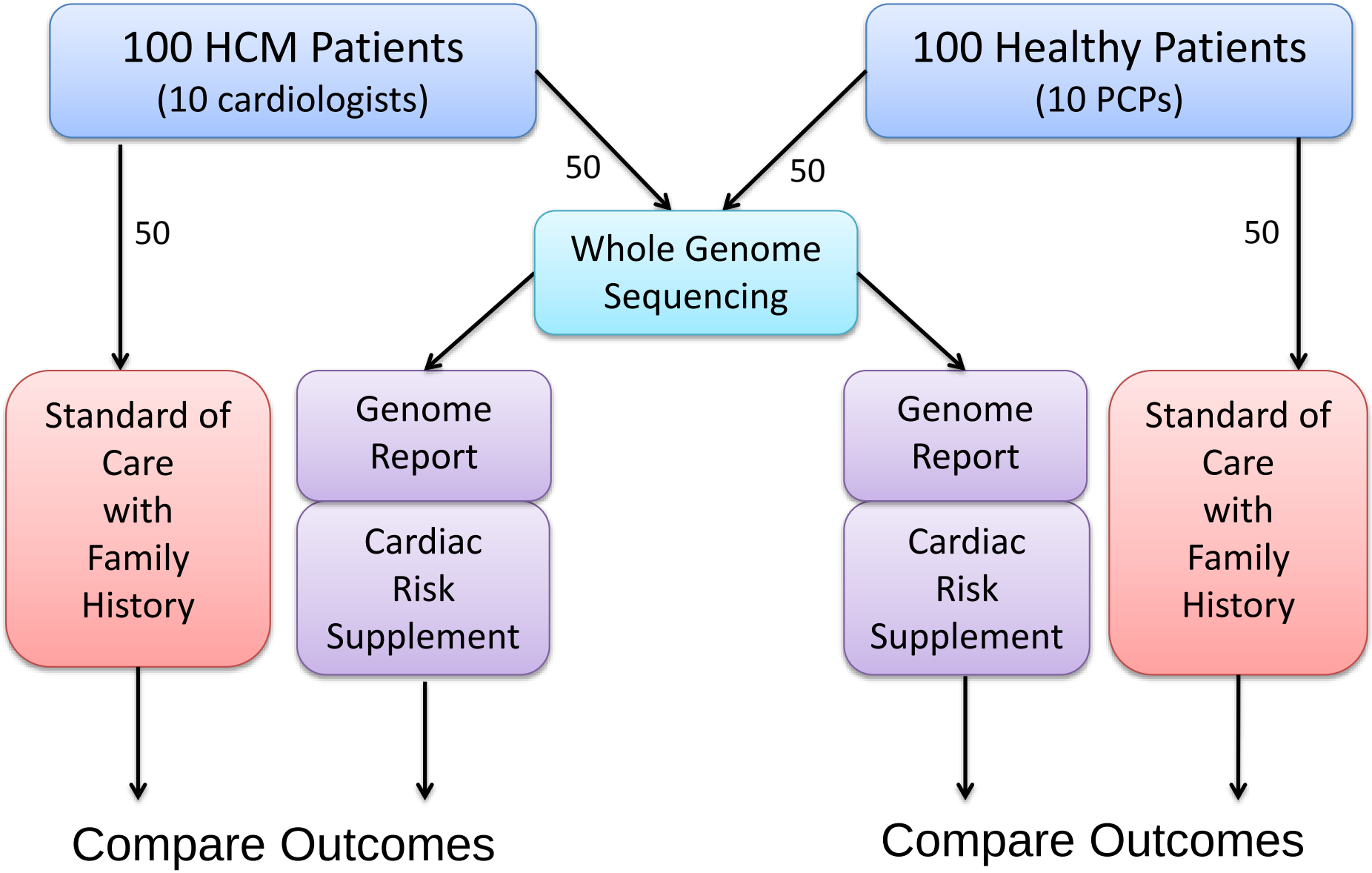

MEDSEQ™

Genome Report

- Generated for all MedSeq subjects in the WGS arm
- One page result summary
  - Monogenic Disease Risk
  - Carrier Risk
  - Pharmacogenomic Associations
  - Blood Groups
- Detailed information for each section provided on later pages

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PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name: [redacted]
DOB: [redacted]
Sex: Male
Race: White
MRN: [redacted]
Specimen: Blood, Peripheral
Received: [redacted]
Accession ID: [redacted]
Family #: [redacted]
Referring physician: Diana Post, M.D.
Referring facility: MedSeq

GENERAL GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.85% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

A. MONOGENIC DISEASE RISK: 1 VARIANT IDENTIFIED

This test identified 1 genetic variant that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene, Variant and Zygosity	Classification
A1. Combined Pituitary Hormone Deficiency (Autosomal Dominant)	Shortage of pituitary hormones and various developmental defects	LHX4 c.452-2A>C Heterozygous	Pathogenic

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorders.

Disease (Inheritance)	Phenotype	Gene, Variant and Zygosity	Classification	Carrier Phenotype*
B1. Primary congenital glaucoma (Autosomal Recessive)	Vision loss	CYP1B1 c.1103G>A (p.Arg368His) Heterozygous	Pathogenic	None reported
B2. Stargardt disease (Autosomal Recessive)	Progressive vision loss	ABCA4 c.5882G>A (p.Gly1961Glu) Heterozygous	Pathogenic	None reported
B3. Hepatic veno-occlusive disease with immunodeficiency (Autosomal Recessive)	Liver failure and susceptibility to infections	SP110 c.877A>T (p.Lys293*) Heterozygous	Likely Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following pharmacogenomic associations. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	**Standard dose requirement**
C2. Clopidogrel	**Decreased response to clopidogrel**
C3. Digoxin	**Typical metabolism and serum concentration of digoxin**
C4. Metformin	**Decreased glycemic response to metformin**
C5. Simvastatin	**Typical risk of simvastatin-related myopathy**

D. RED BLOOD CELL AND PLATELET ANTIGENS

This test identified the ABO Rh Blood Type as O POSITIVE. The RBC and platelet antigens showed a normal absence of low frequency antigens, normal presence of high frequency antigens, and no antigen gene rearrangements. Based on their results this person is a desirable RBC and platelet donor. Additional RBC and platelet antigen information is available at the end of the report.

The Genome Report
(continued)

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GENERAL GENOME REPORT (CONTINUED)

It should be noted that the disease risk section of this report is limited only to variants with strong evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the context of the patient's medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information becomes available. For questions about this report, please contact the Genome Resource Center at GRC@partners.org.

DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE RISK

Disease (Inheritance)	Gene (Transcript)	Variant and Classification	Variant Frequency	Disease Prevalence	References
A1. Combined pituitary hormone deficiency (Autosomal Dominant)	LHX4 (NM_033343.3)	Heterozygous c.452-2A>C (Pathogenic)	Not detected	1 in 8,000	Tajima 2013

VARIANT INTERPRETATION: The c.452-2A>C variant in LHX4 has not been reported in individuals with combined pituitary hormone deficiency (CPHD) or in large population studies. This variant occurs in the invariant region (+/- 1,2) of the splice consensus sequence and is predicted to cause altered splicing leading to an abnormal or absent protein. Loss of function variants in LHX4 in the heterozygous state, particularly splice variants, have been reported in individuals with CPHD (reviewed by Tajima et al., 2013). In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM).

DISEASE INFORMATION: Combined pituitary hormone deficiency is a condition that causes a deficiency of several hormones produced by the pituitary gland. A lack of these hormones may affect the development of many parts of the body. The prevalence of combined pituitary hormone deficiency is estimated to be 1 in 8,000 individuals worldwide. Mutations in at least eight genes have been found to cause combined pituitary hormone deficiency. Most cases of combined pituitary hormone deficiency are sporadic. When the disorder is familial, it can have an autosomal dominant (e.g. LHX4) or an autosomal recessive pattern of inheritance. Adapted from http://ghr.nlm.nih.gov/condition/combined-pituitary-hormone-deficiency.

FAMILIAL RISK: CPHD caused by mutations in LHX4 is inherited in an autosomal dominant manner. An individual with a LHX4 mutation has a 50% chance of passing this variant to any of his/her children. However, penetrance (chance of getting disease) is incomplete and expressivity (how the disease is expressed) is variable.

B. CARRIER RISK

Disease (Inheritance)	Gene (Transcript)	Variant and Classification	Variant Frequency	Disease Prevalence (Carrier Freq.)	References	Carrier Phenotype
B1. Primary congenital glaucoma (Autosomal Recessive)	CYP1B1 (NM_000104.3)	Heterozygous c.1103G>A (p.Arg368His) Pathogenic	0.2% (16/8556) European American	1 in 10,000 US (Unknown)	Bejjani 2000, Reddy 2003, Chitsazian 2007, Choudhary 2008, Pasutto 2010, Mookherjee 2012	None reported

VARIANT INTERPRETATION: The Arg368His variant in CYP1B1 has been reported in several individuals with primary congenital glaucoma. Most of these patients were homozygous or compound heterozygous for this variant (Bejjani 2000; Reddy 2003; Chitsazian 2007). This variant has been identified in 0.2% (16/8556) of European American chromosomes and 0.1% (5/4382) of African American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/; dbSNP rs79204362). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. Several functional studies demonstrated an impact to enzyme function (Choudhary 2008, Pasutto 2010, Mookherjee 2012). In summary, this variant meets our criteria (http://pcpgm.partners.org/LMM) to be classified as pathogenic in a recessive manner for primary congenital glaucoma.

DISEASE INFORMATION: Primary congenital glaucoma (PCG) is characterized by elevated intraocular pressure (IOP), enlargement of the globe (buphthalmos), edema, and opacification of the cornea with rupture of Descemet's membrane (Haabs striae), thinning of the anterior sclera and iris atrophy, anomalously deep anterior chamber, and structurally normal posterior segment except for progressive glaucomatous optic atrophy. Symptoms include photophobia, blepharospasm, and excessive tearing (hyperlacrimation). Typically, the diagnosis is made in the first year of life. Depending on when treatment is instituted, visual acuity may be reduced and/or visual fields may be restricted. In untreated cases, blindness invariably occurs.

FAMILIAL RISK: PCG is inherited in an autosomal recessive manner. The risk of this patient's child having PCG is dependent on the CYP1B1 carrier status of the patient's partner. Other biologically related family members may also be carriers of this variant.

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GENERAL GENOME REPORT (CONTINUED)

PHARMACOGENOMIC ASSOCIATIONS AND BLOOD GROUPS

C. PHARMACOGENOMIC ASSOCIATIONS

Drug (Indication)	Summary	Variants Evaluated and Genotypes Identified	Interpretation	References (PMID)
C1. Warfarin (Anti-coagulation)	**Standard dose requirement**	*CYP2C9* rs1799853 rs1057910 Genotype: *1/*1 c.[430C ;1075A]; c.[430C ;1075A] *VKORC1* rs9923231 Genotype: AA	Patients with the CYP2C9*1/*1 genotype may require a higher dose of warfarin as compared to patients with other CYP2C9 genotypes. Patients with the VKORC1 AA genotype may require a lower dose of warfarin as compared to patients with the VKORC1 GG or GA genotypes. Patients with the combination of the CYP2C9*1/*1 genotype and VKORC1 AA genotype are predicted to require standard doses of warfarin compared to other patients. Refer to warfarindosing.org for dosing based on genotype and other clinical factors.	Johnson 2011
C2. Clopidogrel (Anti-coagulation)	**Decreased response to clopidogrel**	*CYP2C19* rs4244285 rs4986893 rs12248560 Genotype: *1/*2 c.[-806C(;)681G(;)636G]; c.[-806C(;)681G>A(;)636G]	Patients with the CYP2C19 *1/*2 genotype may have reduced metabolism of clopidogrel and decreased response to clopidogrel as compared to patients with a *1/*1 genotype. Additional information and dosing recommendations for this result can be found at: http://www.pharmgkb.org/drug/PA449053.	Scott 2013
C3. Digoxin (Dysrhythmias, heart failure)	**Typical metabolism and serum concentration of digoxin**	*ABCB1* rs1045642 Genotype: CT *Genotype frequencies:* *CC: 22% CT: 51% TT:27%*	Patients with the CT genotype who take oral digoxin may have intermediate metabolism and serum concentrations of digoxin as compared to patients with the CC and TT genotypes.	Aarnoudse 2008, Kurata 2002, Hoffmeyer 2000

VKORC1/CYP2C9 genotype combination frequencies

Dosing Group	VKORC1 rs9923231	CYP2C9 Genotypes	Approximate Frequency
Lower	AA	*1/*3, *2/*2, *2/*3, *3/*3	6%
	GA	*2/*3, *3/*3	3%
Standard	AA	*1/*1, *1/*2	37%
	GA	*1/*2, *1/*3, *2/*2	14%
	GG	*1/*3, *2/*2, *2/*3	<1%
Higher	GA	*1/*1	28%
	GG	*1/*1, *1/*2	13%

CYP2C19 genotype frequencies

Metabolism	Genotypes	Frequency
Ultrarapid	*1/*17, *17/*17	5-30%
Extensive (typical)	*1/*1	35-50%
Intermediate	*1/*2, *1/*3, *2/17, *3/*17	18-35%
Poor	*2/*2, *2/*3, *3/*3	2-15%

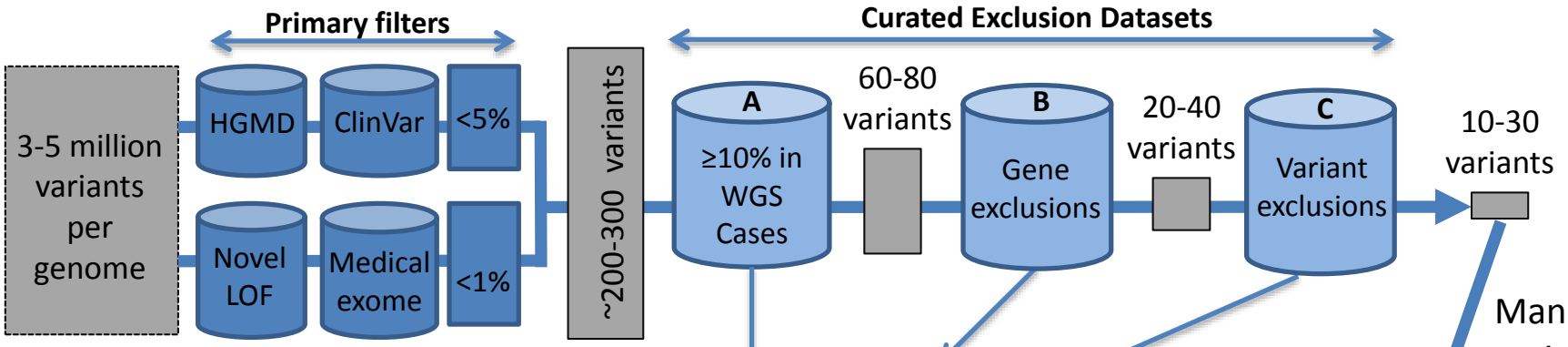
Reported findings from analysis of variants in ~7000 genes

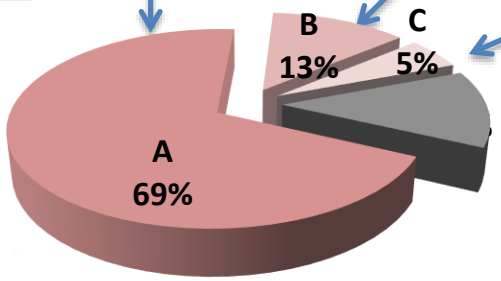
	Mendelian Disease Risk SFs	Carrier Status SFs	Diagnostic Findings in the Cardiology Cohort
# of patients	21/100 (21%)*	92/100 (92%)	24/50 (48%)
Mean reported variants per patient	.21	2.3	0.54
Range of reported variants per patient	0-1	0-7	0-2

*1/90 (1%) by ACMG list

MedSeq™

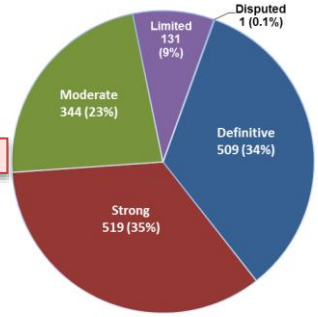
MedSeq Genome and BabySeq Exome Filtering Approach for Monogenic Disease Variants





Data Set A ≥ 10% MAF WGS Cases

- Excludes common technical FPs
- Common indels wrong nomenclature
- Exceptions FV, HFE, SERPINA1



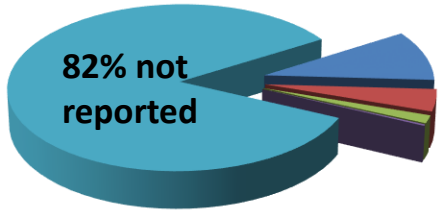
Data Set B - Gene Exclusions

- Evidence for gene-disease association = none, limited, or disputed
- Non medically relevant phenotype

>1500 genes curated for BabySeq

Data Set C - Variant Exclusions

- Benign interpretation
- LOF but LOF not disease mechanism
- GWAS or PGx association only



0-7 variants reported/patient (MedSeq)
0-2 variants reported/patient (BabySeq)

Acknowledgements: Kalotina Machini, Ozge Birsoy, Matt Lebo

Reported Disease Risk Findings

Gene	Variant	Disease	Classification	Inheritance	Notes
ELN	c.1150+1G>A	Supravalvular aortic stenosis	Pathogenic	AD	
LHX4	c.452-2A>C	Combined pituitary hormone deficiency	Pathogenic	AD	
PPOX	p.Leu67X	Variegate porphyria	Pathogenic	AD	
RDH5	p.Trp95X	Fundus albipunctatus	Pathogenic	AR	Homozygous
HFE	p.Cys282Tyr	Hereditary hemochromatosis	Pathogenic	AR	3 biallelic cases
CHEK2	c.1100del	CHEK2-related cancer risk	Pathogenic	AD	
F5	p.Arg534Gln	Factor V Leiden thrombophilia	Risk allele	Multi-factorial	3 cases
ANK2	p.Glu1458Gly	Ankyrin-B related cardiac arrhythmia	Likely pathogenic	AD	
EYA4	c.1739-1G>A	Postlingual hearing loss	Likely Pathogenic	AD	
*KCNQ1**	p.Ser276ProfsX13	Romano-Ward syndrome	Likely Pathogenic	AD	
SQSTM1	p.Pro392Leu	Paget disease of the bone	Likely Pathogenic	AD	2 cases
COL2A1	p.Thr1439Met	Spondyloepiphyseal dysplasia congenita	Likely Pathogenic	AD	
APP	p.Ala713Thr	Alzheimer's disease, late onset	VUS - Favor Pathogenic	AD	
ARSE	p.Gly137Ala	Chondrodysplasia punctata	VUS – Favor Pathogenic	XL	
PDE11A	p.Thr58ProfsX41	Primary pigmented micronodular adrenocortical disease	VUS – Favor Pathogenic	AD	
*TNNT2**	p.Arg278Cys	Hypertrophic cardiomyopathy	VUS – Favor Pathogenic	AD	

To improve our **knowledge** of DNA variation
and **consistency** in variant classification
will require a massive effort in
data sharing

ClinVar Variant Interpretation Comparisons

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

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

NEJM May 27th, 2015

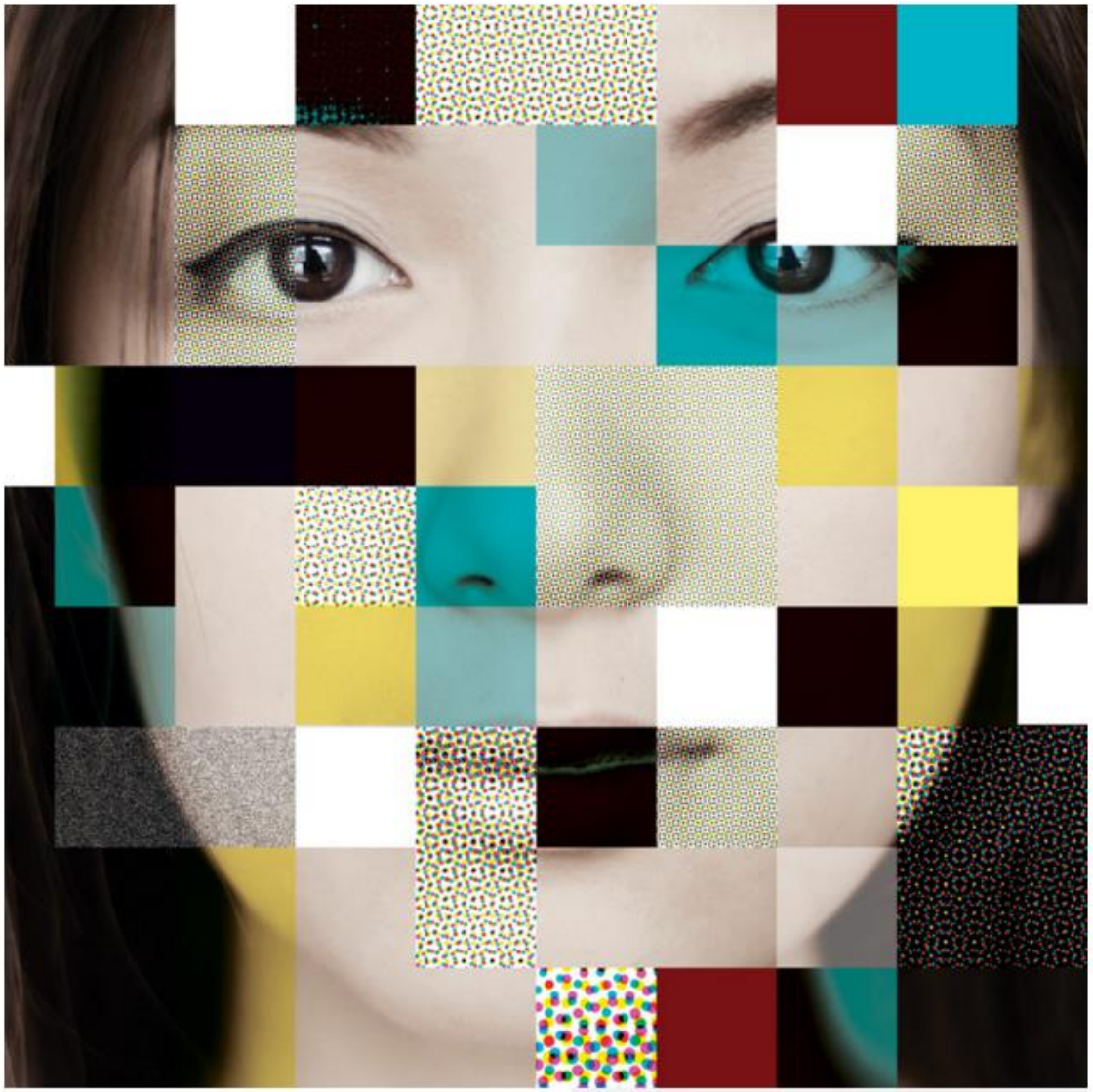
RESEARCH 6 min read

Open to Interpretation

Increasingly, genetic tests provide ambiguous results, leaving doctors and scientists searching to make sense of these 'variants of unknown significance.'

BY ERIC CELESTE

November 24, 2014 | Print | 0 Comments



Clinical Genetics Has a Big Problem That's Affecting People's Lives

Unreliable research can lead families to make health decisions they might regret.

For Heidi Rehm, it looked like a straightforward case. Her lab at Partners Healthcare offers tests for genetic diseases. They had received a blood sample from a fetus after a doctor conducting an ultrasound spotted signs of Noonan syndrome—an inherited disorder involving heart problems and stunted growth. The fetus turned out to have a mutation in PTPN11, a gene that affects the risk of Noonan syndrome.

Rehm found that another team of scientists had published on that very same mutation before. (Not every mutation of PTPN11 increases the rick of Noonan syndrome.) They found that it was more common among Noonan patients than in healthy people, and had billed it as "pathogenic"—that is, likely to cause disease. Rehm reported it as such to the doctor who sent her the sample.

Sometime later, she was listening to a talk by a colleague who had found the same mutation in a patient with Noonan syndrome and, based on the same published study, had also classified it as pathogenic. But this time, the patient—an adult—had contacted the researchers behind the paper. And they had admitted that their conclusions were wrong. In later work, they had found that the mutation is so common in certain ethnic groups that it couldn't possibly be responsible for a rare disease like Noonan syndrome. It wasn't pathogenic after all.

"I immediately contacted the physician to find out the story with that baby," Rehm says. "And that's when I found out that the parents had terminated it."

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Main menu

Mother's Negligence Suit Against Quest's Athena Could Broadly Impact Genetic Testing Labs

Mar 14, 2016 | Turna Ray

NEW YORK (GenomeWeb) – Christian Millare had a severe seizure on Jan. 5, 2008, and died. He was two years old.

His mother Amy Williams is convinced, based on his medical records, the opinions of experts, and the published literature, that her son's life didn't have to come to such a premature end. Eight years later, Williams is suing Quest Diagnostics, one of the largest reference labs in the US, and its subsidiary Athena Diagnostics, which in 2007 tested Christian for mutations in the SCN1A gene.

In a lawsuit filed last month in the fifth judicial circuit court in Richland County, South Carolina, Williams alleges that because Athena failed to follow federal lab regulations and accurately classify the genetic mutation causing her son's epileptic seizures, he continued to receive treatment that worsened his condition and caused his death.

In 2007, Christian's doctors sent his blood sample to Athena to gauge if he had mutations in the SCN1A gene, which is involved in the mechanism that controls the flow of sodium ions from neuron to neuron. Defects in SCN1A can throw off this process, creating an imbalance of excitatory and inhibitory electrical impulses in the brain and causing seizures. Mutations in SCN1A are well known in the literature to cause Dravet syndrome, a severe form of epilepsy that impacts one in 21,000 infants. Dravet syndrome babies start having seizures a few months after birth and have developmental delays. The Dravet Syndrome Foundation estimates that 80 percent of patients will have an SCN1A mutation.

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Lawsuit Underscores Risk of Thinking Genetic Tests Authoritative

By Meredith Salisbury | March 24, 2016, 4:35 PM | *Techonomy Exclusive*

Interpreting the results of genetic testing remains as much art as science. (Image courtesy Shutterstock)

A recently filed lawsuit suggests trouble may be brewing for the new era of genomic testing. The case is a tragic one: a mother claims that an inaccurate result from a genetic test contributed to the death of her two-year-old son, who had a mitochondrial disorder. The mother, Amy Williams, is suing the test provider, Athena Diagnostics, as well as its parent company, Quest Diagnostics, for negligence. (For a good explanation of it, check out this article.)

I am neither a lawyer nor a genome scientist, so I don't intend to weigh in on the lawsuit. I cannot comment on the specifics of the case or the medical chain of events that led to it. What I can discuss is the potentially damaging long-term effect that challenges like this could have on a medical field that is still getting its bearings.

At issue in this lawsuit is the interpretation of a DNA variant that turned up in the results of a genetic test run on the child, Christian Millare. The suit alleges that the variant, which was classified and reported as having "unknown significance," should have been categorized differently based on the evidence available at the time.

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Pathologists' Group Accuses FDA of Making 'Dubious Claims' in LDT Harms Report

Dec 16, 2015 | a GenomeWeb staff reporter

NEW YORK (GenomeWeb) – The Association for Molecular Pathology, a group t
Drug Administration to regulate most lab-developed testing procedures, found a
recent report characterizing such tests as potentially harmful.

In November, the night before a congressional hearing on regulation of lab-deve
released a report highlighting 20 examples where tests not regulated by the age
patients harm. The report was the FDA's long-awaited counterpoint to lab indus
have maintained that LDTs regulated under CLIA, the traditional oversight frame
part aren't harming patients.

Front Line Genomics

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ACMG and AMA call on FDA to reconsider LDT guidance

mportant role in health care today. They also have
everal notable examples of inaccurate tests placing

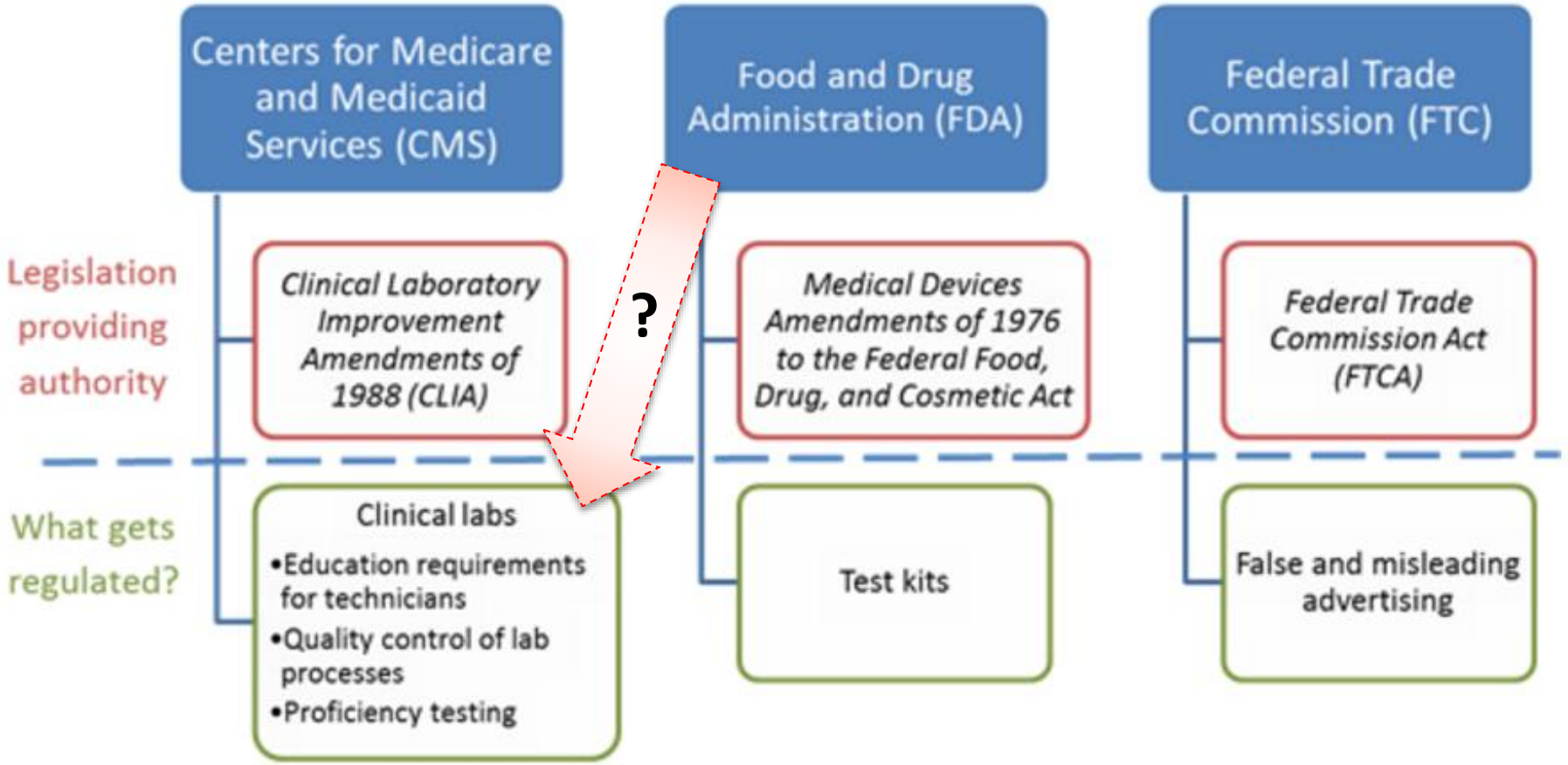
in
rcement
d FDA

ntended
devices.
report

were offered from laboratories following the minimum requirements of CLIA.

Federal Regulation of Genetic Tests

Three federal agencies play a role in the regulation of genetic tests: CMS, FDA, and the Federal Trade Commission (FTC).



http://www.genome.gov/10002335

Will FDA oversight improve the standards for genetic testing?

The genomic community needs to come together and develop its own standards to ensure safe and effective use of genetic and genomic medicine.

CytoChip ISCA

CytoChip ISCA microarrays provide an ideal solution for implementing arrayCGH as a first line assay in molecular cytogenetics laboratories. CytoChip ISCA arrays are designed to investigate constitutional disorders through a combination of increased probe density in regions associated with known constitutional disorders and regular spacing of probes on the genomic backbone.

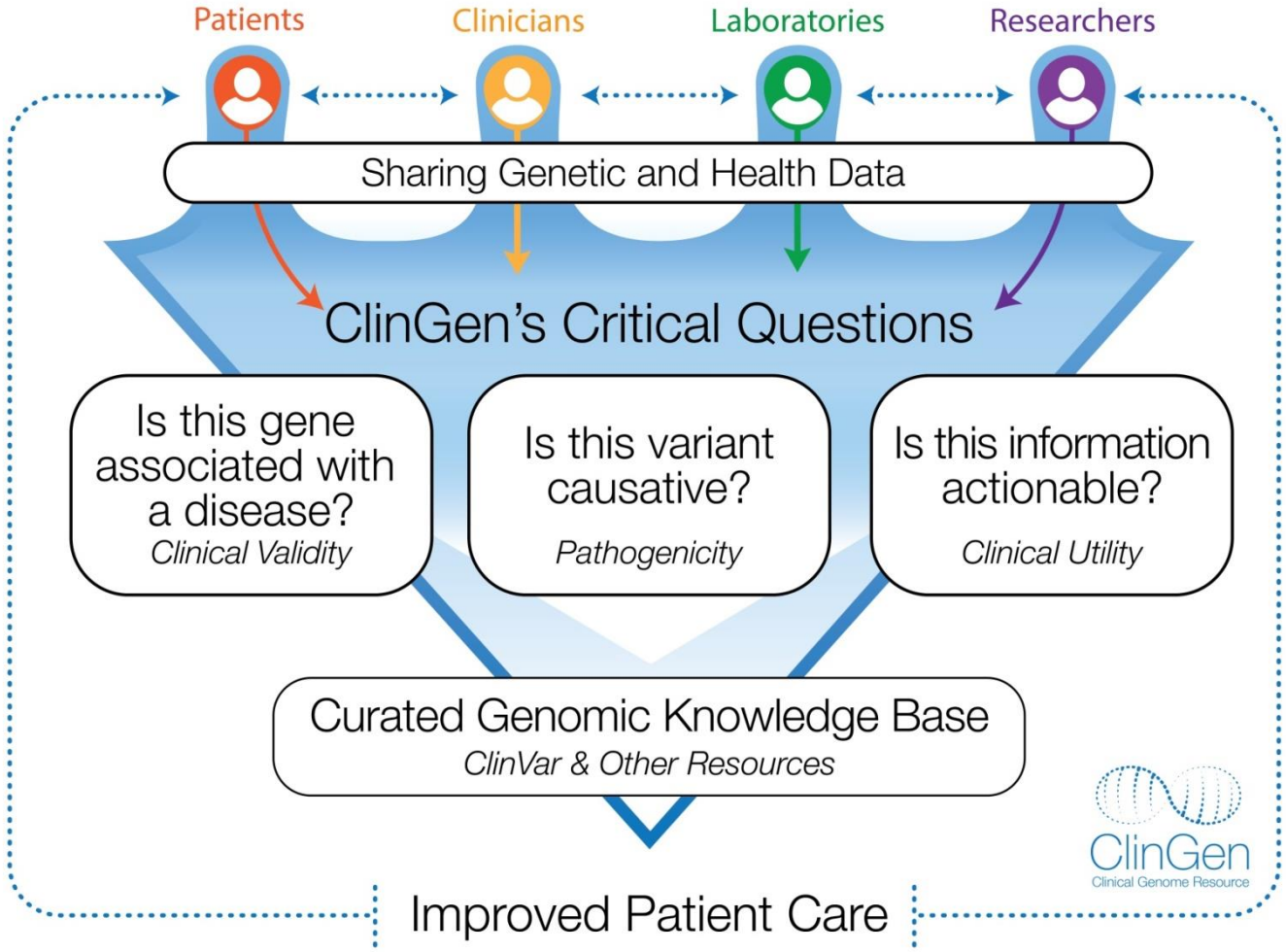
The CytoChip ISCA microarray uses the International Standard Cytogenetic Array (ISCA) design, which is a standardized international design for constitutional disorder investigations (www.iscaconsortium.org). CytoChip ISCA arrays offer several key advantages including:

- Multiple CytoChip ISCA array formats provide flexible options for backbone spacing, probe resolution and sample throughput needs.
- CytoChip ISCA packages include BlueFuse Software for fully automated array processing, data management, and reporting.
- The CytoChip Oligo SNP array incorporates SNP calling to enable the detection of copy number neutral loss of heterozygosity/uniparental isodisomy (LOH/UPD) in the same assay.

CytoChip ISCA microarrays are available in seven different formats. These include the 4×180K, which supports four hybridization areas per slide with 180K probes per hybridization area—for investigations demanding higher resolution—to the 8×60K format, which supports eight hybridization areas per slide with 60K probes each, for higher throughput requirements. The CytoChip Oligo SNP array also enables the detection of LOH in the same assay through the addition

The Clinical Genome Resource

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



Rehm *et al.* ClinGen - The Clinical Genome Resource. N Engl J Med 2015; 372:2235-2242

www.clinicalgenome.org

>400 people from >90 institutions

ClinGen Acknowledgements

ClinGen Steering Committee

Jonathan Berg, UNC
Lisa Brooks, NHGRI
Carlos Bustamante, Stanford
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ClinGen Working Groups (WG)

Genomic Variant WG

Chairs: Christa Martin, Sharon Plon, Heidi Rehm

Sequence Variant Interpretation WG

Chairs: Les Beisecker, Marc Greenblat

Phenotyping WG

Chair: David Miller

ClinVar IT Standards and Data Submission WG

Chair: Karen Eilbeck, Melissa Landrum

Data Model WG

Chairs: Larry Babb, Chris Bizon

Informatics WG

Chair: Carlos Bustamante

Clinical Domain WGs

Hereditary Cancer: Matthew Ferber, Ken Offit, Sharon Plon

Somatic Cancer: Shashi Kulkarni, Subha Madhavan

Cardiovascular: Euan Ashley, Birgit Funke, Ray Hershberger

Metabolic: Rong Mao, Robert Steiner, Bill Craigen

Pharmacogenomic: Teri Klein, Howard McLeod

Education, Engagement, Access WG

Chairs: Andy Faucett, Erin Riggs

Consent and Disclosure Recommendations (CADRe) WG

Chairs: Andy Faucett, Kelly Ormond

Gene Curation WG

Chairs: Jonathan Berg, Christa Martin

Actionability WG

Chairs: Jim Evans, Katrina Goddard

EHR WG

Chair: Marc Williams

Aggregating Variant Interpretations in ClinVar

Sharing Clinical Reports Project

Genome Connect and Free-the-Data

Researchers

Clinical Labs

Expert Groups

Clinics

Patients

Patient Registries

Unpublished or Literature Citations

ClinVar

Variant-level Data

Linked Databases

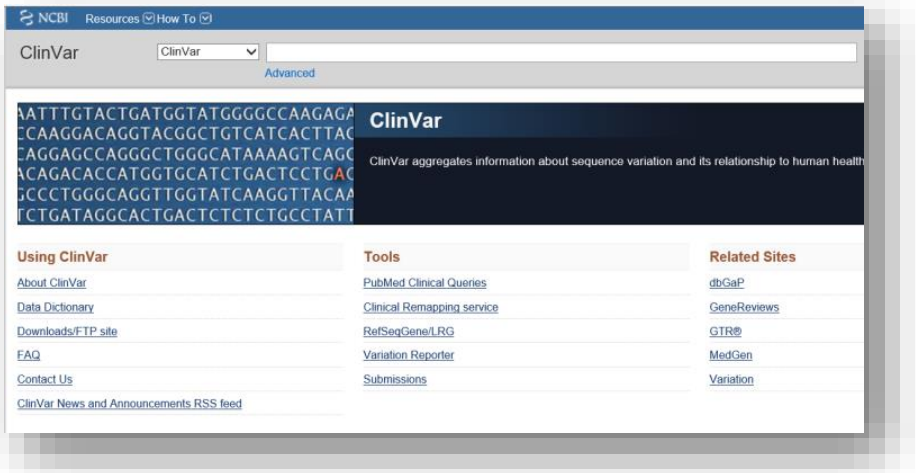
OMIM

CFTR2

BIC

InSiGHT

PharmGKB



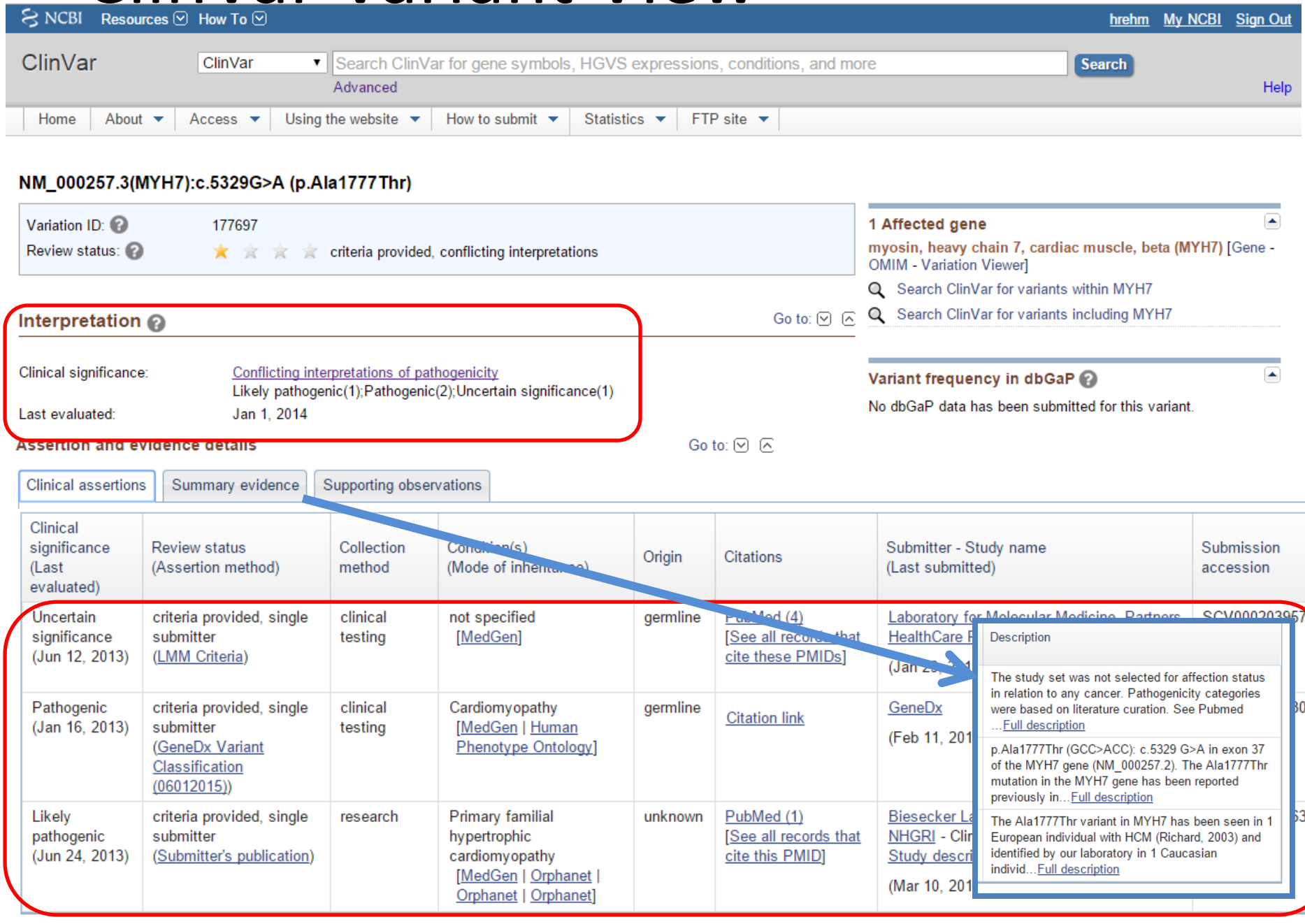
482 ClinVar submitters

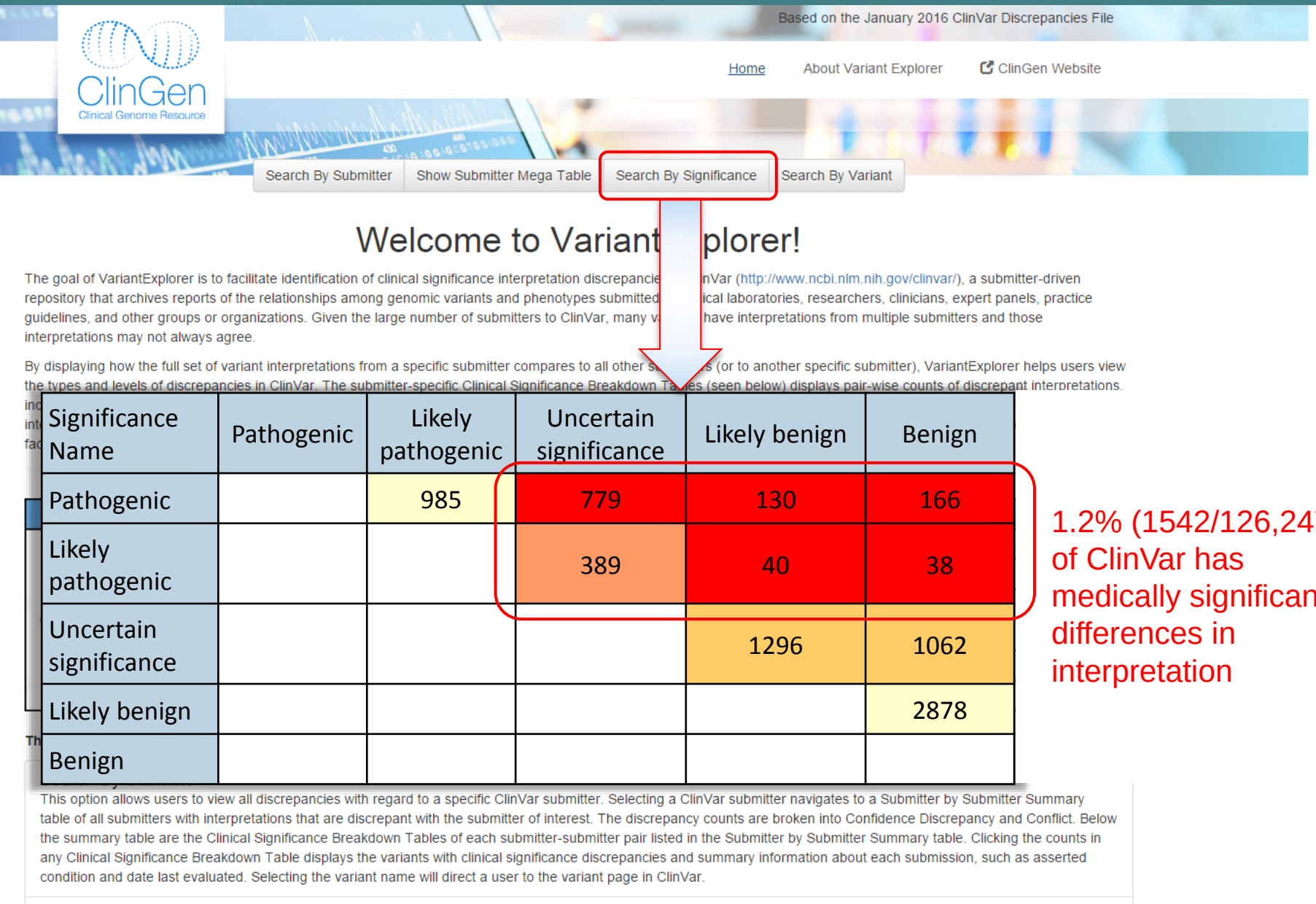
179,845 variants submitted

126,247 unique interpreted variants

ClinVar as of March 21, 2016

ClinVar Variant View



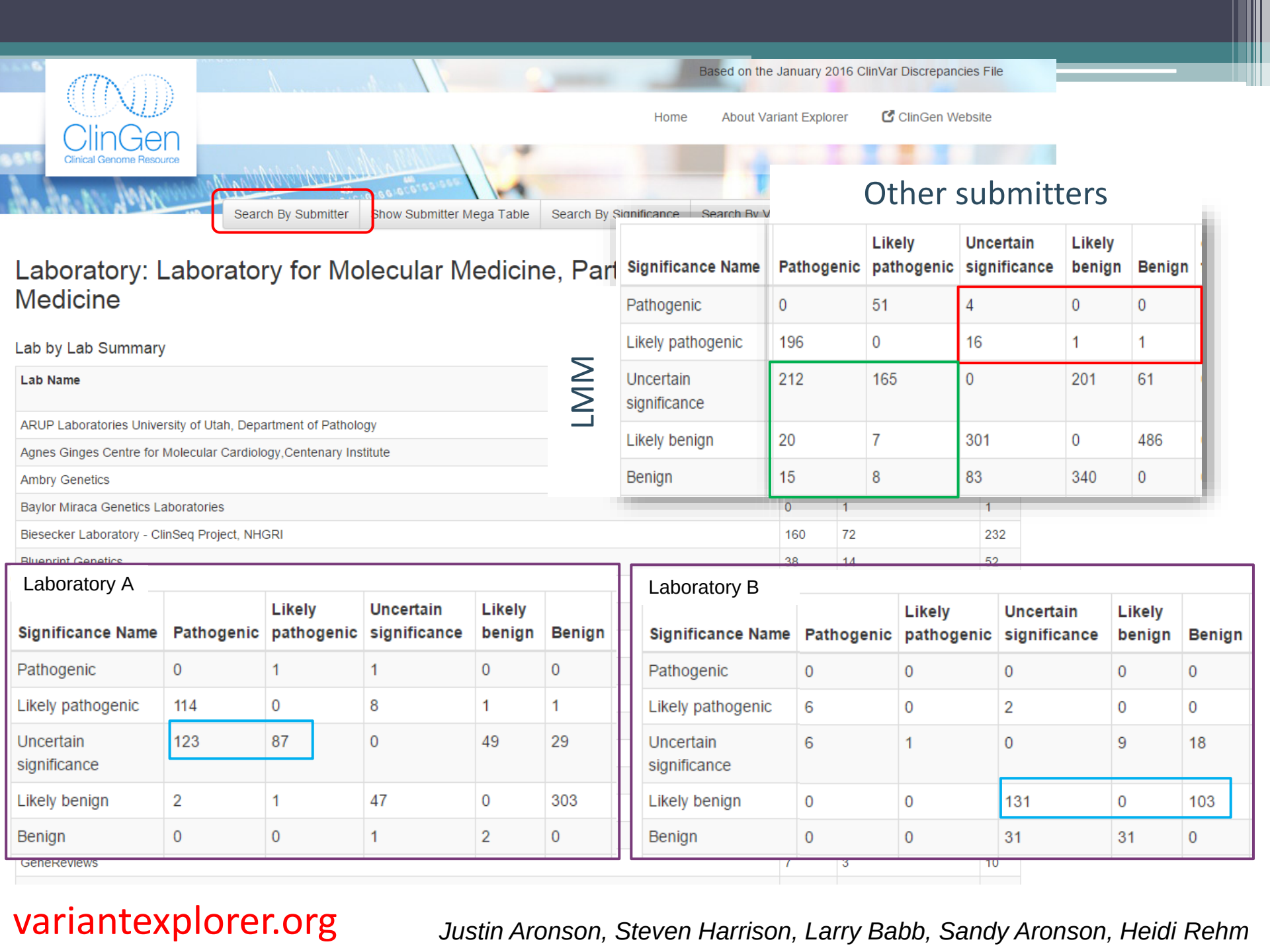


Significance Name	Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign
Pathogenic		985	779	130	166
Likely pathogenic			389	40	38
Uncertain significance				1296	1062
Likely benign					2878
Benign					

1.2% (1542/126,247) of ClinVar has medically significant differences in interpretation

variantexplorer.org

Justin Aronson, Steven Harrison, Larry Babb, Sandy Aronson



Significance Name	Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign
Pathogenic	0	51	4	0	0
Likely pathogenic	196	0	16	1	1
Uncertain significance	212	165	0	201	61
Likely benign	20	7	301	0	486
Benign	15	8	83	340	0

Baylor Miraca Genetics Laboratories	0	1	1
Biesecker Laboratory - ClinSeq Project, NHGRI	160	72	232
Blueprint Genetics	38	14	52
GeneReviews	7	3	10

Significance Name	Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign
Pathogenic	0	1	1	0	0
Likely pathogenic	114	0	8	1	1
Uncertain significance	123	87	0	49	29
Likely benign	2	1	47	0	303
Benign	0	0	1	2	0

Significance Name	Pathogenic	Likely pathogenic	Uncertain significance	Likely benign	Benign
Pathogenic	0	0	0	0	0
Likely pathogenic	6	0	2	0	0
Uncertain significance	6	1	0	9	18
Likely benign	0	0	131	0	103
Benign	0	0	31	31	0

variantexplorer.org

Justin Aronson, Steven Harrison, Larry Babb, Sandy Aronson, Heidi Rehm

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 gu... for the interpretation of sequence variants.[1] In the past d... rapidly with the adv... sequencing. By adopting ... clinical laboratories are nc... genetic testing spanning g... genomes, transcriptomes... By virtue of increased co... accompanied by new ch... context the ACMG conve... sentatives from the ACM... (AMP), and the College ... the standards and guideli... The group consisted of cli... report represents expert ... ACMG, AMP, and Coll... These recommendations ... used in clinical laboratori...

exomes, and genomes. This report recommends the use of specific standard terminology ... "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" ... scribe variants identified ... over, this recommenda- ... into these five categories ... vidence (e.g., population ... regation data). Because ... nterpretation of clinical ... ACMG strongly recom- ... hould be performed in a ... ts–approved laboratory, ... ical molecular geneticist ... ent.

... ch 2015

... clinical genetic testing; ... terminology; variant ...

	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

Monogenic disease terms

Pathogenic

Likely pathogenic

Uncertain significance (VUS)

Likely benign

Benign

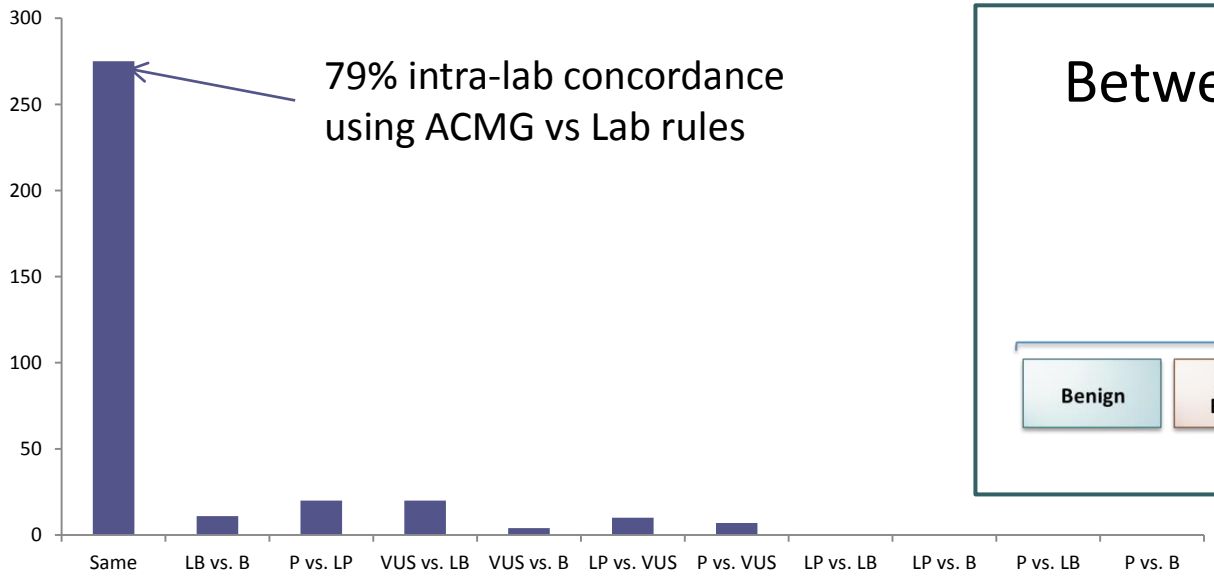
CSER Variant Bakeoff #2

9 sites, 11 variants submitted by each site = 99 variants total

9 variants evaluated by all 9 sites and 90 variants by 3 sites

Sites applied both their own rules and the ACMG rules

Sites: Baylor, DFCI, NIH, Hudson-Alpha, BWH, UNC, Kaiser, NextMed/UW, CHOP



Between lab concordance:

5 level (3 level)

34% (60%)

GLA (NM_000169.2):c.639+919G>A; Fabry disease

Site	Lab Rules	ACMG Rules	PVS1	PS3	PS4	PM4	PP1	PP5	PP3	BP4
Site 1	Pathogenic	Pathogenic	?	X	X		M			
Site 2	Pathogenic	Uncertain Significance		X		X	X	X		X
Site 3	Pathogenic	Likely Pathogenic		X			X		X	

While initial application of the ACMG/AMP rules did not improve concordance, the rules provided a useful framework to resolve differences in classification

DNAH5 c.7468_7488del (p.Trp2490_Leu2496del) Primary ciliary dyskinesia

Site	ACMG Rules	Lab Rules
Site 1	Uncertain Significance	Uncertain Significance
Site 2	Uncertain Significance	Uncertain Significance
Site 3	Uncertain Significance	Likely Pathogenic
Site 4	Uncertain Significance	Likely Pathogenic
Site 5	Likely Pathogenic	Uncertain Significance
Site 6	Likely Pathogenic	Likely Pathogenic
Site 7	Likely Pathogenic	Likely Pathogenic
Site 8	Likely Pathogenic	Likely Pathogenic
Site 9	Likely Pathogenic	Likely Pathogenic
Consensus	Likely Pathogenic	

PS1	PM2	PM3	PM4	PP3	PP4	PP5
	X		X	?	X	
	X		X			
		X	X			
	P	X	X			
	X	P	X			X
	X		X	X	X	
	X	X	X			
X		X	X		X	
	X		X		X	X
	X	X	X		Mixed	

* * *

PM2 – Absent from pop db

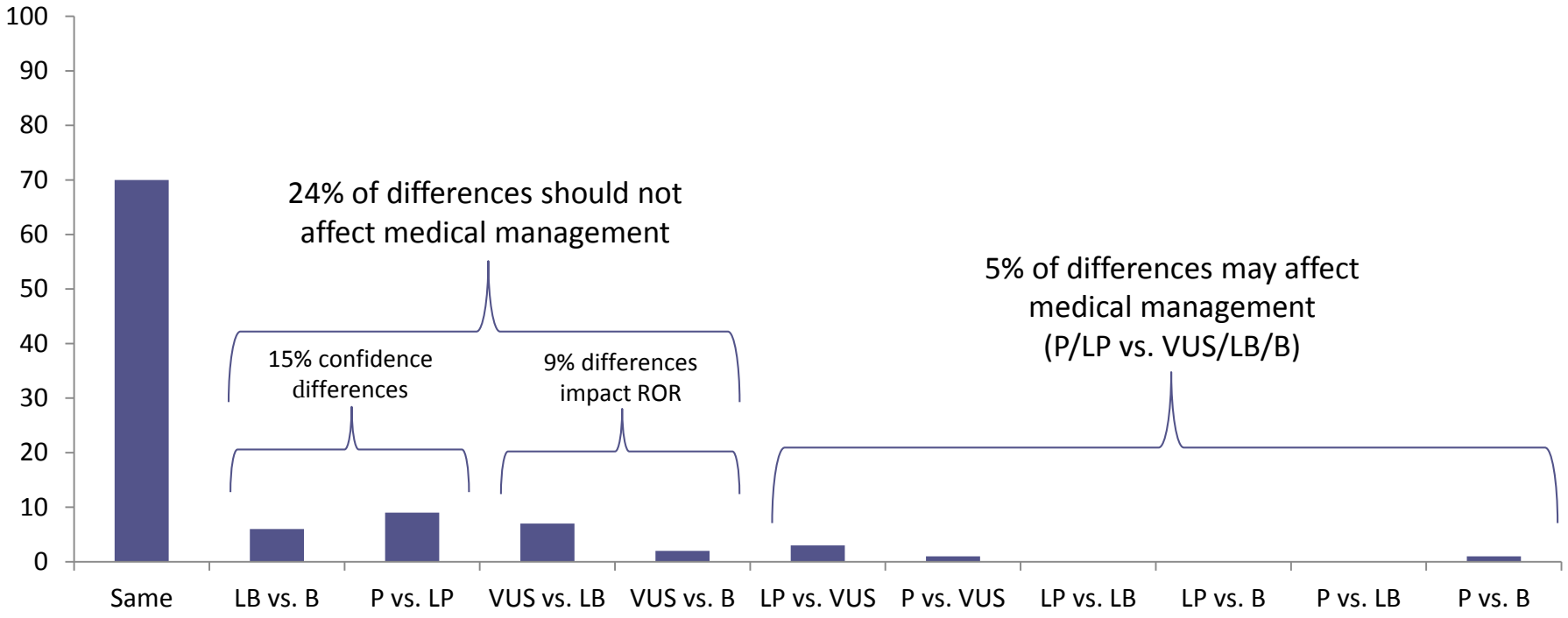
PM3 - Detected in *trans* with a pathogenic variant

PM4 - Protein length changing variant

ACMG rules:
3 moderate = Likely Pathogenic

CSER Variant Bakeoff Consensus Efforts

	5 level (3 level)
• Between lab concordance:	34% (60%)
• Concordance after discussion and evidence sharing:	70% (85%)



Comparison of ClinVar Submitted Variants Across Four Labs:

Ambry, GeneDx, Partners LMM, Univ. Chicago – 49,734 unique variants

Submitted by	# shared variants	# Agreed (%)	# VUS vs. LB/B differences	# P/LP vs. VUS/LB/B differences
Lab 1 / Lab 2	2318	2035 (88%)	125 (5%)	158 (7%)
Lab 3 / Lab 1	2312	2068 (89%)	200 (9%)	44 (2%)
Lab 1 / Lab 4	1256	1086 (86%)	160 (13%)	10 (1%)
Lab 4 / Lab 2	513	478 (93%)	30 (6%)	5 (1%)
Lab 3 / Lab 4	86	77 (90%)	9 (10%)	0
Lab 3 / Lab 2	65	62 (95%)	2 (3%)	1 (2%)
All 4 Labs	6169	5445 (88%)	508 (8%)	216 (4%)
86% (200/232) resolved		5645 (92%)	398 (6%)	126 (2%)

Steven Harrison, Jill Dolinsky, Lisa Vincent, Amy Knight Johnson, Danielle Azzariti, Tina Pesaran, Elizabeth Chao, Soma Das, Sherri Bale, Heidi Rehm

Fifteenth Annual

Bio·IT World

CONFERENCE & EXPO '16

Enabling Technology. Leveraging Data. Transforming Medicine.

Track 10 - April 5 – 7, 2016

Clinical Genomics

Determining Genomic Variation's Contribution to Disease

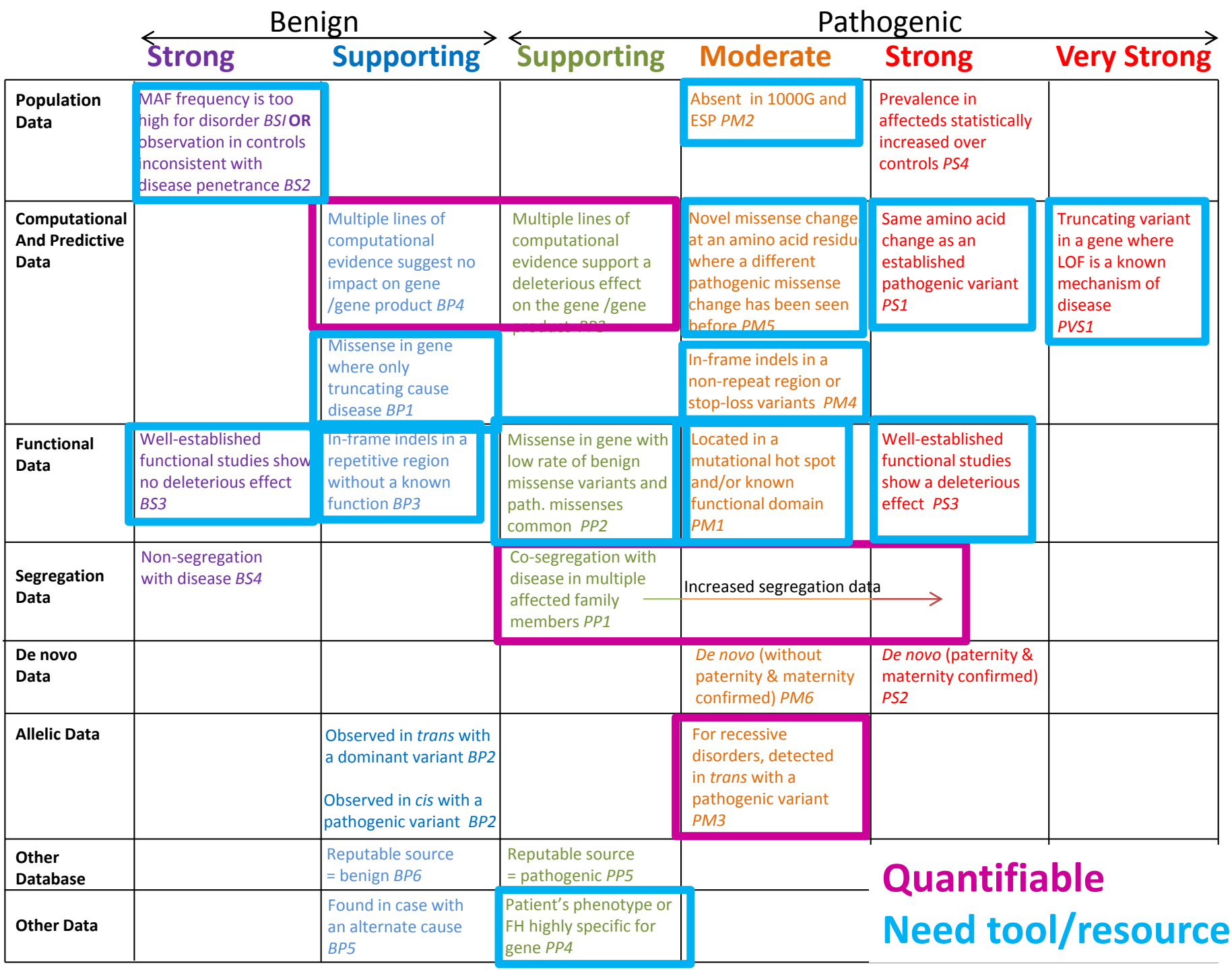
Thursday, April 7

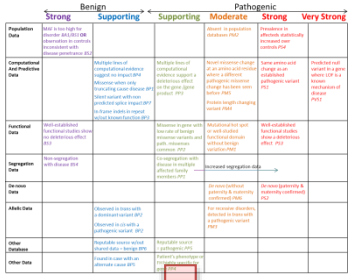
2:30 Community-Driven Approaches to Support Variant Interpretation

Steven Harrison, Ph.D., Variant Scientist, Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine; Harvard Medical School

Lessons Learned

- The majority of differences in variant classification are resolvable through consensus and data sharing
- Variant classification often requires professional judgment (even when using the same rules) and therefore complete consensus may not occur
- But all evidence must be accessible and rules should be applied correctly
- The ACMG/AMP rules would benefit from added quantitative guidance as well as gene/disease specific guidance


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 residu where a different pathogenic missense change has been seen before PM5
Same amino acid change as an established pathogenic variant PS1
Truncating variant in a gene where LOF is a known mechanism of disease PVS1
Missense in gene where only truncating cause disease BP1
In-frame indels in a non-repeat region or stop-loss variants PM4
Functional Data
Well-established functional studies show no deleterious effect BS3
In-frame indels in a repetitive region without a known function BP3
Missense in gene with low rate of benign missense variants and path. missenses common PP2
Located in a mutational hot spot and/or known functional domain 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 = 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
Quantifiable
Need tool/resource



ACMG/AMP Rules

Interlab Seq Var Discrepancy Resolution Task Team

Cardiomyopathy Expert Panel

Noonan Spectrum Expert Panel

Hereditary Cancer Expert Panels

Metabolic Disease Expert Panel

Developmental Delay Expert Panel

Others…….

Gene and disease-specific ACMG/AMP rule specification (frequency thresholds, acceptable functional assays, etc)

ClinGen Sequence Variant Interpretation Work Group

(Co-Chairs Les Beisecker and Marc Greenblat)

Short term: Refine and clarify current ACMG/AMP criteria

Medium term: Modify ACMG/AMP criteria

Long term: Move to quantitative Bayesian framework

Optimization and Utilization of ACMG Variant Classification Criteria for the RASopathies: A ClinGen Initiative

Lisa M. Vincent ,Heather Mason-Suares, Rong Mao, Mitchell W. Dillon, Brad Williams, Patroula Smpokou, Karen W. Gripp, Katherine A. Rauen, Amy E. Roberts, Bruce D. Gelb, and Sherri Bale

Table 1: Assessment of Strength of Evidence Relative to RASopathy Spectrum

		Evidence Requirements			
PATHOGENIC CRITERIA	**OFFICIAL ACMG CRITERIA** [Richards et al. 2015]	**VERY STRONG**	**STRONG**	**MODERATE**	**SUPPORTING**
PS2	De novo (both maternity and paternity confirmed) in a patient with the disease and no family history	≥2 independent occurrences (PVS_NP9)			
PS3	Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product		≥2 unique in vitro or in vivo functional studies OR ≥2 independent groups with concordant deleterious results for the same assay *if no formal assays approved by expert panel available (PS_NP2)*	One in vitro or in vivo functional studies *if no formal assays approved by expert panel available (PM_NP8)*	
PM5	Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before		≥2 different pathogenic missense changes (PS_NP3)		
PM6	Assumed de novo, but without confirmation of paternity and maternity	≥2 independent occurrences plus 1 occurrence of PS2 (PVS_NP9)	≥2 independent occurrences (PS_NP1)		
PP1	Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease		≥7 meioses (PS_NP4)	≥5 meioses (PM_NP6)	≥2 meioses
BENIGN CRITERIA	**OFFICIAL ACMG CRITERIA** [Richards et al. 2015]	**STAND-ALONE**	**STRONG**	**SUPPORTING**	
BA1 BS1	Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, or ExAC Allele frequency is greater than expected for disorder	An allele frequency ≥0.05% subject to a 95% confidence interval based on the population size and a minimum of 5 alleles present in the population. (BA_NB1)	An allele frequency ≥0.025% subject to a 95% confidence interval based on the population size and a minimum of 5 alleles present in the population. Based on disease prevalence of 1:1000		
BS3	Well-established in vitro or in vivo functional studies shows no damaging effect on protein function or splicing		≥2 unique in vitro or in vivo functional studies OR ≥2 independent groups with concordant benign results for the same assay *if no formal assays approved by expert panel available*	One in vitro or in vivo functional studies *if no formal assays approved by expert panel available (BP_NB5)*	
		≥2 meioses (BA_NB2)	≥1 meiosis		
			≥2 independent occurrences where increased clinical severity of disease is not evident (BS_NB4)		
			≥2 independent occurrences where increased clinical severity of disease is not evident (BS_NB4)		

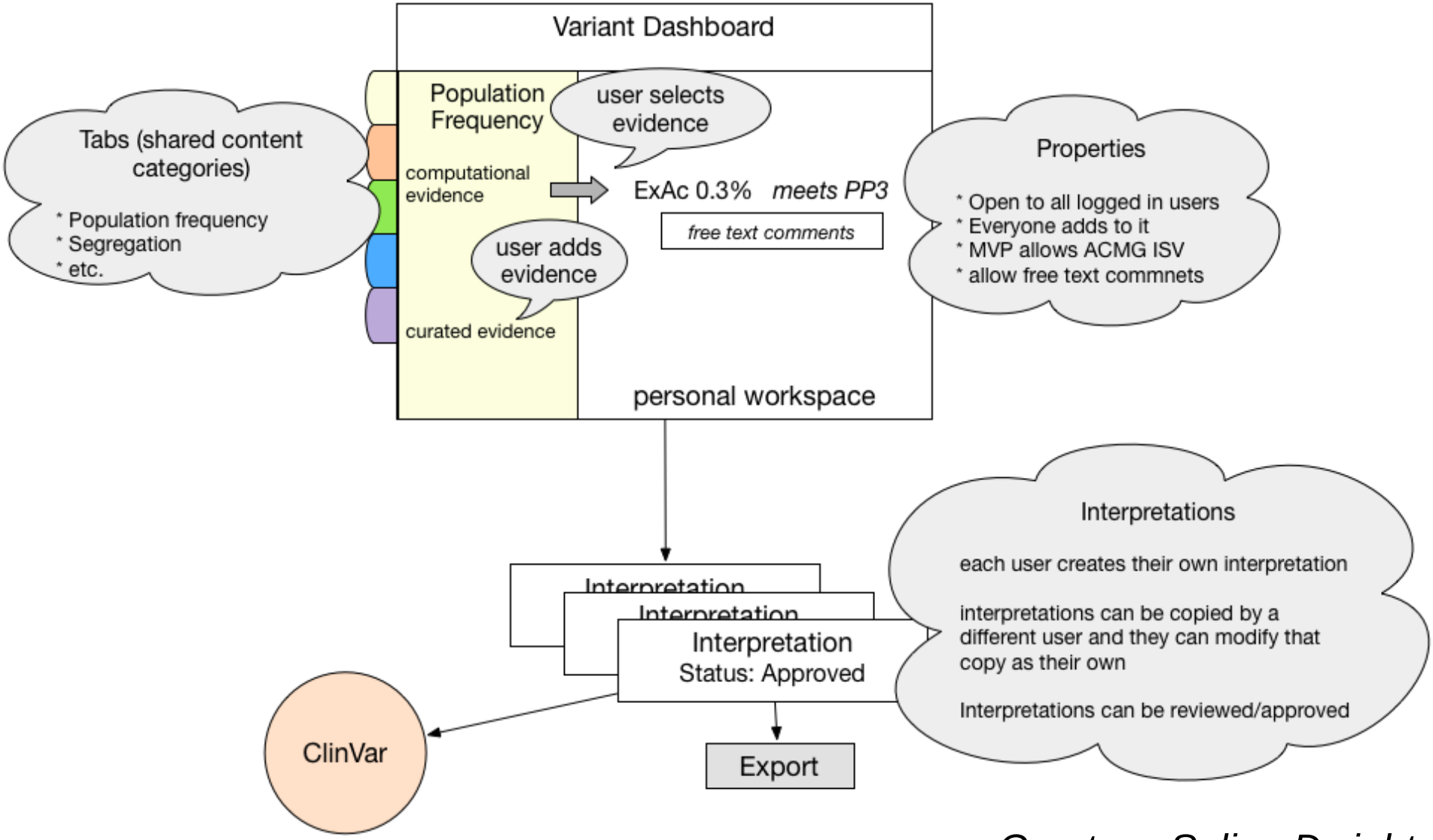
Table 2: Other RASopathy Specific Assessments

	OFFICIAL ACMG CRITERIA [Richards et al. 2015]	ASSESSMENTS
PS1 PM1 PM5	Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation / Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before	Can also be applied for the same analogous residue positions/regions in highly analogous groupings: Group 1: HRAS, NRAS, KRAS Group 2: MAP2K1, MAP2K2
PM2	Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC	The variant must be completely absent from all population databases. Retrospective analysis of the most common pathogenic variant in each of these genes indicated that at most only 1 allele was observed in these large control population databases suggesting the variants should be completely absent unless the variant is well-established as pathogenic.
BS2	Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age	Due to variable expressivity and severity, extensive clinical workup for RASopathy spectrum features is warranted, thus general population data should not be used for this criterion unless there are observed homozygous individuals.
BP7	A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved	Also applicable for intronic or non-coding variants and also can be used in conjunction with BP4.

Table 3: Additional RASopathy- Specific Criteria

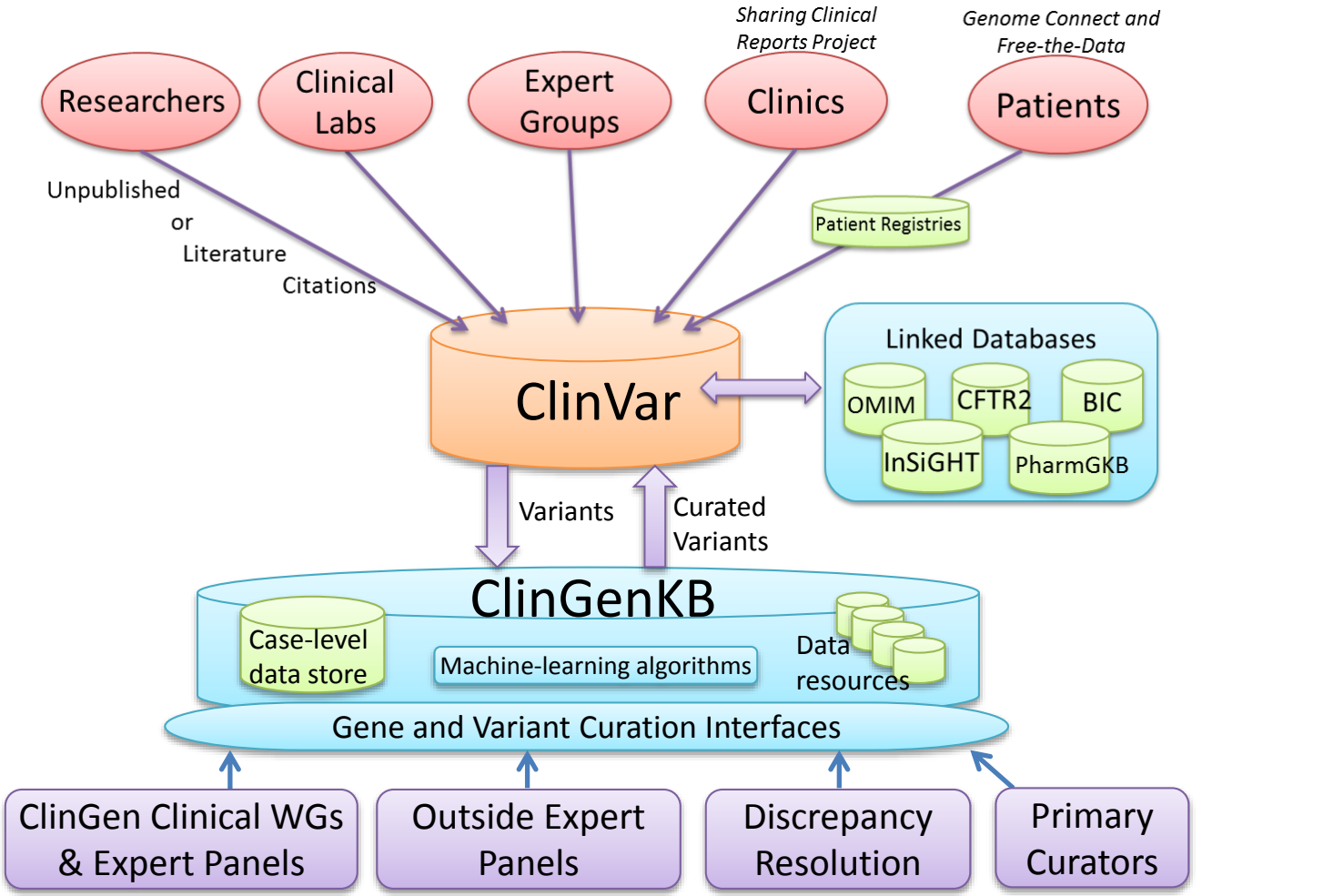
BENIGN- SUPPORTING	Truncating variant (nonsense, frameshift, affects canonical splice sites, initiation codon, entire gene or multi exon deletion) when disease mechanism is gain-of-function and dosage sensitivity information is consistent (BP_NB6)
BENIGN- SUPPORTING	Located in a region/domain of the protein that tolerates variation and lacks pathogenic variants (BP_NB7)

ClinGen Variant Curation Tool



Courtesy Selina Dwight

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



GA4GH Overview

Global Alliance for Genomics & Health

The Global Alliance will:

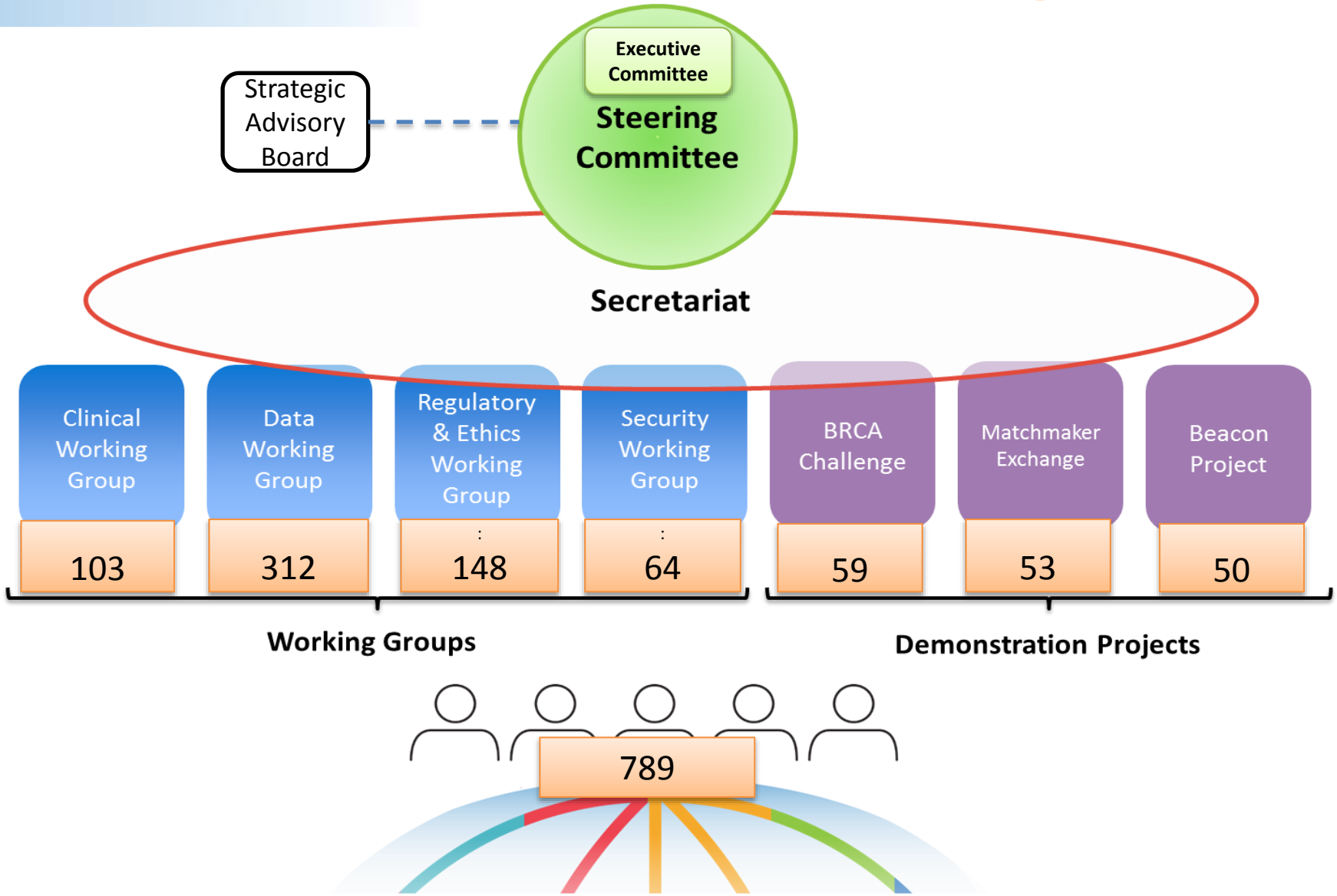
- Convene stakeholders
- Catalyze responsible data sharing
- Create harmonized approaches
- Act as a clearinghouse
- Foster innovation
- Support demonstration projects to implement standards

Host institutions

- Broad Institute of MIT and Harvard
- Ontario Institute for Cancer Research
- Wellcome Trust Sanger Institute

Organizational structure

Global Alliance for Genomics & Health



7.5 professional staff

Last Update: June 4th 2015

BRCA Challenge Steering Committee

Sir John Burn, Newcastle University (United Kingdom) – Co-Chair
Stephen Chanock, National Cancer Institute (United States) – Co-Chair
Antonis Antoniou, University of Cambridge (United Kingdom)
Larry Brody, National Human Genome Research Institute (United States)
Robert Cook-Deegan, Duke University (United States)
Fergus Couch, Mayo Clinic (United States)
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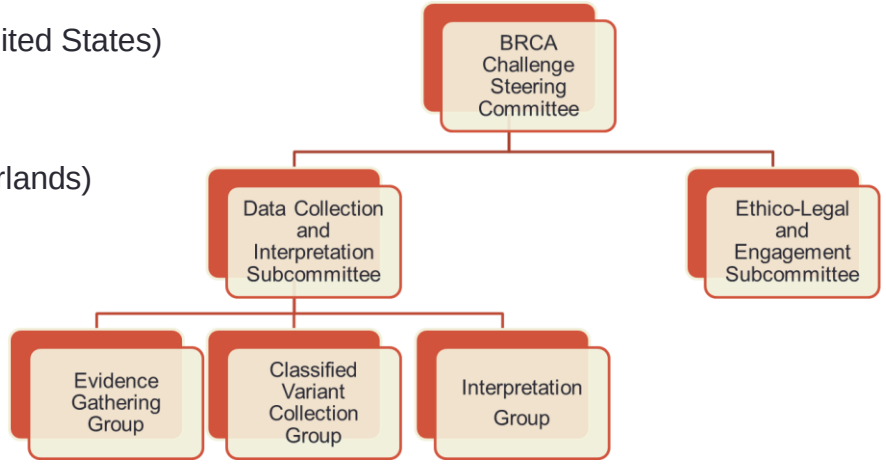
Dominique Stoppa-Lyonnet, Curie Institute (France)
Sean Tavtigian, University of Utah (United States)



Coordination:

Rachel Liao
Broad Institute

Underline denotes leadership on a subgroup

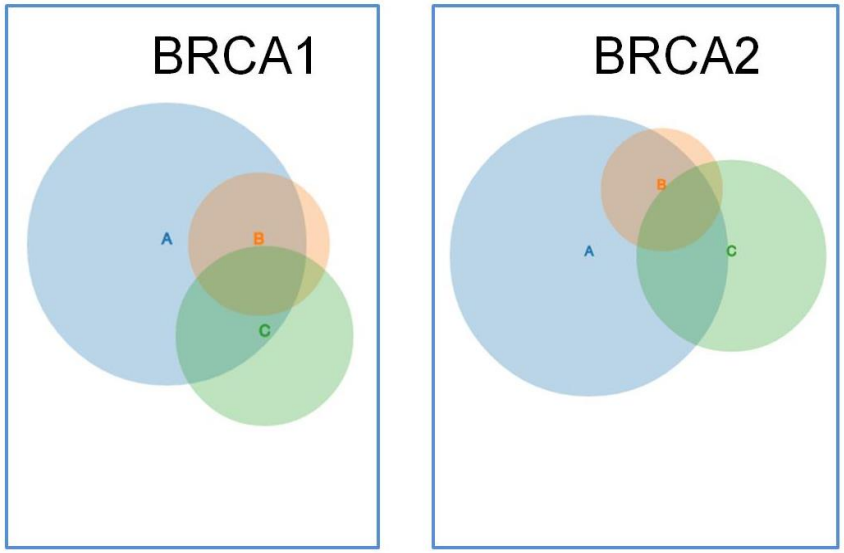
Goals of the Challenge

To improve the care of patients at risk of breast and ovarian cancer using global data sharing and collaboration in the analysis of *BRCA1* and *BRCA2*

1. Share *BRCA1* and *BRCA2* variants publically via a web portal
   - Includes an environment for collaborative variant curation with access to evidence (e.g. phenotypes, family history, genetic data, and functional studies)
   - Displays a curated list of BRCA variants, interpreted by expert consensus, to enable, without dictating, accurate clinical care
2. Address the social, ethical, and legal challenges to global data sharing
3. Create a model for all disease genes

Distinct databases contain non-overlapping content

	# BRCA Variants
EXPERT PANELS	
ENIGMA	1030
CLINICAL LABS	
InVitae	4829
Ambry Genetics	2794
Sharing Clinical Reports Project	2146
GeneDx	1222
Counsyl	272
Children's Hospital of Eastern Ontario	257
University of Washington Medical Center	69
Pathway Genomics	86
Emory University	204
Medical University Innsbruck	44
International Standard Cytogenetic Arrays Cons.	37
Strand Life Sciences	2
University of Chicago	7
ARUP	3
Children's Hospital of Philadelphia	20
Oregon Health and Sciences University	1
RESEARCH & LSDBs	
Breast Cancer Information Core (BIC)	3776
Inova Health System	132
ClinSeq Project, NHGRI	89
Shahid Beheshti University of Medical Sciences	17
Ain Shams University	6
Samuel's Laboratory - NHGRI/NIH	0
Leeds Institute of Molecular Medicine	0
King Faisal Specialist Hospital and Research Ctr	3
Shiraz Institute for Cancer Research	1
Curoverse	6
Novartis Institutes for BioMedical Research	3
Aggregate Databases	
Online Mendelian Inheritance in Man (OMIM)	78
GeneReviews	4
# of unique BRCA1/2 variants in ClinVar	**8478**

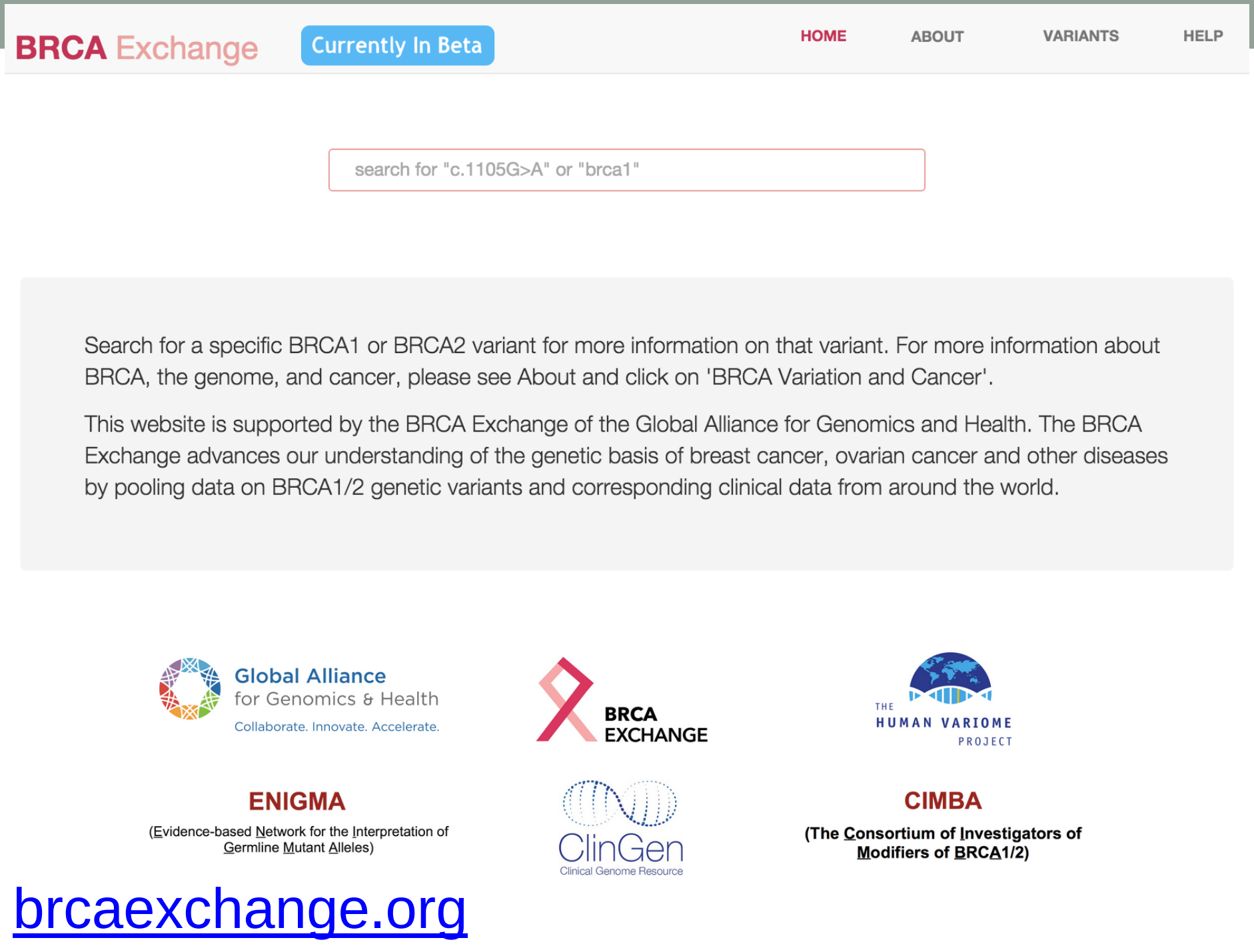


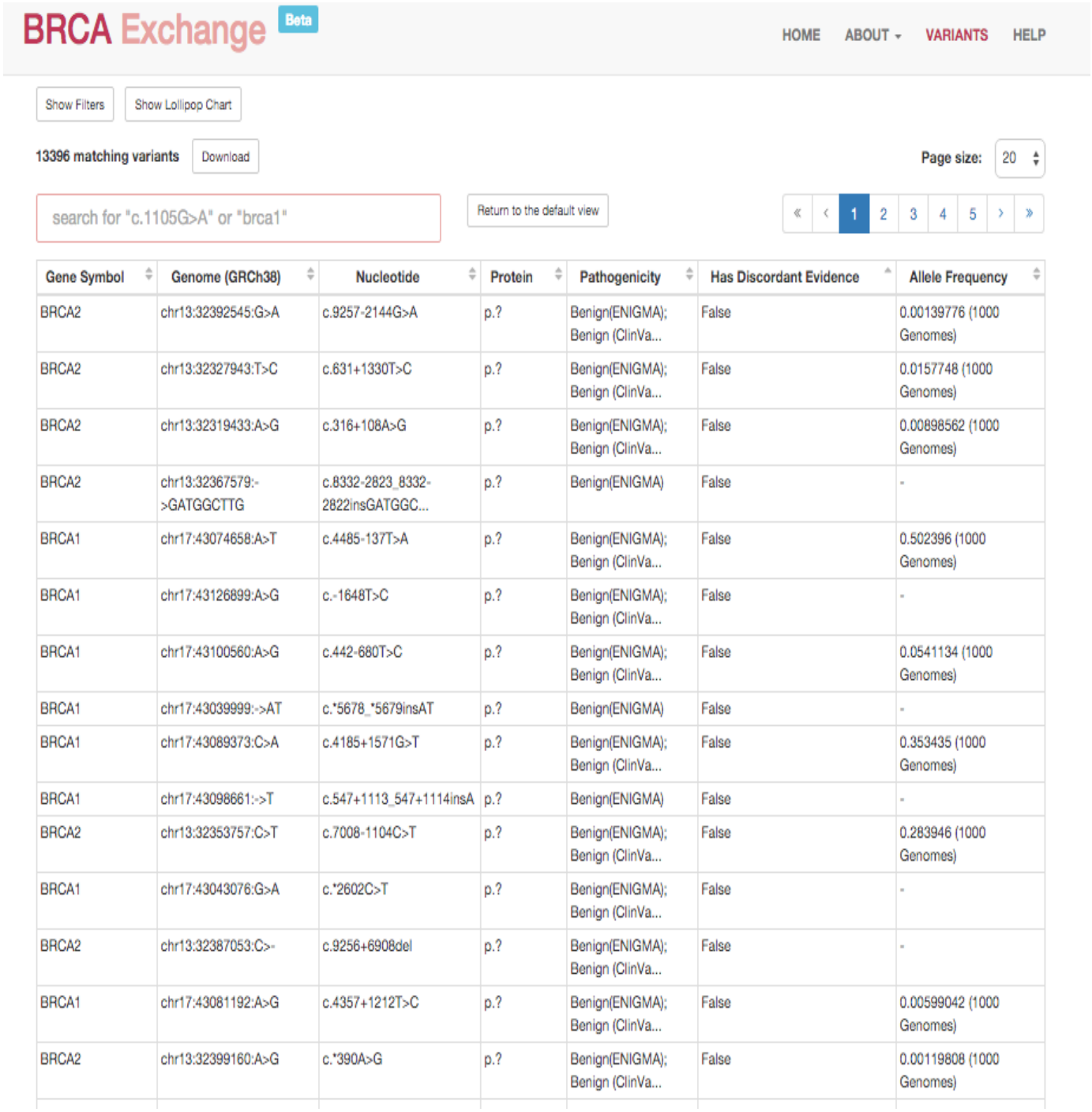
A=ClinVar B=LOVD C=UMD

LSDB Updates

Courtesy of Xin Feng

ClinVar: 8478
LOVD: >3675
BRCA Share/UMD: 4838


BRCA Exchange
Currently In Beta
HOME
ABOUT
VARIANTS
HELP
search for "c.1105G>A" or "brca1"
Search for a specific BRCA1 or BRCA2 variant for more information on that variant. For more information about BRCA, the genome, and cancer, please see About and click on 'BRCA Variation and Cancer'.
This website is supported by the BRCA Exchange of the Global Alliance for Genomics and Health. The BRCA Exchange advances our understanding of the genetic basis of breast cancer, ovarian cancer and other diseases by pooling data on BRCA1/2 genetic variants and corresponding clinical data from around the world.
Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.
BRCA
EXCHANGE
THE
HUMAN VARIOME
PROJECT
ENIGMA
(Evidence-based Network for the Interpretation of Germline Mutant Alleles)
ClinGen
Clinical Genome Resource
CIMBA
(The Consortium of Investigators of Modifiers of BRCA1/2)
brcaexchange.org



Gene Symbol	Genome (GRCh38)	Nucleotide	Protein	Pathogenicity	Has Discordant Evidence	Allele Frequency
BRCA2	chr13:32392545:G>A	c.9257-2144G>A	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.00139776 (1000 Genomes)
BRCA2	chr13:32327943:T>C	c.631+1330T>C	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.0157748 (1000 Genomes)
BRCA2	chr13:32319433:A>G	c.316+108A>G	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.00898562 (1000 Genomes)
BRCA2	chr13:32367579:->GATGGCTTG	c.8332-2823_8332-2822insGATGGC...	p.?	Benign(ENIGMA)	False	-
BRCA1	chr17:43074658:A>T	c.4485-137T>A	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.502396 (1000 Genomes)
BRCA1	chr17:43126899:A>G	c.-1648T>C	p.?	Benign(ENIGMA); Benign (ClinVa...	False	-
BRCA1	chr17:43100560:A>G	c.442-680T>C	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.0541134 (1000 Genomes)
BRCA1	chr17:43039999:->AT	c.*5678_*5679insAT	p.?	Benign(ENIGMA)	False	-
BRCA1	chr17:43089373:C>A	c.4185+1571G>T	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.353435 (1000 Genomes)
BRCA1	chr17:43098661:->T	c.547+1113_547+1114insA	p.?	Benign(ENIGMA)	False	-
BRCA2	chr13:32353757:C>T	c.7008-1104C>T	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.283946 (1000 Genomes)
BRCA1	chr17:43043076:G>A	c.*2602C>T	p.?	Benign(ENIGMA); Benign (ClinVa...	False	-
BRCA2	chr13:32387053:C>-	c.9256+6908del	p.?	Benign(ENIGMA); Benign (ClinVa...	False	-
BRCA1	chr17:43081192:A>G	c.4357+1212T>C	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.00599042 (1000 Genomes)
BRCA2	chr13:32399160:A>G	c.*390A>G	p.?	Benign(ENIGMA); Benign (ClinVa...	False	0.00119808 (1000 Genomes)

Research Portal

Acknowledgements:

Gunnar Rautsch (BRCA Evidence Gathering Group)

UCSC Team (Melissa Cline, Benedict Paten, Molly Zhang, Mary Goldman, Brian Craft, Charles Markello, David Haussler)

BRCA Steering Committee

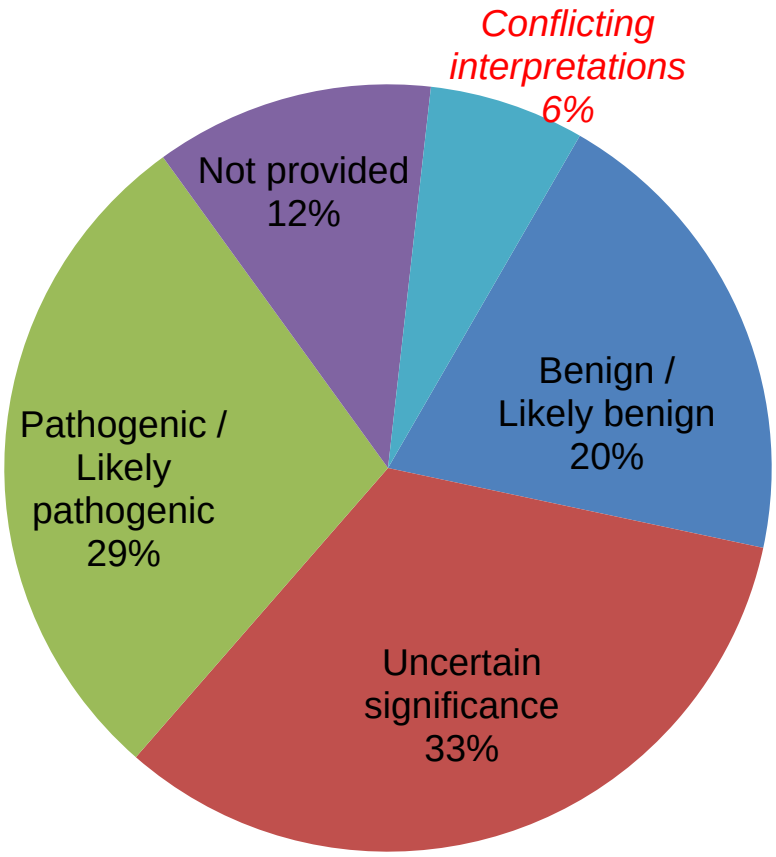
Next Steps for Release 3
BRCA Exchange for Research (v2)

Purpose: To support variant classification by aggregating relevant public and controlled access data AND serve as a data exchange hub to receive and distribute data submissions

Details:

- Requires authentication, rights management & controlled access protocols to properly handle case-level evidence
- Solicits case-level data submissions directly to a BRCA Exchange database from academic and commercial sources
- Provides workflows for variant curation by registered experts
- Provides additional analysis tools for case-level data
- Includes publicly available variant data in v1

BRCA1/2 variants in ClinVar

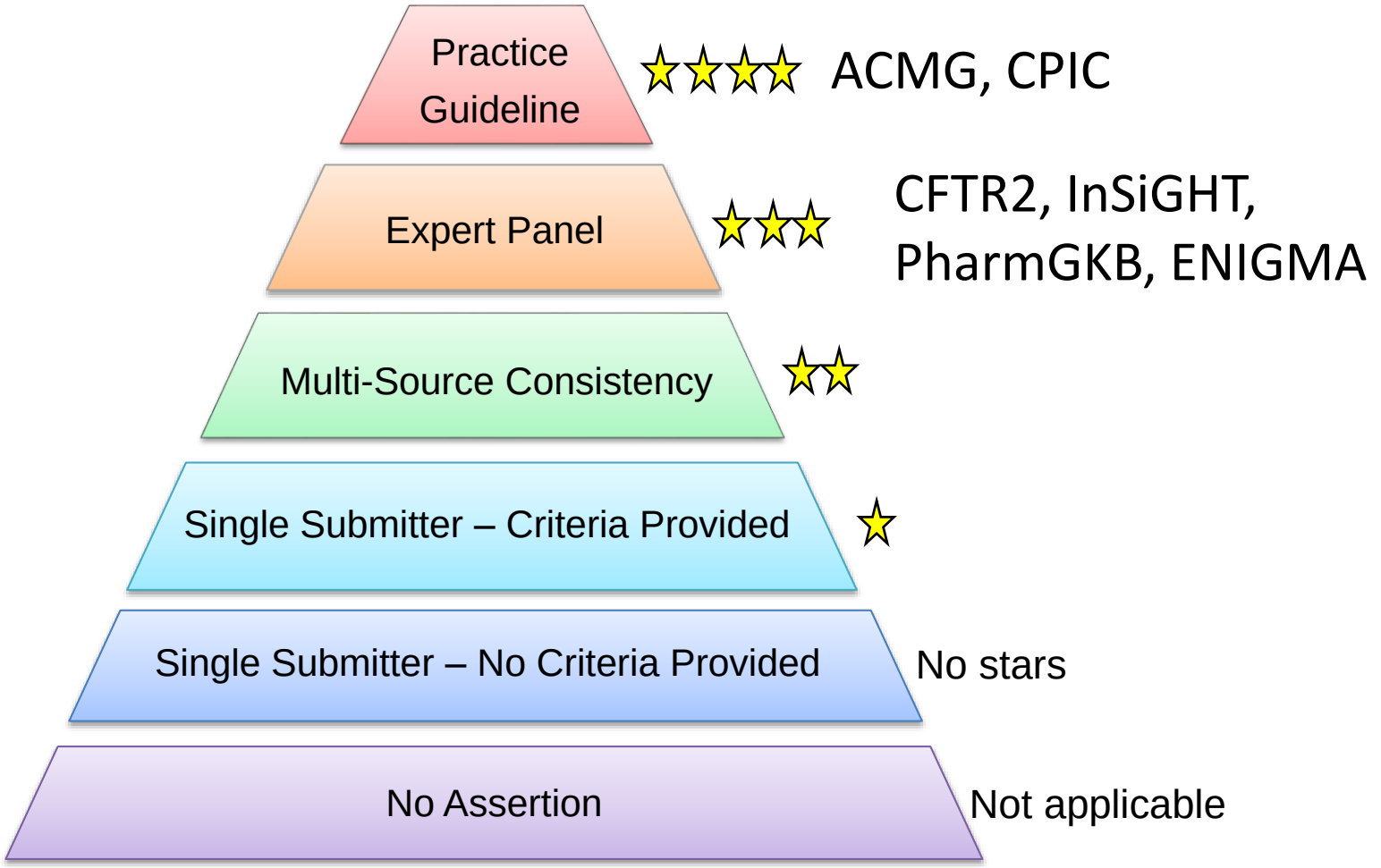


Variant Classifications in ClinVar	BRCA1/2
Benign / Likely benign	1696
Uncertain significance	2804
Pathogenic / Likely pathogenic	2426
Not provided	997
Conflicting interpretations	*555 (6%)*
Total unique variants	**8478**

Conflicting Interpretation Types in ClinVar	BRCA1/2
Uncertain significance vs Benign/Likely Benign	483 (87%)
Pathogenic/Likely pathogenic vs Uncertain significance	72 (13%)

2/26/2016

Review Levels in ClinVar



ClinVar Variant View

NM_007294.3(BRCA1):c.5158A>G (p.Thr1720Ala)

Variation ID: 55438

Review status: ★ ★ ★ ☆ reviewed by expert panel

Interpretation

Go to:

Clinical significance: Benign

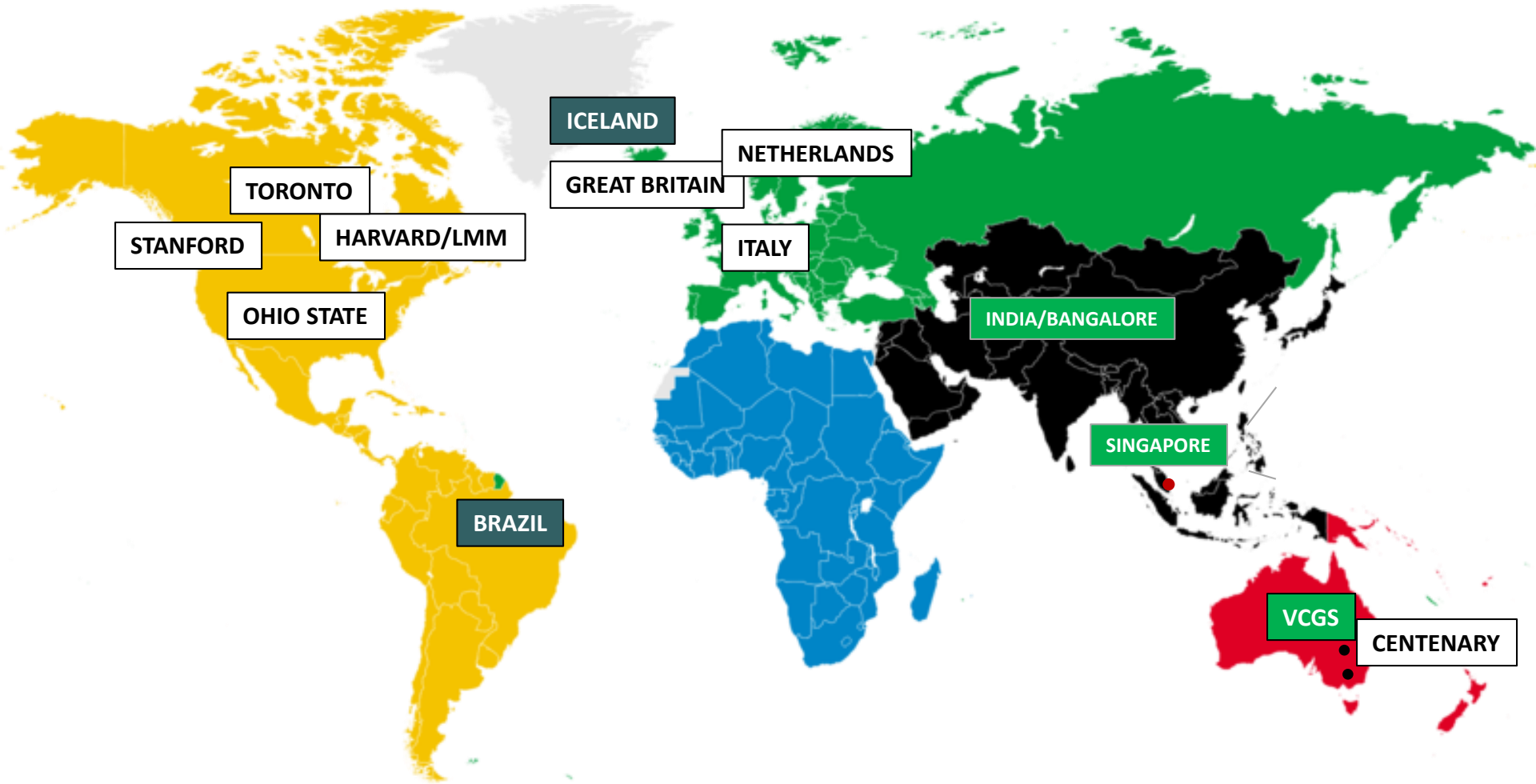
Last evaluated: Aug 10, 2015

Number of submission(s): 7

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name (Last submitted)	Submission accession
Benign (Aug 10, 2015)	reviewed by expert panel (ENIGMA BRCA1/2 Classification Criteria (2015))	curation	Breast-ovarian cancer, familial 1 [MedGen | OMIM]	germline	• PubMed (1) [See all records that cite this PMID] • Other citation	Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Study description (Aug 17, 2015)	SCV000244390.1
Benign (Sep 20, 2015)	criteria provided, single submitter (Invitae Variant Classification Sherloc (09022015))	clinical testing	Hereditary breast and ovarian cancer syndrome [MedGen | Orphanet]	germline	• PubMed (2) [See all records that cite these PMIDs]	Invitae (Jan 6, 2016)	SCV000076849.3
Likely benign (Mar 10, 2015)	criteria provided, single submitter (EGL Classification Definitions)	clinical testing	not specified [MedGen]	germline		Emory Genetics Laboratory (Jun 9, 2015)	SCV000226798.1
Uncertain significance (Nov 14, 2008)	no assertion criteria provided	clinical testing	Breast-ovarian cancer, familial 1 [MedGen | OMIM]	germline		Sharing Clinical Reports Project (SCRP) (Jun 26, 2013)	SCV000109408.2
Uncertain significance (Dec 30, 1999)	no assertion criteria provided	clinical testing	Breast-ovarian cancer, familial 1 [MedGen | OMIM]	germline		Breast Cancer Information Core (BIC) (BRCA1) (Mar 28, 2014)	SCV000145365.1

ClinGen Disease Areas	Existing Expert Panels	ClinGen Expert Panels	Gene Curation Projects	Variant Curation Projects	ClinVar Submissions
Cardiovascular Disease		1. Cardiomyopathy 2. Channelopathy 3. Aortopathy 4. FH	1. Cardiomyopathy 2. Channelopathy 3. Aortopathy	MYH7	FH groups
Hereditary Cancer	ENIGMA/BRCA Challenge InSiGHT		1. Breast cancer 2. GI polyposis 3. Paraganglioma	PTEN	
Inborn Errors of Metabolism				PKU, MCAD, VLCAD	Nenad Blau BioPKU
Pharmacogenetics	CPIC PharmGKB				PharmGKB
Rasopathies		Rasopathies		9 genes (BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, SOS1)	Many
Developmental Delay		In development		8 genes (ARX, CDKL5, MECP2, UBE3A, FOXG1, MEF2C, SLC9A6, TCF4)	Many
Congenital Muscular Dystrophy		In development		12 genes (COL6A1, COL6A2, COL6A3, FKRP, FKTN, ITGA7, LAMA2, LARGE, SEPN1, POMGNT1, POMT1, POMT2)	>32 submitters
Malignant hyperthermia		Malignant hyperthermia		RYR1	
Somatic Cancer		Initially focusing on standards development			
Pediatric Neurology					
Hearing loss		In development	Hearing loss and related syndromes	In development	

Cardiomyopathy Expert Panel



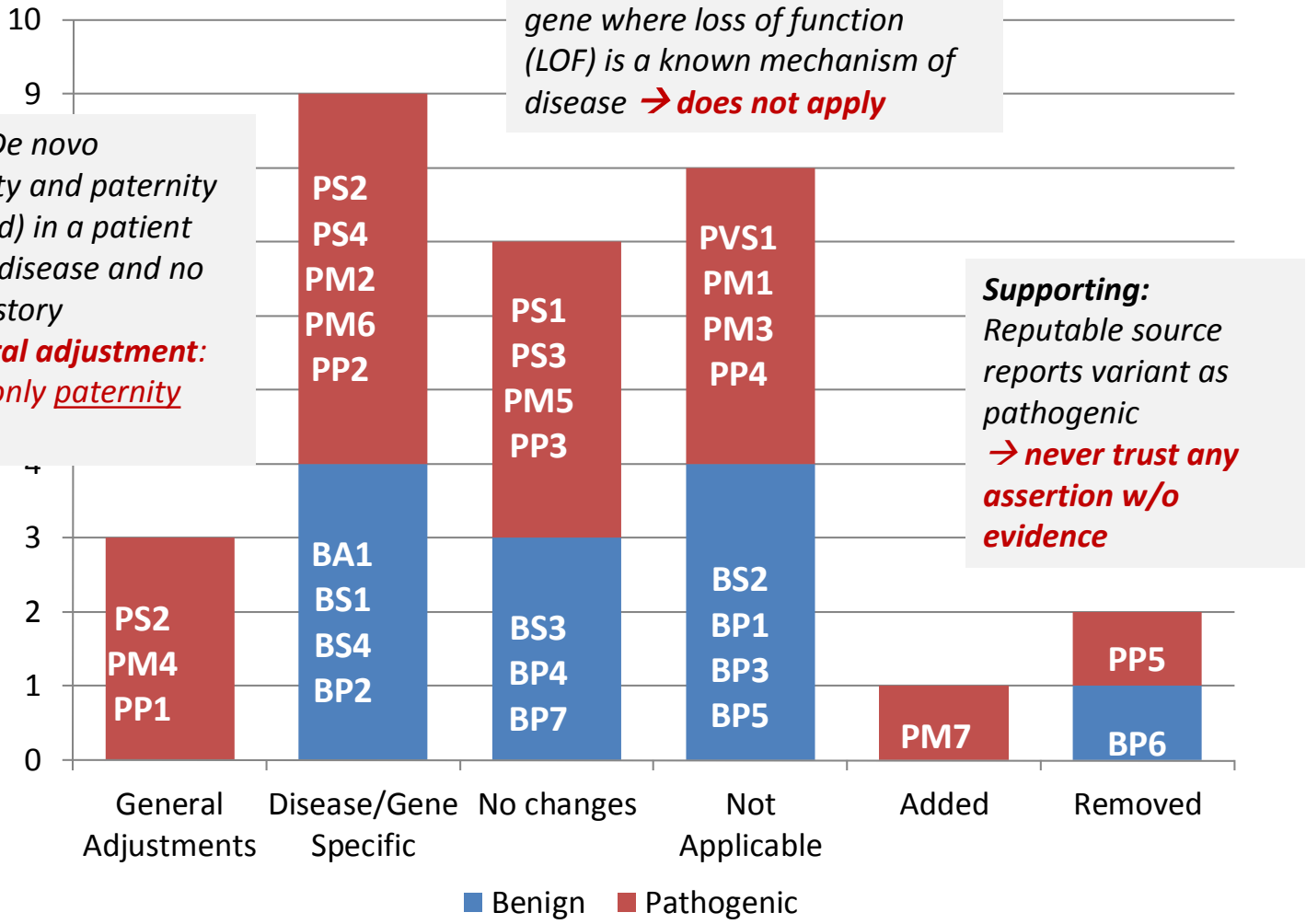
Courtesy Birgit Funke

SUMMARY ACMG RULE ADJUSTMENTS

Very strong**: Null variant in a gene where loss of function (LOF) is a known mechanism of disease → **does not apply

***Strong:** De novo (maternity and paternity confirmed) in a patient with the disease and no family history*
***→ General adjustment**: Require only paternity testing*

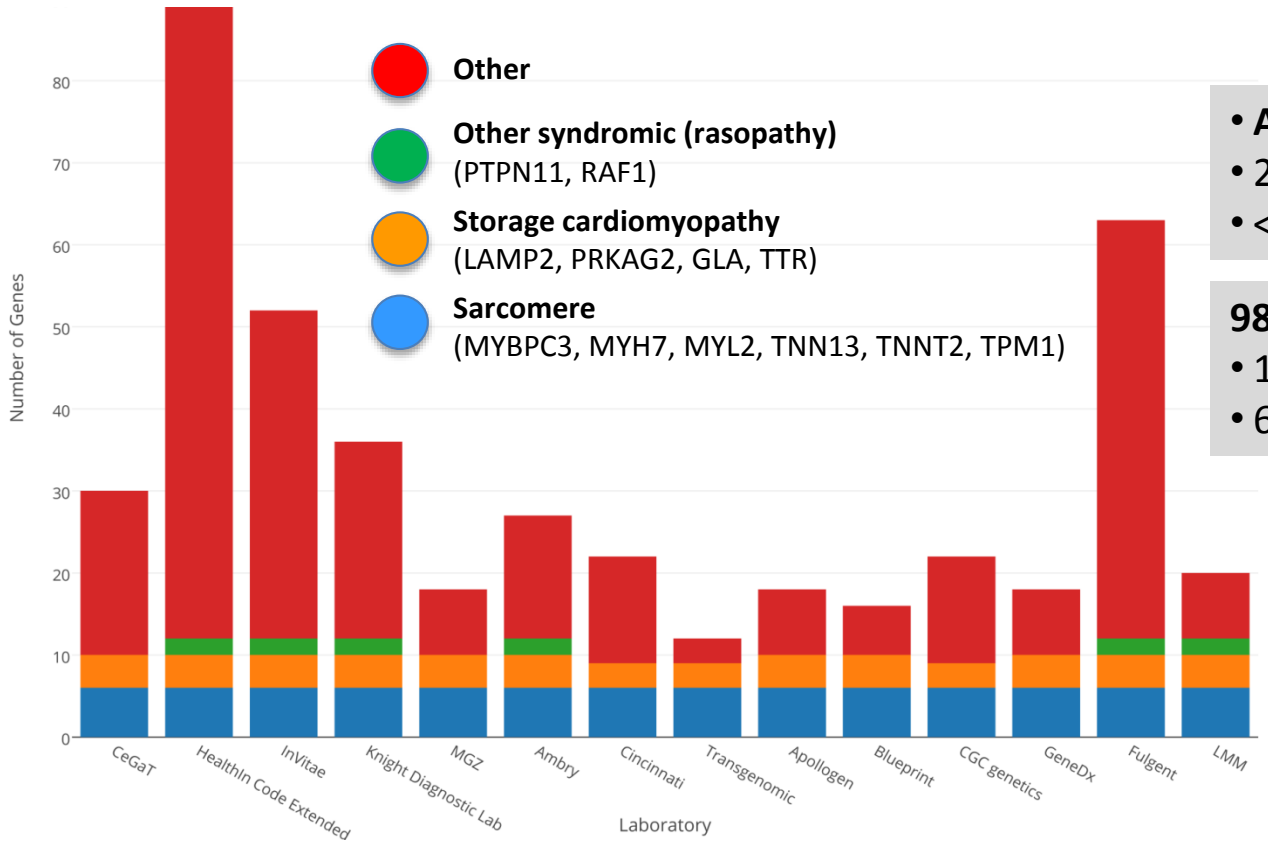
***Supporting:** Reputable source reports variant as pathogenic*
→ never trust any assertion w/o evidence



Courtesy Birgit Funke

HCM: CLINICALLY OFFERED GENE PANELS

GTR search for "Hypertrophic cardiomyopathy" (Jan 2016): 45 labs (14 shown)

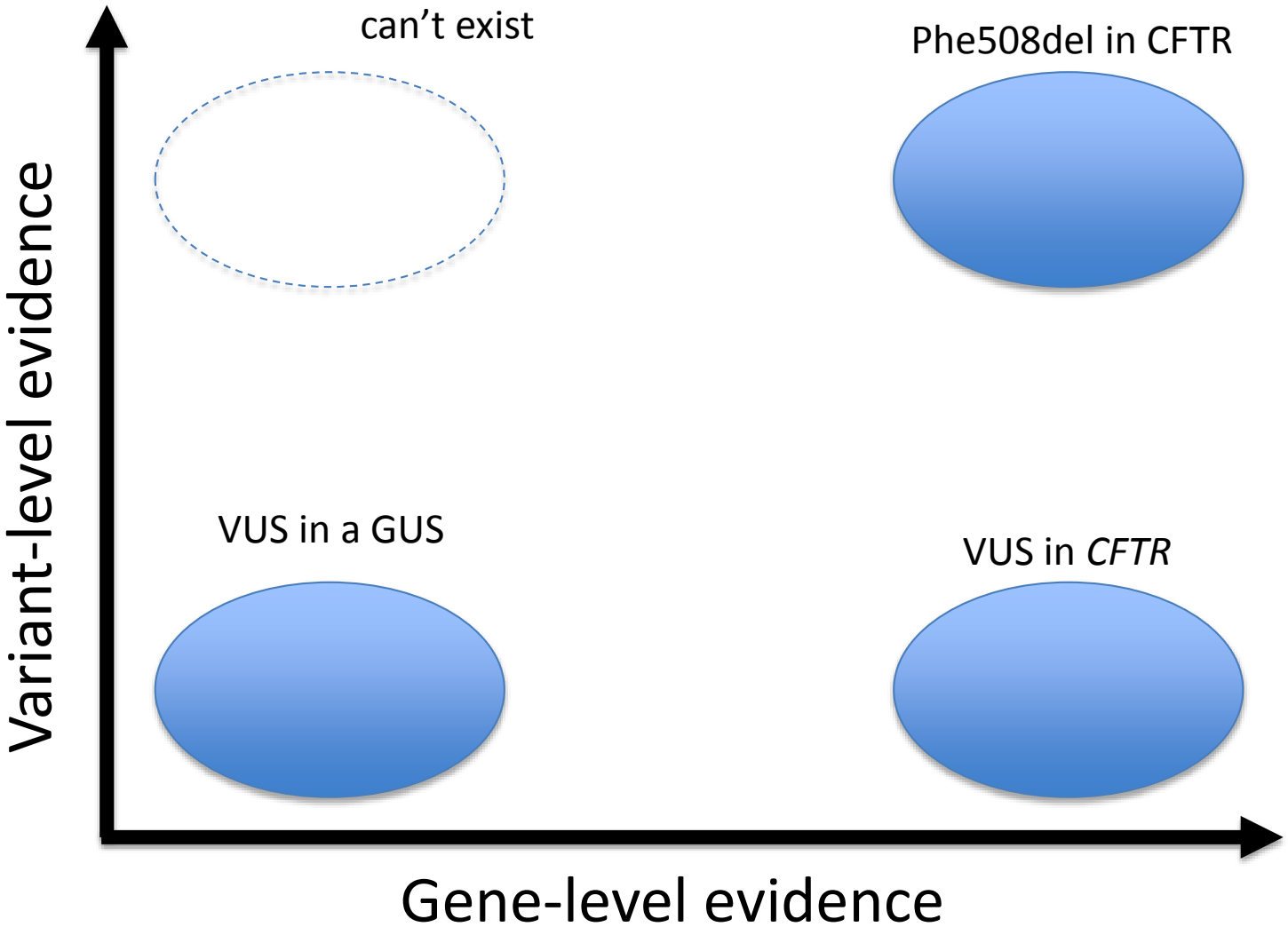


- **All labs offer key genes**
- 2 do not include all storage
- <50% include rasopathy

98 "other" genes
- 17 offered by ≥5 labs
- 68 offered by 1 lab

Courtesy Birgit Funke

The two axes of implication



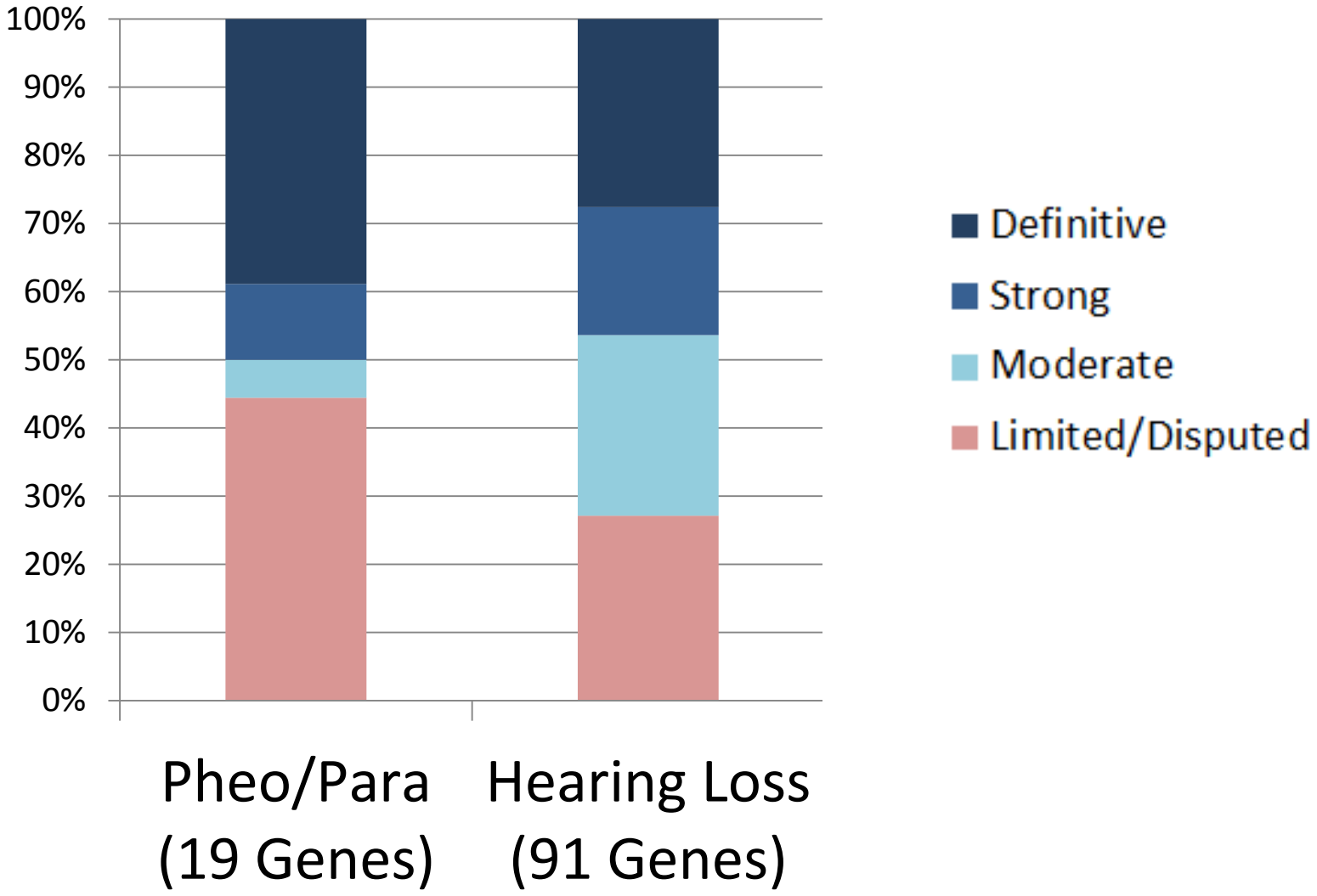
Modified from Daniel MacArthur

ClinGen Gene-Disease Validity Classification

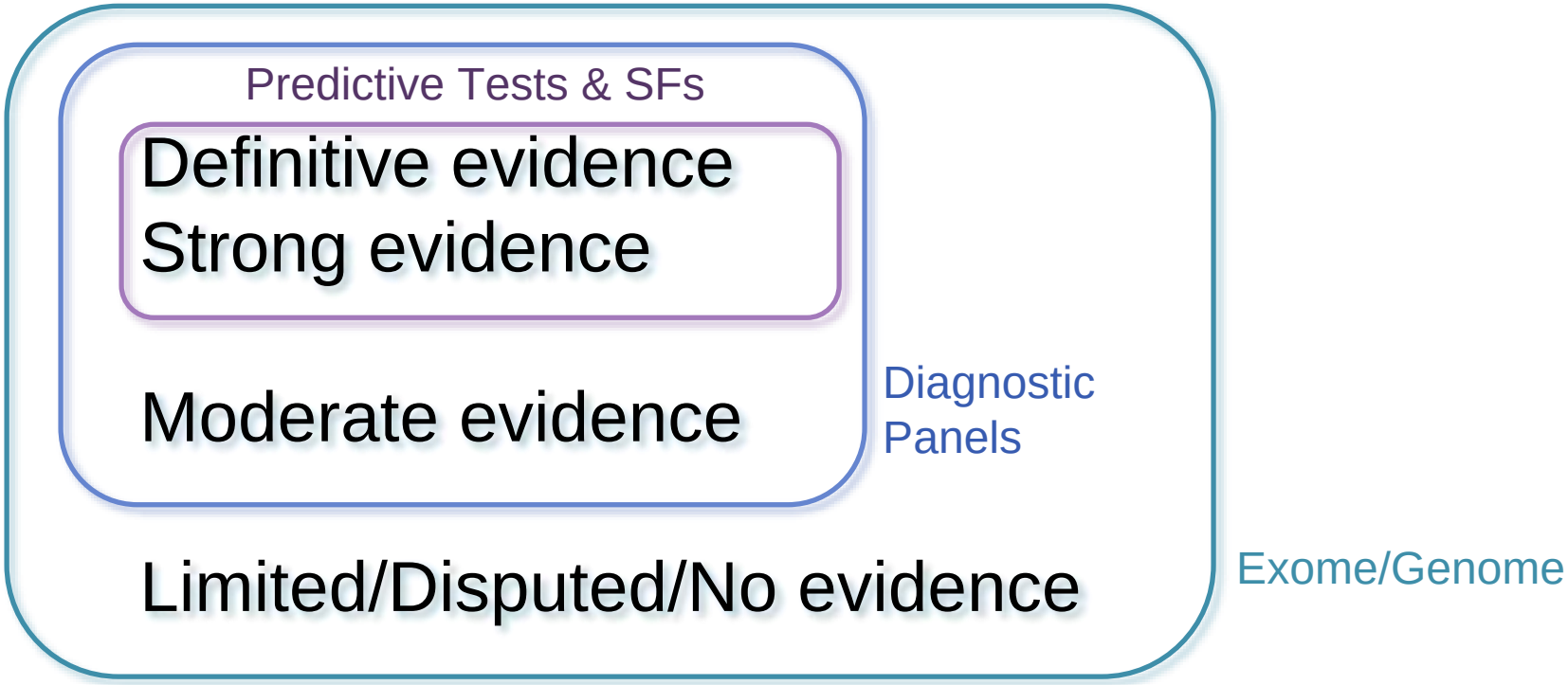
Definitive	Role has been repeatedly demonstrated in research & clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No convincing contradictory evidence
Strong	≥2 independent studies with: • Multiple pathogenic variants in unrelated probands • AND • Several different types of supporting experimental data • OR • Excess of pathogenic variants in cases vs. controls • No convincing contradictory evidence
Moderate	≥1 independent study with: • ≥3 unrelated probands with pathogenic variants • Some supporting experimental data • No convincing contradictory evidence
Limited	≥1 independent study with: • <3 unrelated probands with pathogenic variants • OR • Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity • No convincing contradictory evidence
No Evidence Reported	No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.
Conflicting Evidence Reported	
Disputed	Convincing evidence disputing a role for this gene in this disease has arisen • Disputing evidence need not outweigh existing evidence supporting the gene:disease association
Refuted	Evidence refuting the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role • Applied at the discretion of clinical domain experts after thorough review of available evidence

http://www.clinicalgenome.org/knowledge-curation/gene-curation/

Application of ClinGen Gene-Disease Evidence Rules



Proposed Gene Inclusion for Clinical Tests



Many ClinGen Clinical Domain WGs are initially focused on Gene Curation

Define genes appropriate for clinical testing and genes where additional evidence is needed

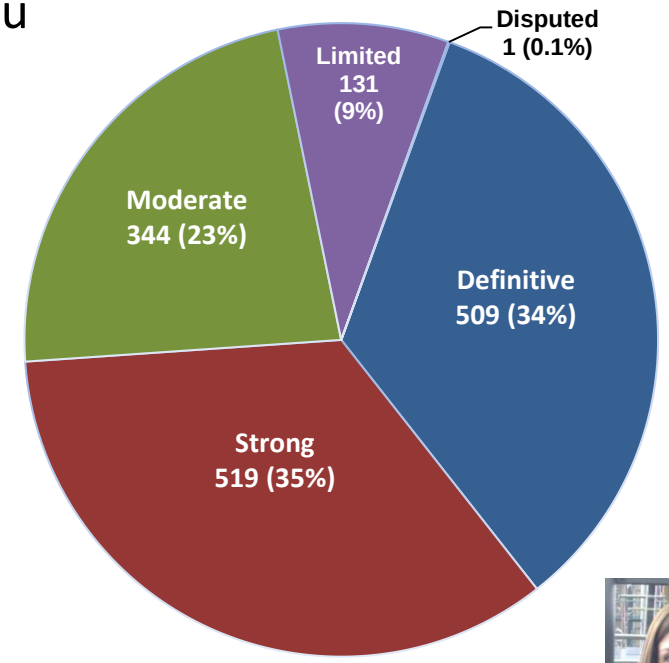
The BabySeq Project

Well babies

NICU babies

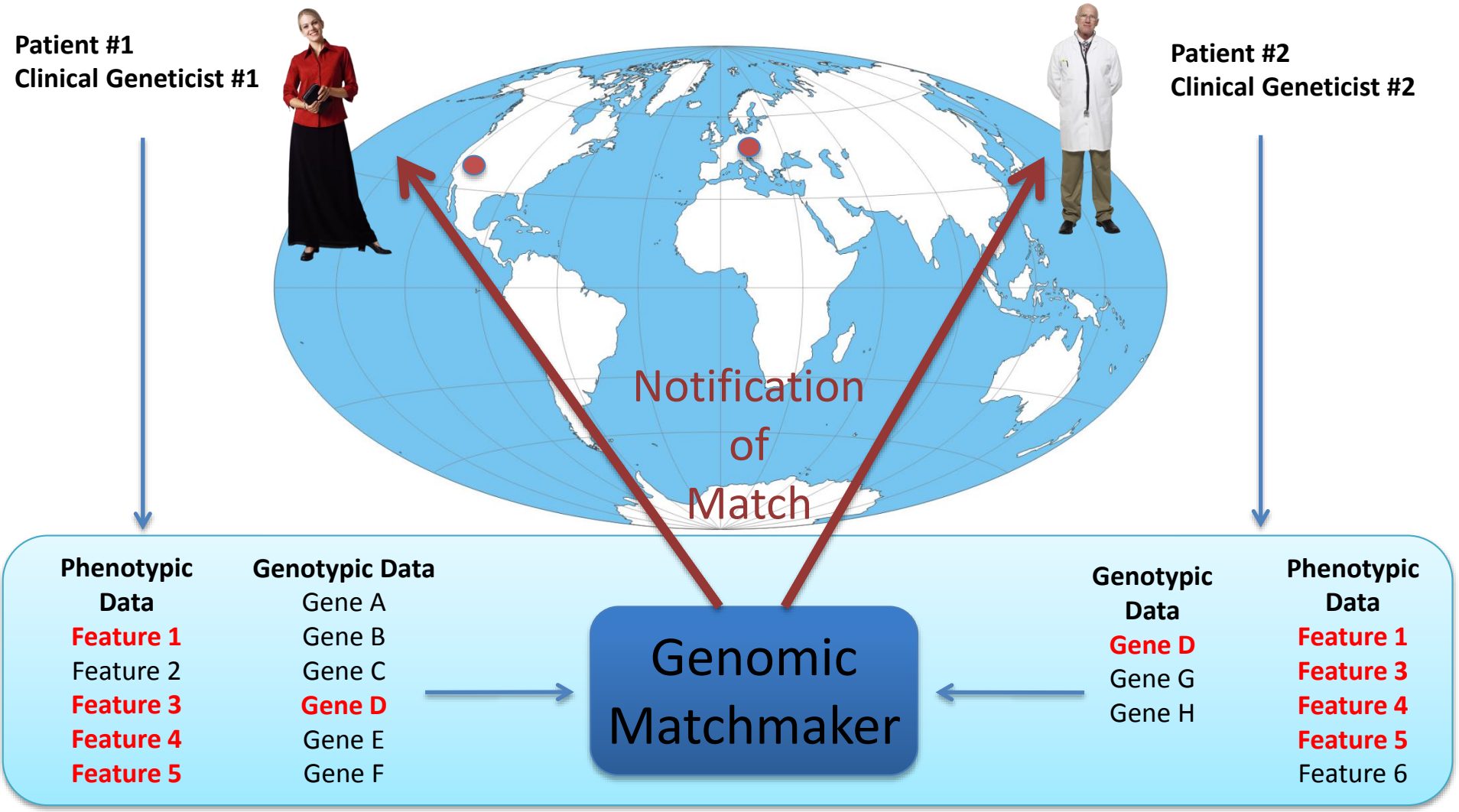
Leadership:
Robert Green & Alan Beggs
Pankaj Agrawal, Ingrid Holm, Amy McGuire, Richard Parad, Peter Park, Heidi Rehm, Tim Yu

- Curating ~4000 monogenic disease-associated genes
- 1566 genes curated so far
- 906/1566 met criteria for return (highly penetrant, childhood onset or treatable with strong or definitive evidence for gene's cause for disease



Ozge Birsoy

Matchmaker Needed!

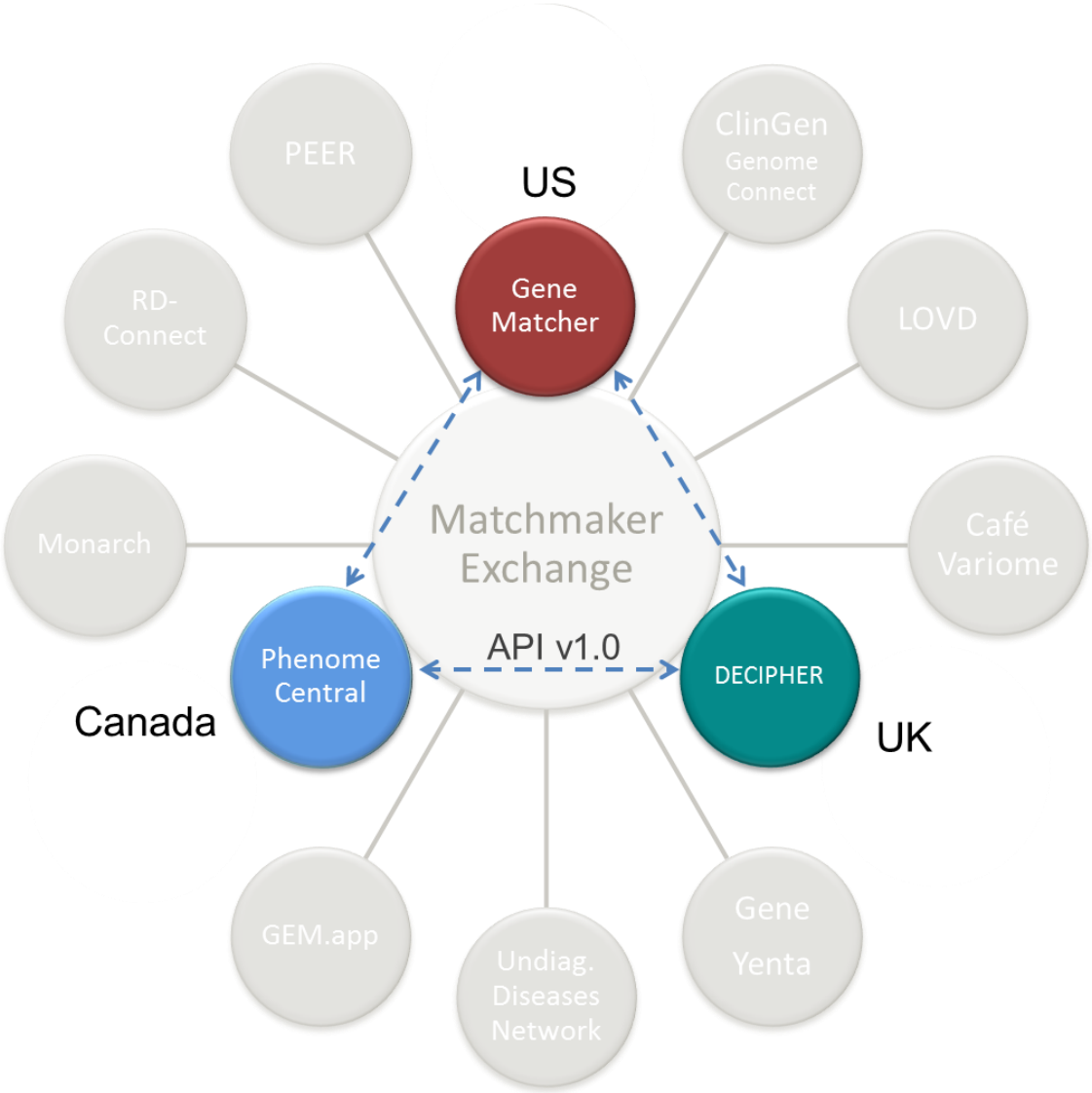


Courtesy of Joel Krier

Matchmaker Exchange
Collaboration and Support from GA4GH and IRDiRC

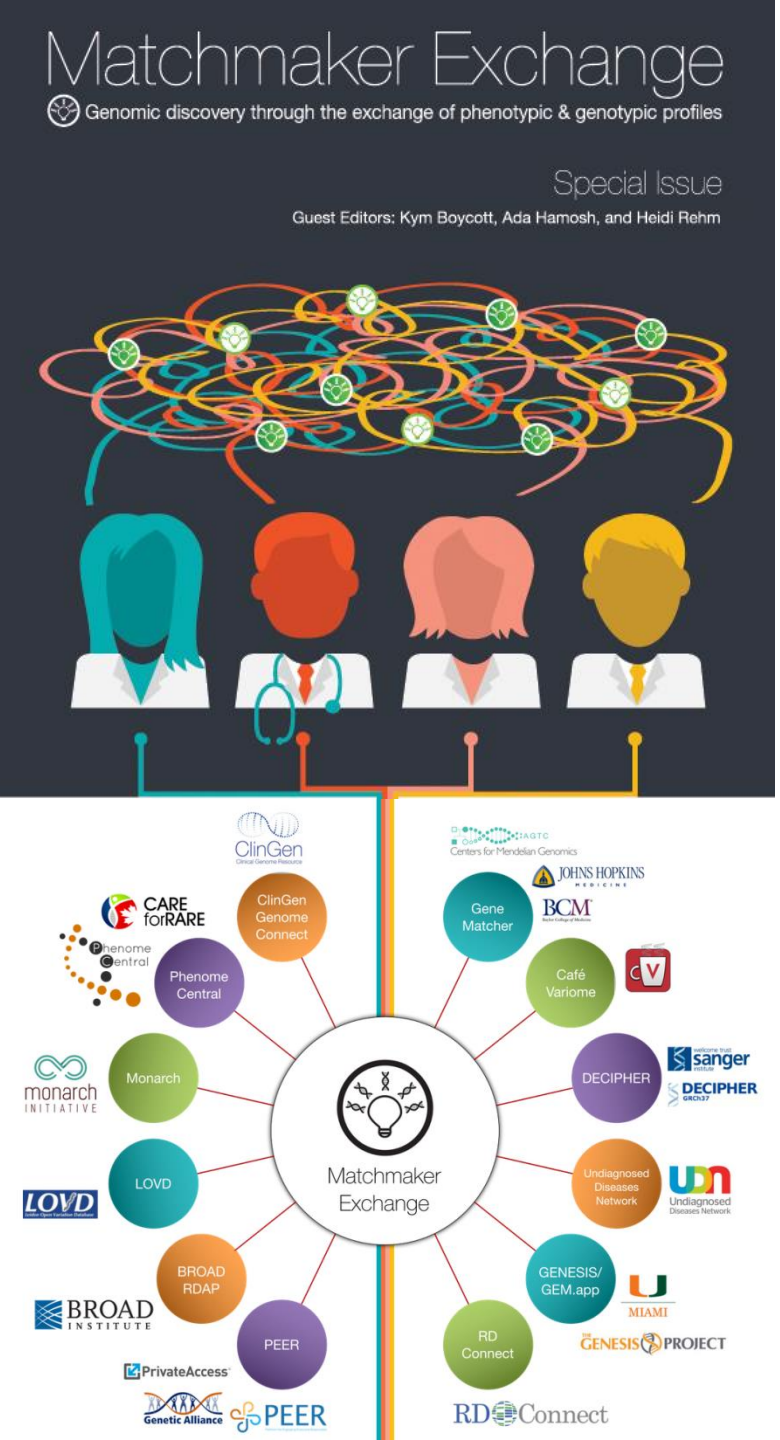
Needs span multiple GA4GH workgroups

- Data Work Group (data format and interfaces)
- Regulatory and Ethics (patient consent)
- Security (patient privacy and user authentication)



Philippakis et al. **The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery.** Hum Mutat. 2015;36(10):915-21.

Buske et al. **The Matchmaker Exchange API: automating patient matching through the exchange of structured phenotypic and genotypic profiles.** Hum Mutat. 2015;36(10):922-7



Human Mutation Special Issue

The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery

The Matchmaker Exchange API: automating patient matching through the exchange of structured phenotypic and genotypic profiles

GeneMatcher: A Matching Tool for Connecting Investigators with an Interest in the Same Gene

PhenomeCentral: a Portal for Phenotypic and Genotypic Matchmaking of Patients with Rare Genetic Diseases

Facilitating collaboration in rare genetic disorders through effective matchmaking in DECIPHER

Innovative genomic collaboration using the GENESIS (GEM.app) platform

Cafe Variome: general-purpose software for making genotype-phenotype data discoverable in restricted or open access contexts

Participant-led matchmaking

GenomeConnect: matchmaking between patients, clinical laboratories and researchers to improve genomic knowledge

Use of Model Organism and Disease Databases to Support Matchmaking for Human Disease Gene Discovery

Data sharing in the Undiagnosed Disease Network

The Genomic Birthday Paradox: How Much is Enough?

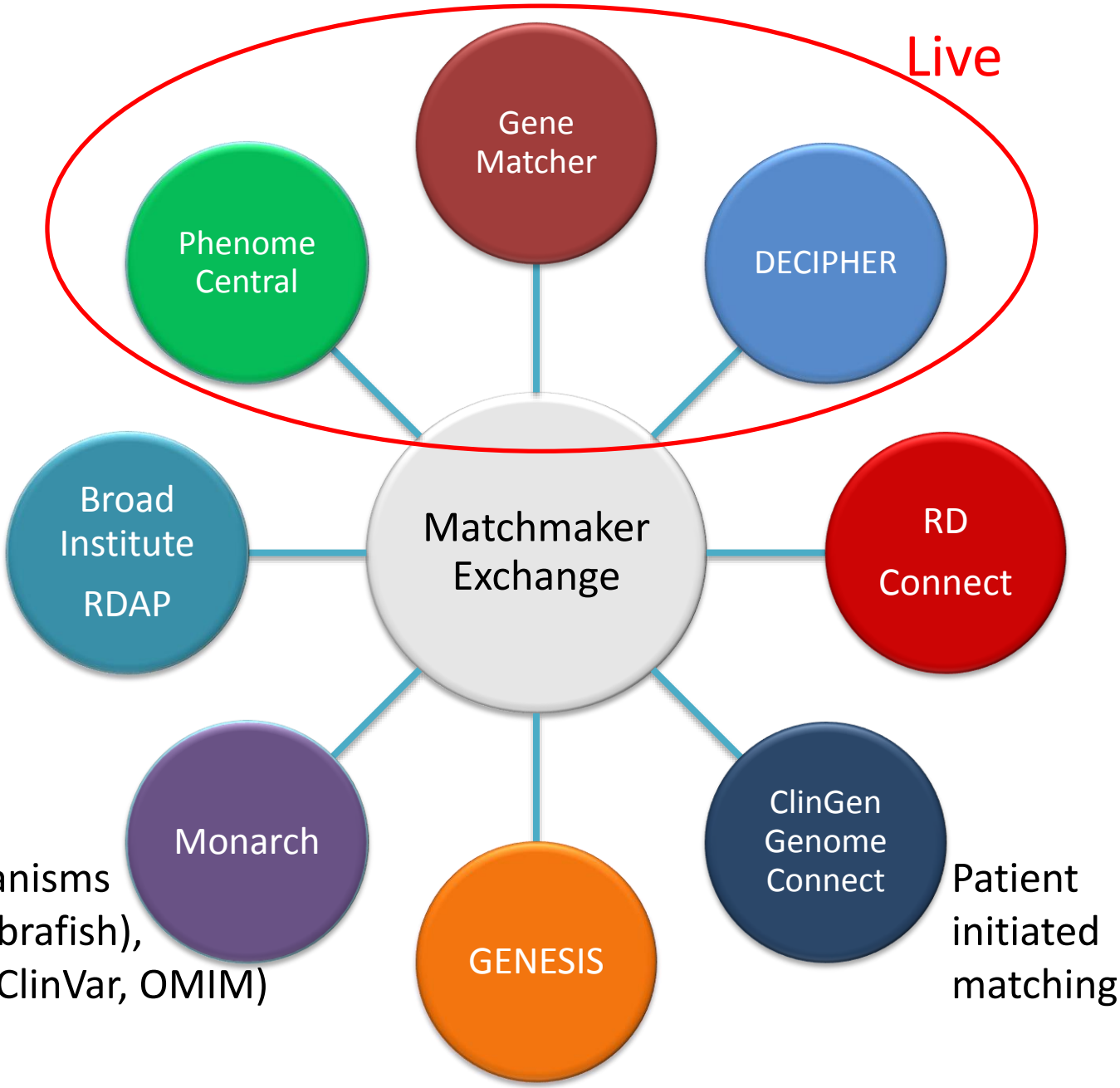
Quantifying and mitigating false-positive disease associations in rare disease matchmaking

Type II collagenopathy due to a novel variant (p.Gly207Arg) manifesting as a phenotype similar to progressive pseudorheumatoid dysplasia and spondyloepiphyseal dysplasia, Stanescu type

GeneMatcher aids in the identification of a new malformation syndrome with intellectual disability, unique facial dysmorphisms, and skeletal and connective tissue caused by de novo variants in HNRNPK

Matching two independent cohorts validates DPH1 as a gene responsible for autosomal recessive intellectual disability with short stature, craniofacial and ectodermal anomalies

Connected and Soon to be Connected Matchmakers



Model organisms (mouse, zebrafish), Orphanet, ClinVar, OMIM)

Patient initiated matching

Fifteenth Annual

Bio·IT World

CONFERENCE & EXPO '16

Enabling Technology. Leveraging Data. Transforming Medicine.

Track 2 - April 5– 7, 2016

Data Computing

Advances in Computing Application for Big Data

Wednesday, April 6

4:00 The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery

Anthony Philippakis, M.D., Ph.D., Chief Data Officer, Broad Institute

Track 10 - April 5 – 7, 2016

Clinical Genomics

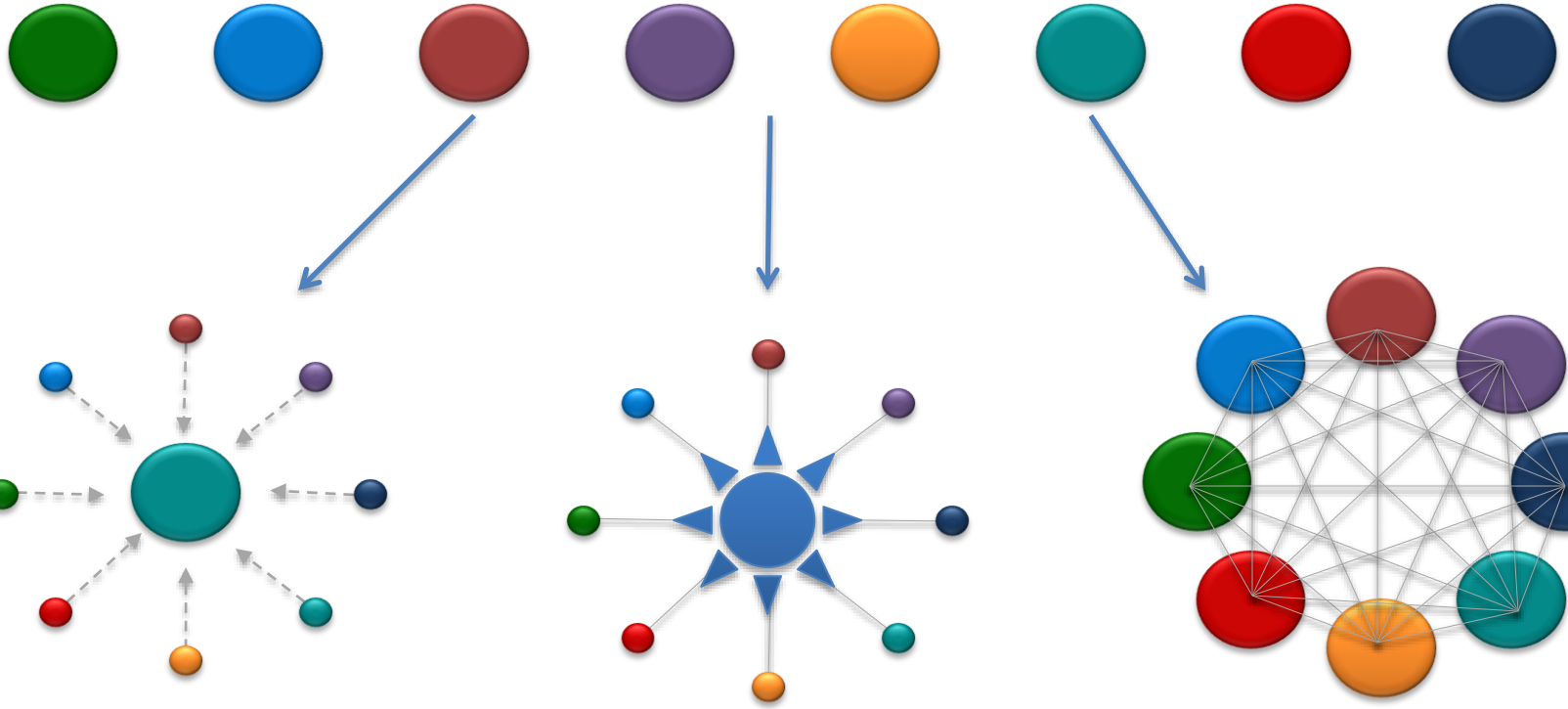
Determining Genomic Variation's Contribution to Disease

Wednesday, April 6

2:25 Connecting Rare Disease Patient Databases with the Matchmaker Exchange API

Orion Buske, Research Scientist, Department of Computer Science, University of Toronto; Genetics and Genome Biology Program, Hospital for Sick Children

Connecting Data in the Big Data World



Centralized Database

Everyone submits data to a single central database

Examples:
ClinVar,
dbGaP, EGA

Centralized Hub

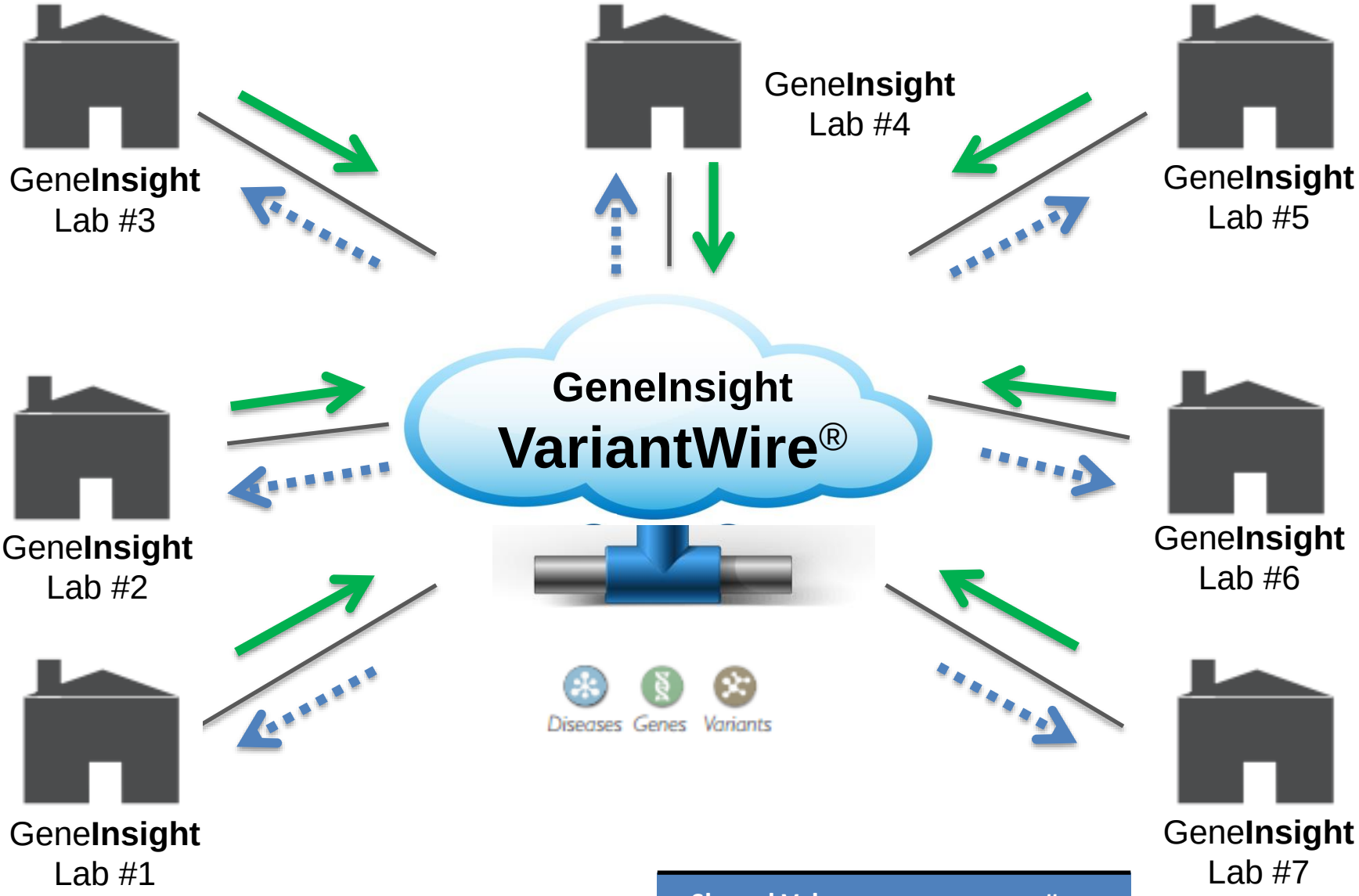
APIs connect each database to a central hub

Example:
Many commercial platforms

Federated Network

All databases connected through multiple APIs

Example:
Matchmaker Exchange

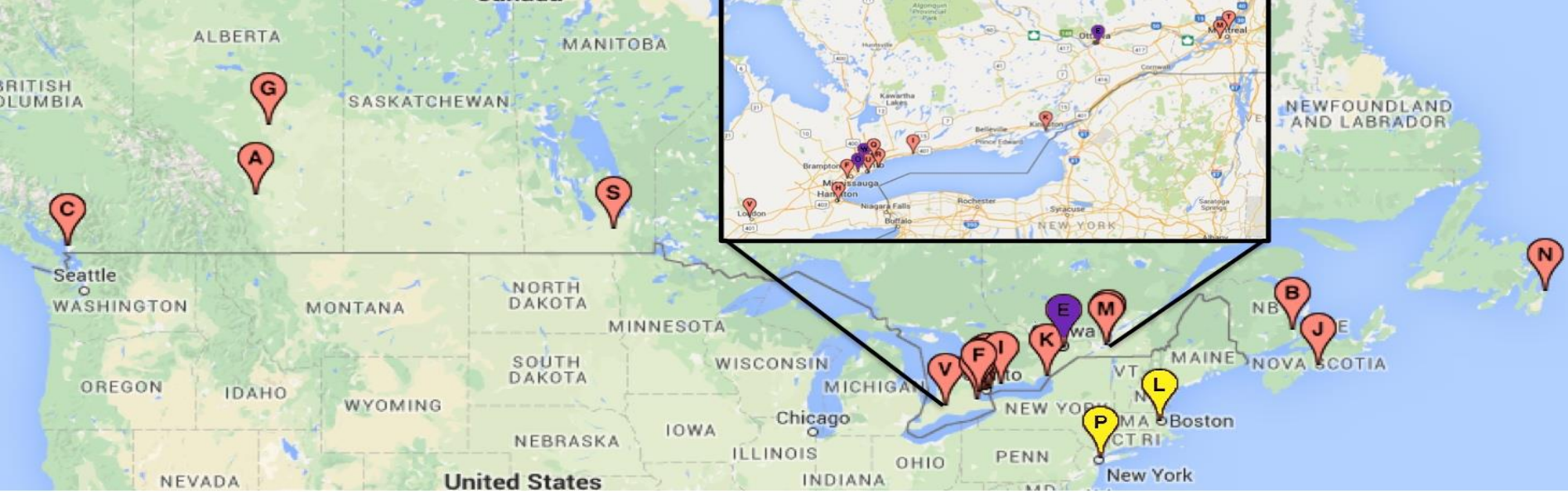


Clinically validated, de-identified, and approved data

Read-only viewing with ability to validate and import

Shared Values	#
Labs	7
Interpreted Variants	32,401
Genes	546
Diseases	235

GeneInsight® a sunquest company



A. Alberta Children's Hospita (Calgary, AB)
B. Atlantic Cancer Research Institute (Moncton, NB)*
C. British Columbia Cancer Agency (Vancouver BC)
D. Children's & Women's Health Centre of BC (Vancouver BC)*
E. Children's Hospital of Eastern Ontario (Ottawa ON)
F. Credit Valley Hospital, Trillium Health Centre (Mississauga ON)
G. Dept of Medical Genetics, University of Alberta (Edmonton, AB)
H. Hamilton Health Sciences, McMaster University (Hamilton, ON)
I. Impact Genetics Inc. (Bowmanville, ON)*
J. Izaak Walton Killam Health Centre (Halifax, NS)*
K. Kingston General Hospital, Queen's University (Kingston, ON)
L. Laboratory for Molecular Medicine (Cambridge, MA)
M. McGill University Health Complex (Montréal, QC)
N. Memorial Health University Medical Center (St. John's, NL)*
O. Mount Sinai Hospital, University of Toronto (Toronto, ON)
P. Mt. Sinai Genetic Testing Laboratory (New York City, NY)
Q. North York General Hospital (Toronto ON)
R. Ontario Institute of Cancer Research (OICR) (Toronto, ON)
S. Regional Health Authority, University of Manitoba (Winnipeg, MB)
T. Sainte-Justine Hospital, University of Montreal (Montréal, QC)*
U. SickKids Hospital and McLaughlin Centre (Toronto, ON)
V. University Hospital, Western University (London, ON)*
W. Women's College Hospital, University of Toronto (Toronto, ON)
X. Jewish General Hospital, Montreal (Montréal, QC)*

*Pending variant upload

COGR-only Site

VariantWire-only Site

COGR & VariantWire Site

COGR
Canadian Open Genetics Repository

Total Variants	Unique Variants	Genes	Diseases
17,266	12,890	1,266	66

Broad data sharing is becoming increasingly common and enabling increasing success in genomics.

But will everyone participate?

Stakeholder Roles to Support Data Sharing

- **Research organizations:** Work with journals to require data submission (variant interpretations at a minimum) to public databases as a requirement for publication
- **Lab accreditation organizations:** Require submission of variant interpretations at quality control for lab accreditation
- **Hospitals, clinics and providers:** Order tests from labs that share variant interpretations
- **Insurers:** Require variant interpretation submission for test reimbursement
- **FDA:** Consider tests from labs that do not share interpretations (and/or use proprietary algorithms not subject to peer review) to be considered higher risk and therefore subject to FDA test approval

Thank You!

Curating the Clinical Genome Conference

Wellcome Genome Campus, Hinxton

June 22-24, 2016

https://registration.hinxton.wellcome.ac.uk/events/item.aspx?e=581