Supporting Genomics in the Practice of Medicine

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Partners Healthcare Personalized Medicine
Department of Pathology, Brigham and Women's Hospital
Harvard Medical School
Broad Institute of MIT and Harvard

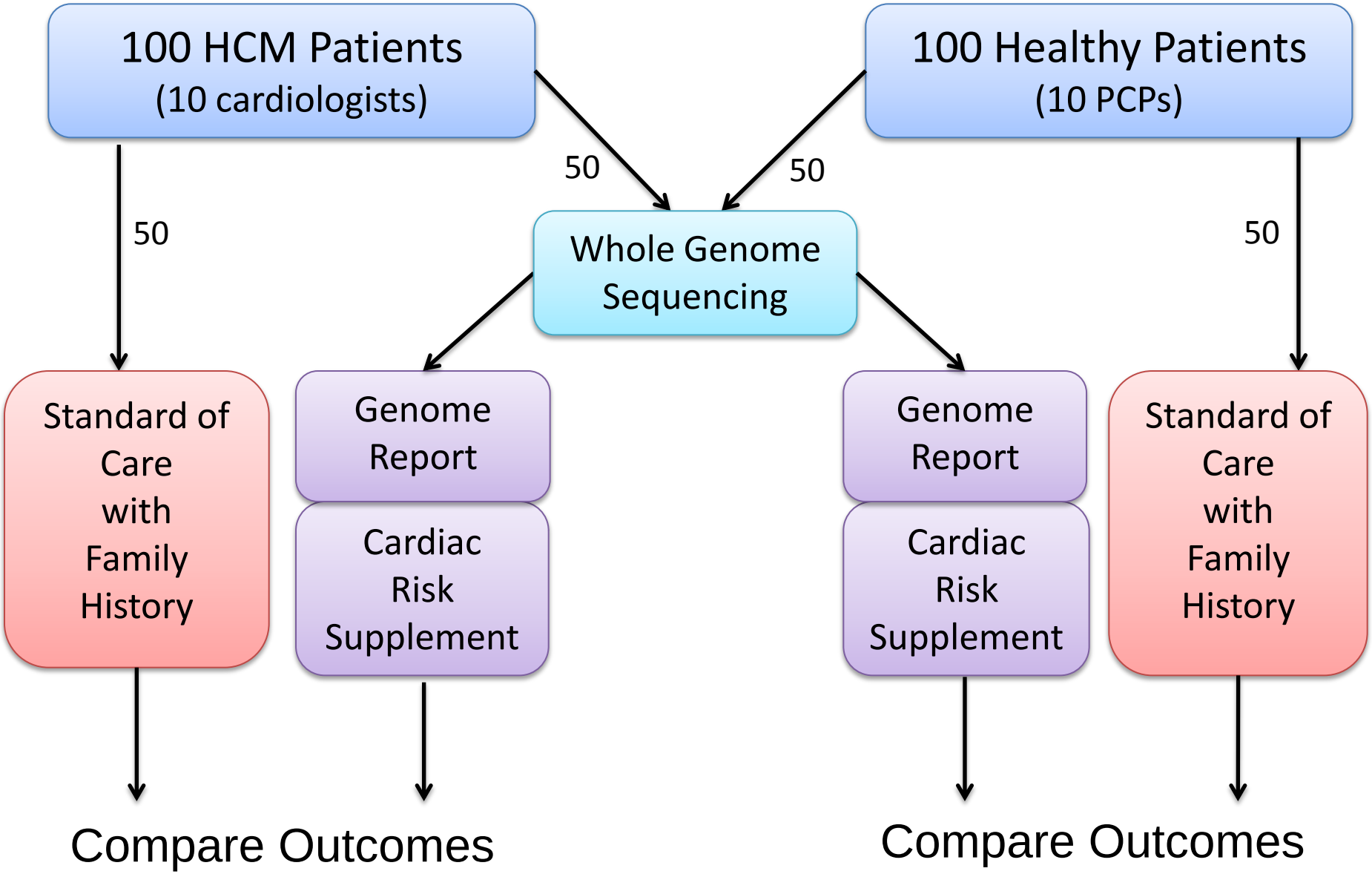
PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

BWH

HARVARD MEDICAL SCHOOL

BROAD INSTITUTE

MedSeq WGS Pilot Clinical Trial



The Genome Report

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http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Sex: Male
Race: Caucasian
Specimen: Peripheral Whole Blood
Received: 12/20/12
Referring physician: Dr. Martin Solomon
Referring facility: Brigham and Women's Hospital

GENERAL GENOME REPORT

Sequencing of this individual's genome was performed and covered 95.8% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to a 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 provided on subsequent pages.

RESULT SUMMARY

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	Classification
Chondrodysplasia punctata (X-linked)	Abnormal bone and cartilage development	ARSE c.410G>C p.Gly137Ala	Uncertain Significance: Favor Pathogenic

CARRIER RISK: 2 VARIANTS IDENTIFIED

This test identified carrier status for 2 autosomal recessive disorders.

Disease (Inheritance)	Phenotype	Gene Variant	Classification	Carrier Phenotype*
Methylmalonic aciduria and homocystinuria, cblC type (Autosomal recessive)	Disorder of cobalamin metabolism	MMACHC c.271dupA p.Arg91LysfsX14	Pathogenic	None reported
Leber congenital amaurosis (Autosomal recessive)	Retinal dystrophy and blindness	SPATA7 c.94+2T>C	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 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 mild phenotypes. Please see variant descriptions for more information

PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
Warfarin	Decreased dose requirement
Clopidogrel	Typical risk of bleeding and cardiovascular events
Digoxin	Increased serum concentration of digoxin
Metformin	Typical glycemic response to metformin
Simvastatin	Lower risk of simvastatin-related myopathy

BLOOD GROUPS

This test identified the ABO Rh blood type as B positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with 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

MONOGENIC DISEASE RISK

Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence	References (PMID)
Chondrodysplasia punctata (X-linked)	ARSE (NM_000047.2)	c.410G>C p.Gly137Ala Hemizygous (Uncertain Significance)	1/6728 European American	1:500,000	9863597 18348268 7720070 23470839

VARIANT INTERPRETATION: The Gly137Ala variant in ARSE has been previously identified in 2 individuals with chondrodysplasia punctata; however, this variant was also identified in one unaffected family member (Sheffield 1998, Nino 2008). Variants in a paralogous gene (ARSB) at the same position have also been identified in an individual with Maroteux-Lamy syndrome, which also features skeletal abnormalities (Franco 1995). Functional studies indicate that the Gly137Ala variant leads to reduced ARSE activity (Matos-Miranda 2013). In summary, although some data support a disease-causing role, there is currently insufficient evidence for pathogenicity leading to a current classification of uncertain significance.

DISEASE INFORMATION: X-linked chondrodysplasia punctata 1 (CDPX1), a congenital disorder of bone and cartilage development, is caused by a deficiency of the Golgi enzyme arylsulfatase E (ARSE). It is characterized by chondrodysplasia punctata (stippled epiphyses), brachytelephalangy (shortening of the distal phalanges), and nasomaxillary hypoplasia. Although most affected males have minimal morbidity and skeletal findings that improve by adulthood, some have significant medical problems including respiratory compromise, cervical spine stenosis and instability, mixed conductive and sensorineural hearing loss, and abnormal cognitive development. From GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1544/

FAMILIAL RISK: Chondrodysplasia punctata is typically inherited in an X-linked recessive manner, with primarily males being affected. Each child is at a 50% (or 1 in 2) chance of inheriting the variant from a carrier female, while all daughters will inherit the variant from an affected male.

CARRIER RISK

Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence (Carrier Freq.)	References (PMID)	Carrier Phenotype
Methylmalonic aciduria and homocystinuria, cblC type (Autosomal recessive)	MMACHC (NM_015506.2)	c.271dupA p.Arg91LysfsX14 (Pathogenic)	14/8068 European American	Unknown (Unknown)	16311595 19760748 20631720	None reported

VARIANT INTERPRETATION: The Arg91LysfsX14 variant in MMACHC has been identified in homozygosity in 81 individuals and in compound heterozygosity in 86 individuals with methylmalonic aciduria and homocystinuria, cblC type (Lerner-Ellis 2006, Richard 2009, Liu 2010). This frameshift variant is predicted to alter the protein's amino acid sequence beginning at position 91 and lead to a premature termination codon 14 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein. In summary, this variant meets our criteria for pathogenicity.

DISEASE INFORMATION: The clinical manifestations of disorders of intracellular cobalamin metabolism can be highly variable. The age of initial presentation of cblC ranges from (1) newborns who can be small for gestational age (SGA) and have microcephaly; to (2) infants who can have poor feeding, failure to thrive, pallor, and neurologic signs, and occasionally hemolytic uremic syndrome (HUS) and/or seizures including infantile spasms; to (3) toddlers who can have failure to thrive, poor head growth, cytopenias (including megaloblastic anemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures; and to (4) young adults/adults who can have confusion, other mental status changes, cognitive decline, and megaloblastic anemia. From GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1328/

FAMILIAL RISK: Disorders of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. A carrier of methylmalonic aciduria and homocystinuria, cblC type has a 50% chance of passing on the MMACHC variant to any of his/her children. The risk of this patient's child having methylmalonic aciduria and homocystinuria, cblC type is dependent on the MMACHC carrier status of the patient's partner. This patient likely inherited the MMACHC variant from one of his parents. Other biologically related family members may also be carriers of this variant.

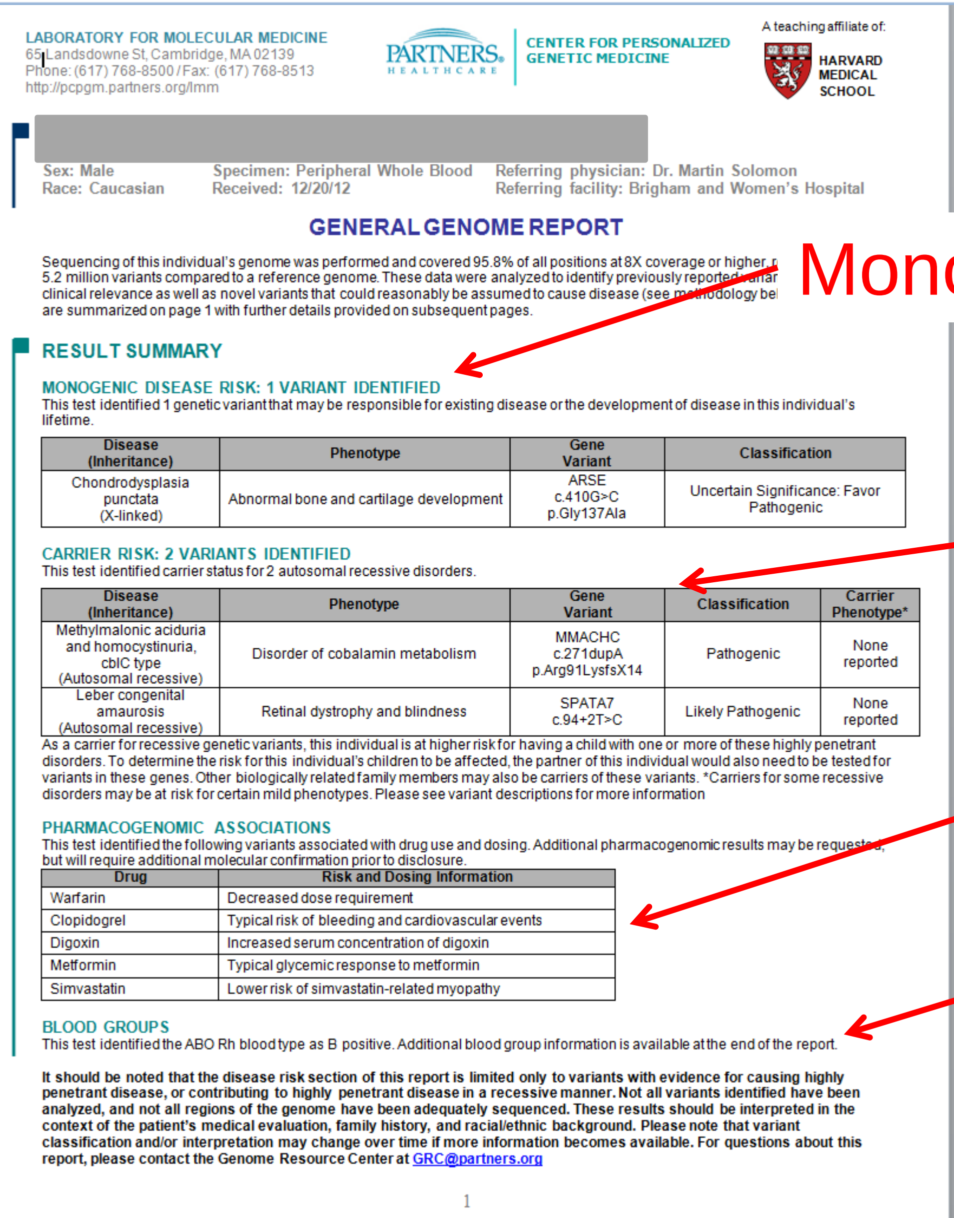
Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence (Carrier Freq.)	References (PMID)	Carrier Phenotype
Leber congenital amaurosis (Autosomal recessive)	SPATA7 (NM_018418.4)	c.94+2T>C (Likely Pathogenic)	Not previously reported	2-3/100,000 (Unknown)	N/A	None reported

VARIANT INTERPRETATION: The 94+2T>C variant in SPATA7 has not been previously reported. This variant is located in the 5' splice region. Computational tools suggest this variant may lead to activation of a cryptic splice site, resulting in a frameshift. Computational tools do suggest an impact to splicing. However, this predictive information, in the absence of functional data, is not enough to conclude pathogenicity but does suggest the variant is likely pathogenic.

DISEASE INFORMATION: Leber congenital amaurosis, a severe dystrophy of the retina, typically becomes evident in the first year of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia, and keratoconus. From GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1298/

FAMILIAL RISK: Leber congenital amaurosis is typically inherited in an autosomal recessive manner. A carrier of Leber congenital amaurosis has a 50% chance of passing on the SPATA7 variant to any of his/her children. The risk of this patient's child having Leber congenital amaurosis is dependent on the SPATA7 carrier status of the patient's partner. This patient likely inherited the SPATA7 variant from one of his parents. Other biologically related family members may also be carriers of this variant.

The Genome Report



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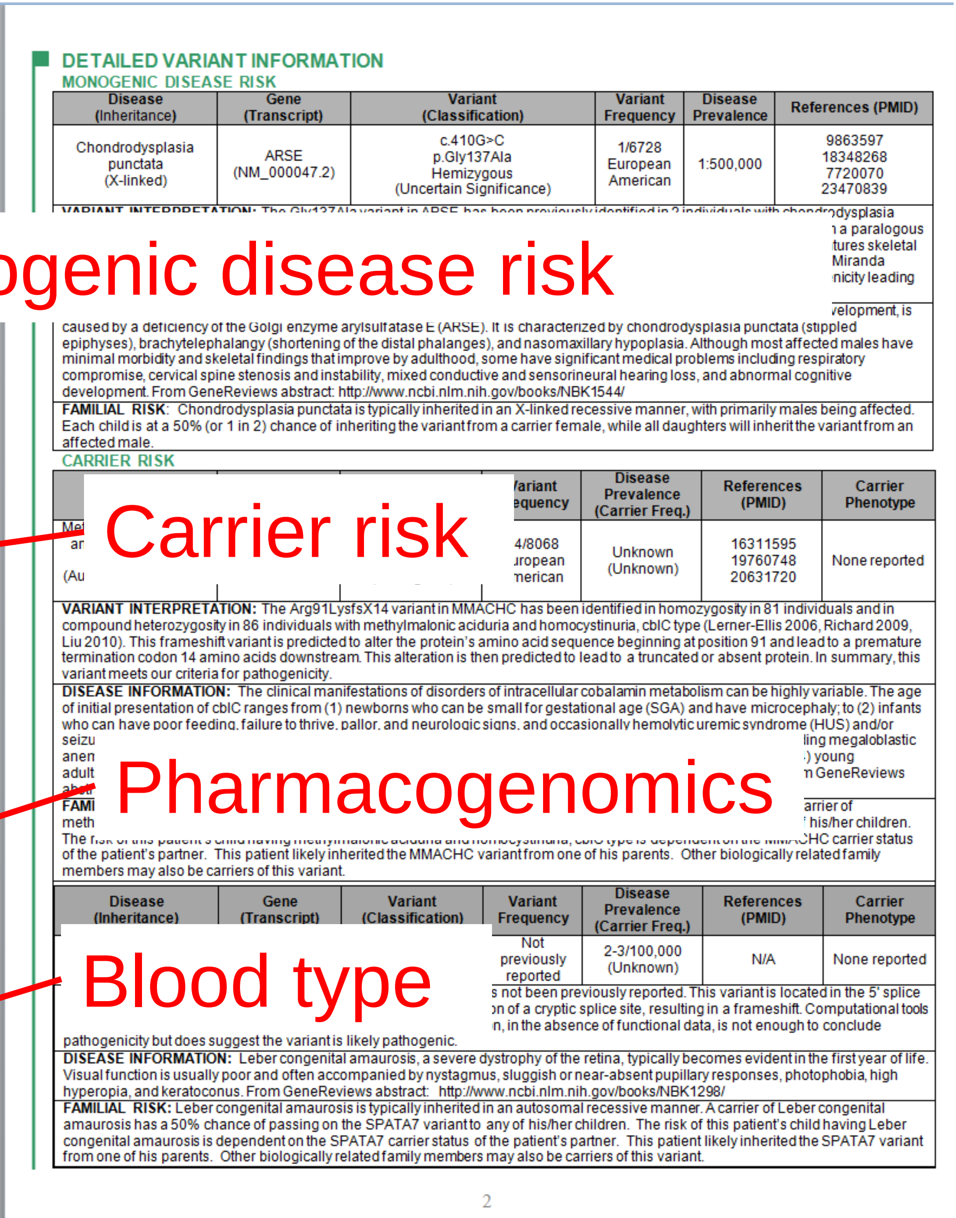

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Monogenic disease risk

Carrier risk

Pharmacogenomics

Blood type

Reported findings from analysis of variants in ~4600 genes

	Mendelian Disease Risk IFs	Carrier Status IFs	Diagnostic Findings in the Cardiology Cohort
# of patients	11 / 53 (21%)*	50 / 53 (94%)	12 / 24 (50%)
Mean reported variants per patient	.21	2.3	0.58
Range of reported variants per patient	0-1	0-6	0-2

*2/53 (4%) from ACMG list

MedSeq™

Can Primary Care Physicians Understand Genomic Reports?

MedSeq™

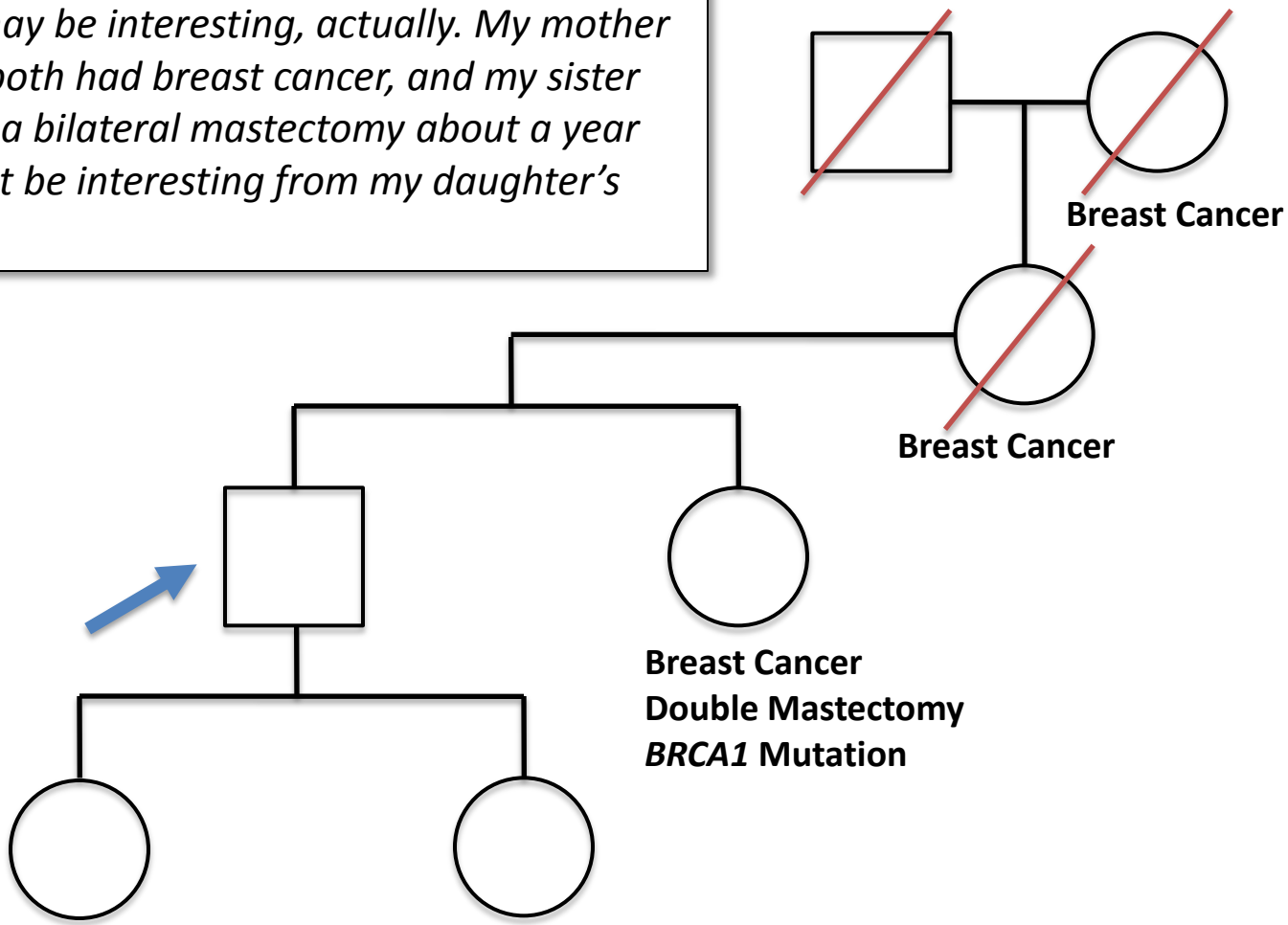
Case #1
PCP Interpretation of Genomic Results

- Context: Physicians have 6 hours of genetic/genomic training at start of study (2 hours didactic; 4 hours case modules; receive CME credit)
- MedSeq Genome reports are delivered without explanation by laboratory or medical geneticist
- Physicians can contact a Genetic Resource Center for assistance at any point
- Physician disclosures are recorded and reviewed by the study team

Incidental "Negative" Finding

PCP asked what type of information the patient thought he might learn through sequencing:

"Only one thing that may be interesting, actually. My mother and my grandmother both had breast cancer, and my sister had breast cancer and a bilateral mastectomy about a year ago. And so, that might be interesting from my daughter's point of view."



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Name: [redacted]
DOB: [redacted]
Sex: Male
Race: Caucasian

Accession ID: PM13-00410
Specimen: P
Received: 02

MRN: [redacted]
Family #: [redacted]

Patient: "I didn't have anything monogenic, which I thought was the main thing I would look for."

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A. MONOGENIC DISEASE RISK: 0 VARIANTS IDENTIFIED

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

B. CARRIER RISK: 1 VARIANT IDENTIFIED

This test identified carrier status for 1 autosomal recessive disorder.

Disease (Inheritance)	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Hypothyroidism (Autosomal recessive)	Underactive thyroid	DUOX2 c.3847+2T>C	Pathogenic	NA

As a carrier for a recessive genetic variant, this individual is at higher risk for having a child with this highly penetrant disorder. To determine the risk for this individual's 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 mild phenotypes. Please see variant descriptions for more information.

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Drug	Risk and Dosing Information
C1. Warfarin	Increased dose requirement

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Name: [redacted] **MRN:** [redacted]
DOB: [redacted] **Accession ID: PM13-00410** **Family #:** [redacted]
Sex: Male **Specimen: P**
Race: Caucasian **Received: 02**

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B1. Hypothyro (Autosomal rec				

As a carrier for a r
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PCP: "Don't assume that *BRCA 1* and *2* were checked here … Don't assume it … I would not make any assumptions whatsoever that this covered that."

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C1. Warfarin	Increased dose requirement

Why was the PCP Correct?

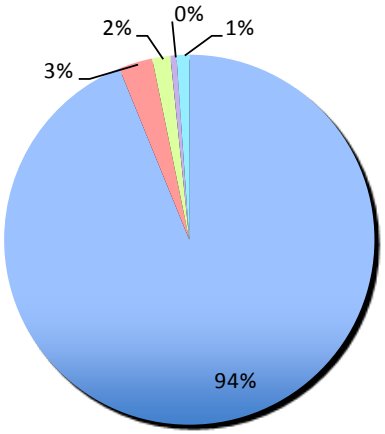
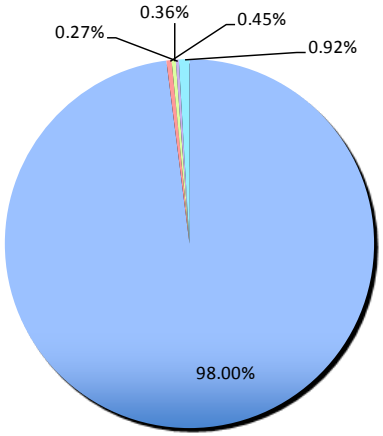
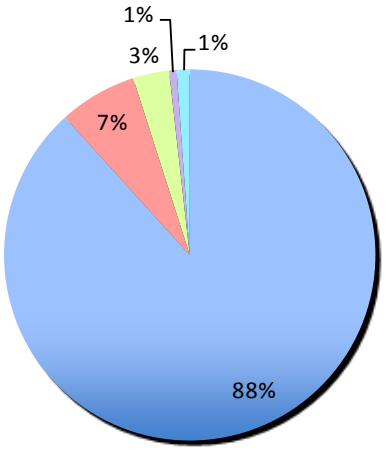
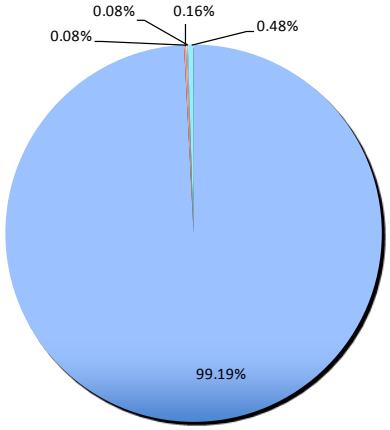
You can’t assume BRCA1 was fully analyzed (sequencing and CNV analysis).

You can’t assume all variants were interpreted from BRCA1.

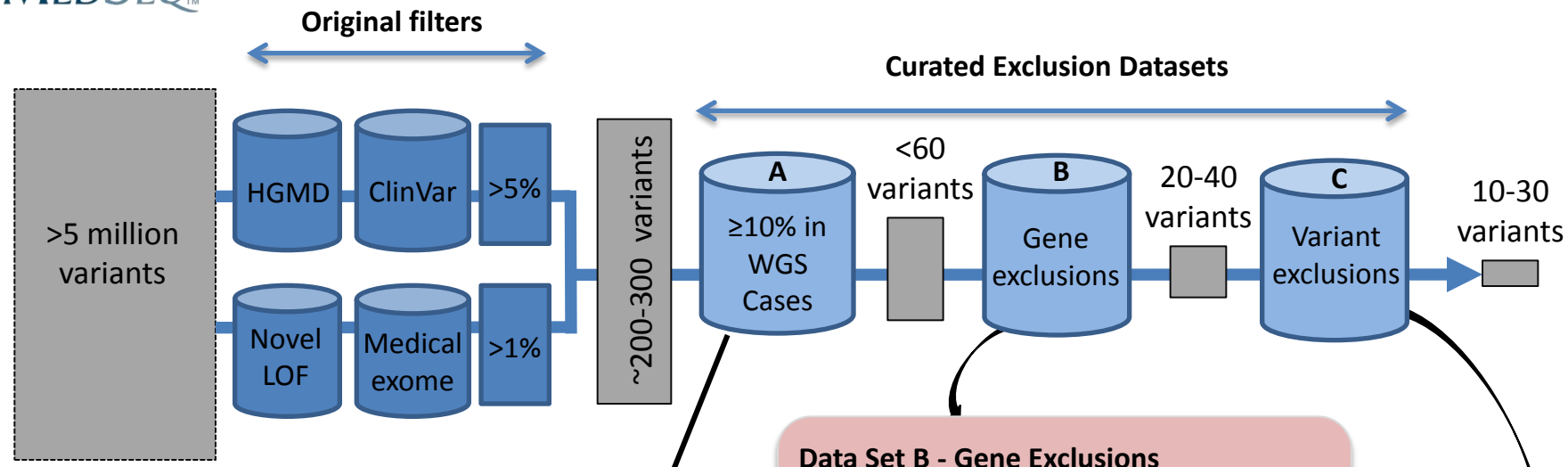
MedSeq™

Birgit Funke

Improved Coverage with Medical Exome Enhancement

	ICE Exome (~200x)	Agilent v5-PLUS (~200x) *HISEQ 2500 rapid ; 4 samples/lane*
Medical Exome 4,631 genes 10.7 Mb fully covered exons (100% ≥ 20x)	 94%	 98%
Pan Cardio Pnl 51 genes 262 kb fully covered exons (100% ≥ 20x)	 88%	 99%

MedSeq Genome Filtering Approach



Data Set A ≥ 10% MAF WGS Cases

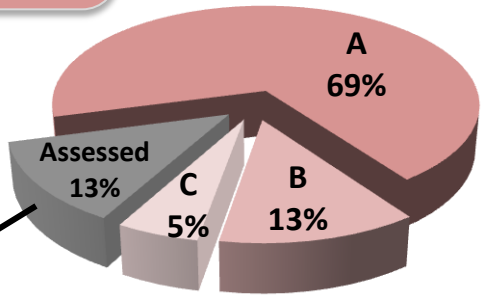
- Excludes common technical FPs
- Common indels wrong nomenclature
- Exceptions FV, HFE, SERPINA1

Data Set B - Gene Exclusions

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

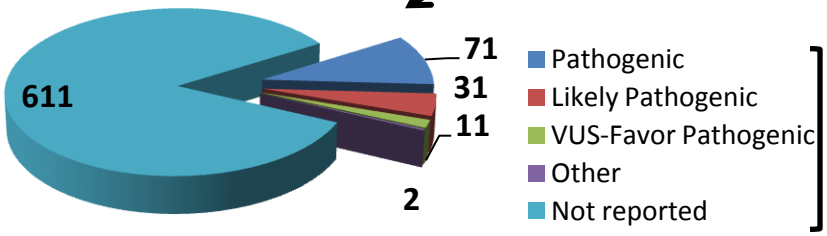
Data Set C - Variant Exclusions

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



Not reported variants: 82%

- VUS, Likely Benign, Benign
- False positive variants

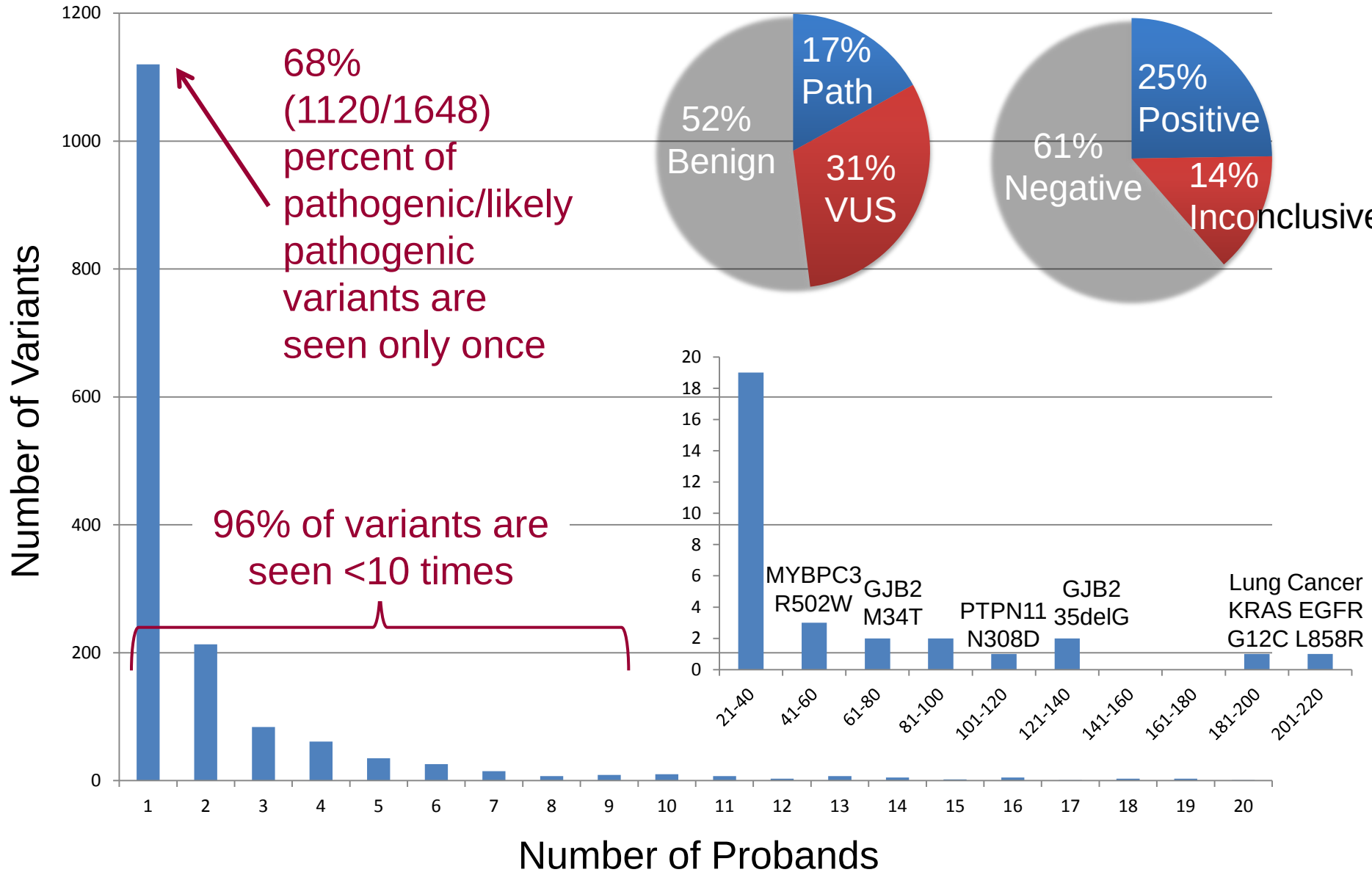


Reported variants: 18%

The development of curated exclusion datasets after 50 cases dramatically reduced variant review

Histogram of Pathogenic Variants from Diagnostic Testing of 15,000 Probands

(cardiomyopathy, hearing loss, rasopathies, aortopathies, somatic and hereditary cancer pulmonary disorders, skin disorders, other genetic syndromes)



To improve our knowledge of DNA variation will require a massive effort in data sharing

ClinVar vs. ClinGen?

- ClinVar is a database
- ClinGen includes both ClinVar as well as other projects, all funded by NIH

Key Participants:

NCBI ClinVar	**U41 Grant - Partners/ Geisinger/UCSF**	**U01 Grant - UNC/ ACMG/Geisinger**	**U01 Grant - Stanford/Baylor**	**NIH Program**
Melissa Landrum Donna Maglott Steve Sherry	David Ledbetter Christa Martin Bob Nussbaum Heidi Rehm	Jonathan Berg Jim Evans David Ledbetter Mike Watson	Carlos Bustamante Sharon Plon	Erin Ramos Lisa Brooks Danuta Krotoski Sheri Schully

Goals of ClinGen

- **Share genomic and phenotypic data through *centralized databases* for clinical and research use**
- ***Standardize* clinical annotation and interpretation of variants**
- **Develop *machine-learning approaches* to improve the throughput of variant interpretation**
- **Implement *evidence-based expert consensus* for curating genes and variants**
- **Assess the *medical actionability* of genes and variants to supporting their use in *clinical care systems***
- ***Disseminate* the collective knowledge/resources**

ClinGen Website: www.clinicalgenome.org

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Clinical Genome Resource

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ClinGen / About / Supporters

ClinGen has over 352 Supporters

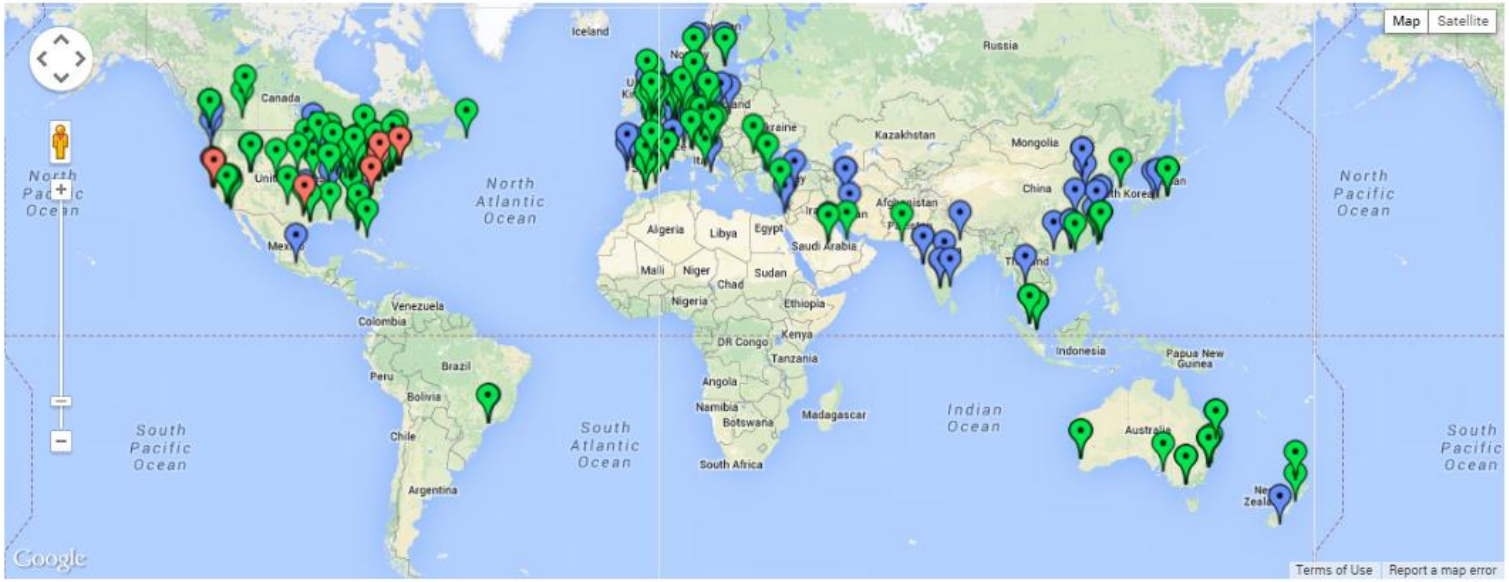
We are proud of our international support by institutions, corporations, & hospitals.

How to participate

ClinVar Submitters

43% TO FIRST TARGET GOAL 200000 Variants

Over 85000 variants with clinical assertions have been shared by ClinGen supporters.



Supporter | Submitter | PI Institutions

- 1000 Genomes
- ACL Laboratories
- Aga Khan University Hospitals
- Abituv Lab: University of California San Francisco
- Academic Unit of Haematology
- Affymetrix
- Agilent Technologies
- Alberta Children's Hospital

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Data Sharing

ClinVar

ClinVar, a publicly available database hosted by the National Center for Biotechnology Information (NCBI) aggregates information about sequence variation and its relationship to human health. Click here to learn more about the database and how to use it.

more »

Data Submission Toolkit

Interested in submitting data? Click here for the information and resources you need to get started, including sample IRB templates.

more »

Phenotype Data Submission

ClinGen encourages the responsible sharing of phenotypic data from laboratories and clinicians. Learn more about resources available to facilitate the collection of phenotype data in structured formats.

Sharing Clinical Reports Project (SCRP)

SCRP is a grass-roots effort to encourage open sharing of variant information, particularly variants within BRCA1 and BRCA2.

more »

GenomeConnect

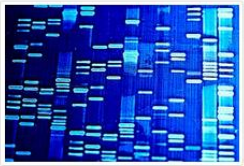
GenomeConnect

GenomeConnect is the ClinGen Patient Portal, allowing patients to share their own phenotype and genotype information. Click here to learn more.

more »

Knowledge Curation

ClinGen is currently developing a curation infrastructure to annotate and interpret the strength of gene-disease relationships and the degree of variant pathogenicity. Core groups work closely to develop standardized methods and procedures that can be implemented by ClinGen groups within the clinical domain and, eventually, the clinical genetics community. Learn more about our various curation efforts.



Gene Curation

The Gene Curation Working Group is tasked with assessing the clinical validity of purported gene-condition pairs. Learn more about their process here.

more »

Actionability

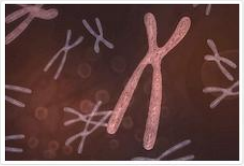
The Actionability Working Group is tasked with assessing the clinical actionability of gene-condition pairs. Click here to learn more about their framework and scoring process.

more »

Sequence Variant Curation

The Sequence Variant Working Group is tasked with resolving conflicts amongst submitted sequence variant data and piloting disease-specific curation projects. To learn more about their efforts and how YOU can participate in the pilot projects, click here.

more »



Structural Variation Curation

The Structural Variant Working Group is tasked with resolving conflicts amongst submitted structural variant data, as well as evaluating genes and genomic regions for dosage sensitivity. To learn more about their efforts and access tools related to structural variant data analysis, click here.

more »

Support

ns, corporations, & h

Iceland

North Atlantic Ocean

Aga Khan University Hospitals

Affymetrix

Agilent Technologies

Alberta Children's Hospital

ClinVar Variant View

NCBI Resources How To Sign in to NCBI

ClinVar ClinVar Search ClinVar for gene symbols, HGVS expressions, conditions, and more Search

Advanced Help

Home | About | Data use and maintenance | Using the website | How to submit | Statistics | FTP site

NM_000059.3(BRCA2):c.10087A>G (p.Ile3363Val)

NM_000059.3(BRCA2):c.10087A>G (p.Ile3363Val) Go to:

Variant type:	single nucleotide variant
Cytogenetic location:	13q13.1
Genomic location:	Chr13:32398600 (on Assembly GRCh38) Chr13:32972737 (on Assembly GRCh37)
Protein change:	I3363V
HGVS:	NG_012772.3:g.88121A>G NM_000059.3:c.10087A>G NC_000013.11:g.32398600A>G ...more
Molecular consequence:	NM_000059.3:c.10087A>G: missense variant [Sequence Ontology SO:0001583]

Clinical significance

NM_000059.3(BRCA2):c.10087A>G (p.Ile3363Val) Help

Clinical significance:	conflicting data from submitters Likely benign(1);Uncertain significance(1)
Review status:	★ ★ ★ ★ (0/4)
Number of submission(s):	2

Condition(s)

Familial cancer of breast [MedGen - OMIM]

Neoplastic Syndromes, Hereditary [MedGen]

See supporting ClinVar records

1 Affected Gene

breast cancer 2, early onset (BRCA2) [Gene - OMIM - Variation viewer]

Haploinsufficiency - *Sufficient evidence for dosage pathogenicity* (Jul 6, 2012)

Triplosensitivity - *No evidence available* (Jul 6, 2012)

Search ClinVar for variants within BRCA2

Assertion and evidence details Go to:

Clinical Assertions | Evidence

Help

Germline

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter (Last submitted)	Submission accession
Likely benign	classified by single submitter (clinical testing)	clinical testing	Familial cancer of breast [MedGen | OMIM]	germline		GeneDx (Nov 8, 2013)	SCV000108593
Uncertain significance (Feb 20, 2014)	classified by single submitter (clinical testing)	clinical testing	Neoplastic Syndromes, Hereditary [MedGen]	germline		Ambry Genetics (Jul 25, 2014)	SCV000187150

Data Flows in ClinGen

(>200 ClinVar submitters)

Sharing Clinical Reports Project

Genome Connect and Free-the-Data

Researchers

Clinical Labs

Expert Groups

Clinics

Patients

Unpublished or Literature Citations

Patient Registries

Case-level Data

ClinVar

Variant-level Data

Linked Databases

OMIM

CFTR2

BIC

InSiGHT

PharmGKB

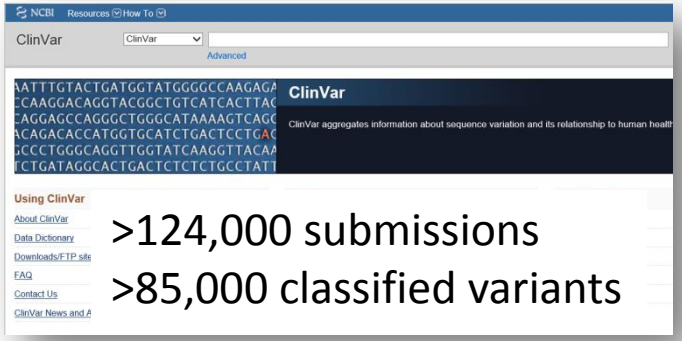
Data

Expert Curated Variants

ClinGenDB

Curation Interface

ClinVar Review Status



>124,000 submissions

>85,000 classified variants

www.genomeconnect.org

GenomeConnect
The ClinGen Patient Portal

How do genes affect health?

YOU have the information that can help scientists answer this question.

Share your genetic and health information with **GenomeConnect** to help us make these connections!

CONNECTING IS EASY:

- Sign up at genomeconnect.org for your personal portal account.
- Fill out your health history survey.
- Upload your genetic testing report(s).
- Share your information with researchers, clinicians, families, and more!

- Collect patient-entered phenotypic information and genetic testing reports through PatientCrossroads registry platform
- Transfer associated phenotypic and genotypic data into ClinGen-hosted database
- Connect participants with other families/individuals with same genetic variant(s) and researchers

ClinVar Submitters

Submitter	Variants with Assertions	Genes
Clinical Laboratories		
Partners Healthcare	6996	177
GeneDx	6624	573
Emory Genetics Laboratory; Emory University	5192	536
Ambry Genetics	4150	47
Genetic Services Laboratory; University of Chicago	3687	481
Sharing Clinical Reports Project	2049	2
ARUP Laboratories	1417	7
LabCorp	1391	140
InVitae	1102	35
Unité Médicale des Maladies Autoinflammatoires, France	637	10
McGill University Health Center (DeBelle Laboratory for Biochemical Genetics)	544	1
University of Washington Collagen Diagnostic Laboratory	411	1
GenMed Metabolism Lab	317	1
Blueprint Genetics	123	56
Counsyl	112	2
University of Pennsylvania School of Medicine	68	1
Pathway Genomics	16	2
Baylor College of Medicine, Molecular Genetics Laboratory	15	9
	34851	
Expert Consortia and Professional Organizations		
International Standards For Cytogenomic Arrays Consortium	14519	17705
InSiGHT	2362	8
CFTR2	133	1
American College of Medical Genetics and Genomics (ACMG)	23	1
	17037	

ClinVar Submitters

Submitter	Variants with Assertions	Genes
Aggregate Databases		
OMIM	24727	3538
GeneReviews	3939	447
	28666	
Locus-Specific Databases and Research Laboratories		
Breast Cancer Information Core (BIC)	3734	2
Cardiovascular Biomedical Research Unit (Royal Brompton & Harefield NHS Foundation Trust)	1346	10
Juha Muilu Group; Institute for Molecular Medicine Finland (FIMM)	840	39
ClinSeq Project	425	35
Lifton Laboratory	295	278
PALB2 database	242	2
Martin Pollak (Beth Israel Deaconess Medical Center, Dept. of Nephrology)	234	39
Kyoto University Department of Ophthalmology and Visual Sciences	171	59
Northcott Neuroscience Laboratory ANZAC Research Institute	37	15
Genomic Research Center	37	11
Demyelinating Disease Laboratories; VA Medical Center and University of Tennessee	26	1
Undiagnosed Disease Lab	15	12
	7402	

http://www.ncbi.nlm.nih.gov/clinvar/submitters/

Global Alliance
for Genomics & Health

Key Project:

BRCA Challenge

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)
Fergus Couch, Mayo Clinic (United States)
Johan den Dunnen, Leiden University Medical Center (Netherlands)
Susan Domchek, University of Pennsylvania (United States)
Douglas Easton, University of Cambridge (United Kingdom)
William Foulkes, McGill University (Canada)
Judy Garber, Dana Farber Cancer Institute (United States)
David Golgar, Huntsman Cancer Center (United States)
Robert Nussbaum, University of California, San Francisco (United States)
Ken Offit, Memorial Sloan Kettering Cancer Center (United States)
Sharon Plon, Baylor College of Medicine (United States)
Nazneen Rahman, Institute of Cancer Research (United Kingdom)
Heidi Rehm, Harvard Medical School (United States)
Mark Robson, Memorial Sloan Kettering Cancer Center (United States)
Wendy Rubinstein, National Institute of Health (United States)
Amanda Spurdle, QIMR Berghofer Medical Research Institute (Australia)
Dominique Stoppa-Lyonnet, Curie Institute (France)
Sean Tavtigian, University of Utah (United States)

Global Alliance
for Genomics & Health

Goals of the Challenge

MISSION: To improve the care of patients at risk of monogenic disease using, as an exemplar, global data sharing and collaboration in the analysis of *BRCA1* and *BRCA2*

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

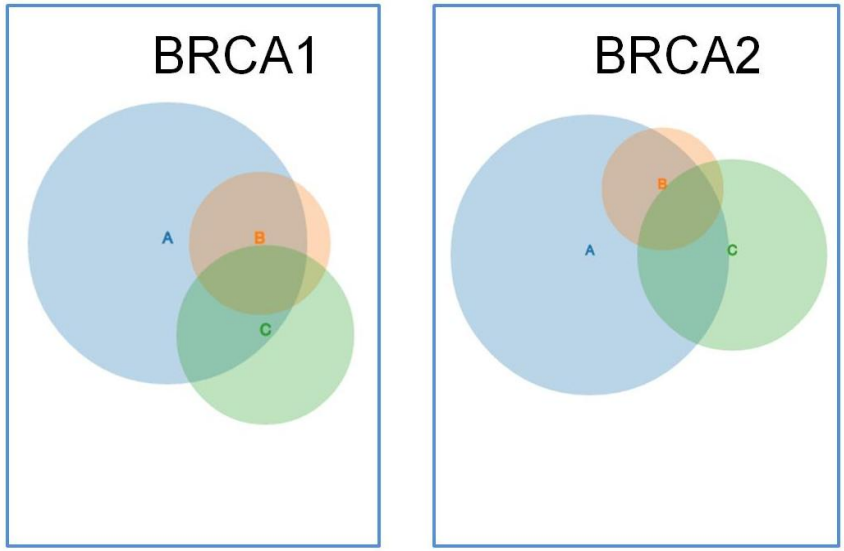
Public BRCA1/2 Variants

ClinVar: 6431 variants

Breast Cancer Information Core (BIC)	3793
Sharing Clinical Reports Project (SCRP)	2148
Invitae	4220
Ambry Genetics	1318
GeneDx	286
Counsyl	112
OMIM	81

LOVD: 3262 variants

UMD (France): 3913 variants

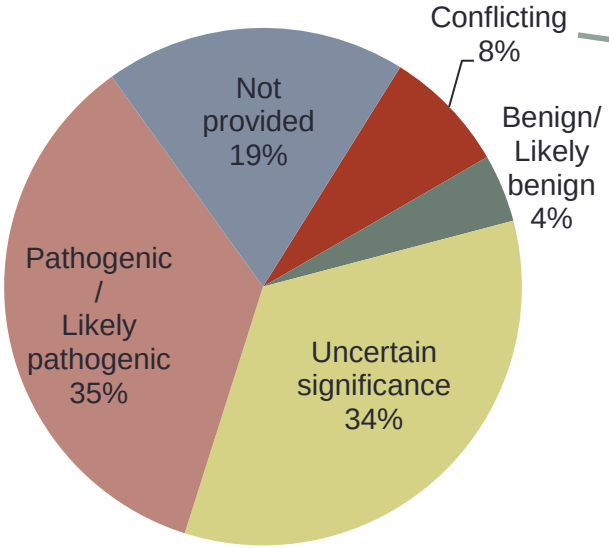


A=ClinVar B=LOVD C=UMD

LSDB Updates

Courtesy of Xin Feng

BRCA1 and BRCA2 Variants in ClinVar



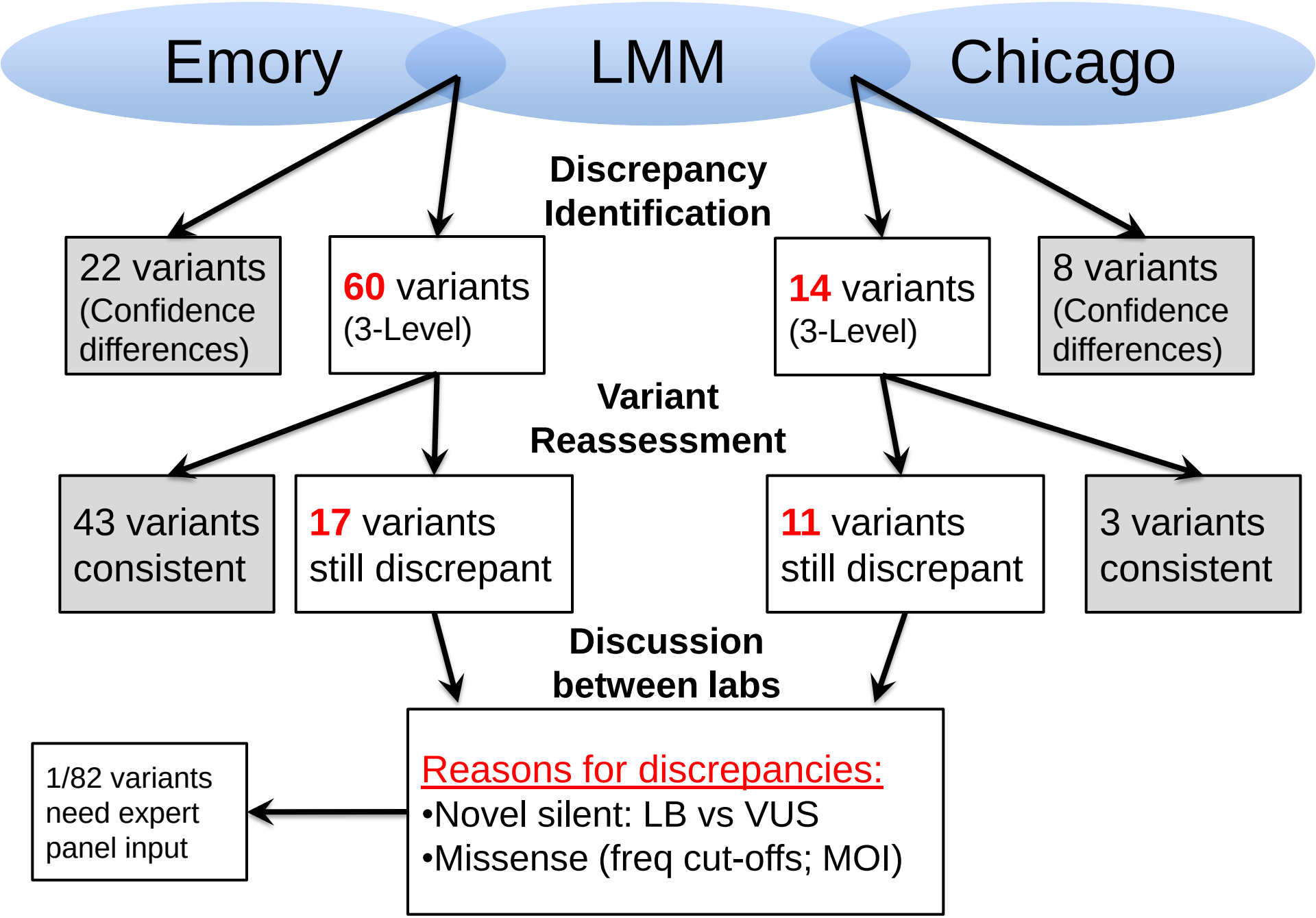
BRCA1/2 Conflicts	
P/LP vs B/LB	5
P/LP vs. VUS	59
VUS vs. B/LB	395

BRCA1/2 Variants in ClinVar	
Conflicting interpretations	465
Benign/Likely benign	254
Uncertain significance	2035
Pathogenic/likely pathogenic	2105
Not provided	1127
Total	**5986**

11,958 Submissions:

Invitae	4220
Breast Cancer Information Core (BIC)	3793
Sharing Clinical Reports Project (SCRP)	2148
Ambry Genetics	1318
GeneDx	286
Counsyl	112
OMIM	81

Data from ClinVar August 7, 2014


Emory
LMM
Chicago
Discrepancy Identification
22 variants (Confidence differences)
60 variants (3-Level)
14 variants (3-Level)
8 variants (Confidence differences)
Variant Reassessment
43 variants consistent
17 variants still discrepant
11 variants still discrepant
3 variants consistent
Discussion between labs
Reasons for discrepancies:
•Novel silent: LB vs VUS
•Missense (freq cut-offs; MOI)
1/82 variants need expert panel input

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF frequency is too high for disorder **OR** observation in controls inconsistent with disease penetrance[6]			Absent in 1000G and EVS	Prevalen affecteds increase controls	
Computational Data		Multiple lines of computational evidence suggest no impact on gene /gene product[9] Type of variant does not fit known mechanism of disease	Multiple lines of computational evidence support a deleterious effect on the gene /gene product [9]	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before[2] In-frame indels in a non-repeat region Stop-loss variants[12]	Same an change a establish pathoge	
Functional Data	Well-established functional studies show no deleterious effect[4]	In-frame indels in a repetitive region without a known function[7]	Missense in gene with low rate of benign missense variation and pathogenic missenses common	Located in a mutational hot spot and/or known functional domain[7]	Well-est function show a c effect [4]	
Segregation Data	Non-segregation with disease[5]		Co-segregation with disease in multiple affected	Co-segregation with disease in multiple affecteds in multiple families[5]		
De novo Data				*De novo* (without paternity & maternity confirmed)[3]	*De novo* maternit	
Allelic Data				For recessive disorders, detected in *trans* with a pathogenic variant[11]		
Other Database						
Other Data						
		an alternate cause	or FH matches gene			

Pathogenic
1 Very Strong *AND*
1 Strong *OR*
≥2 (Moderate *OR* Supporting)
2 Strong
1 Strong *AND*
≥3 Moderate *OR*
≥2 Moderate and 2 Supporting *OR*
≥1 Moderate and 4 Supporting

Likely Pathogenic
1 Very strong or Strong *AND*
≥1 Moderate *OR*
≥2 Supporting
≥3 Moderate
≥2 Moderate *AND* 2 Supporting
≥1 Moderate *AND* 4 Supporting

Uncertain Significance
If other criteria are unmet or arguments for benign and pathogenic are equal in strength

Likely Benign
1 Strong and ≥1 Supporting *OR*
>2 Supporting

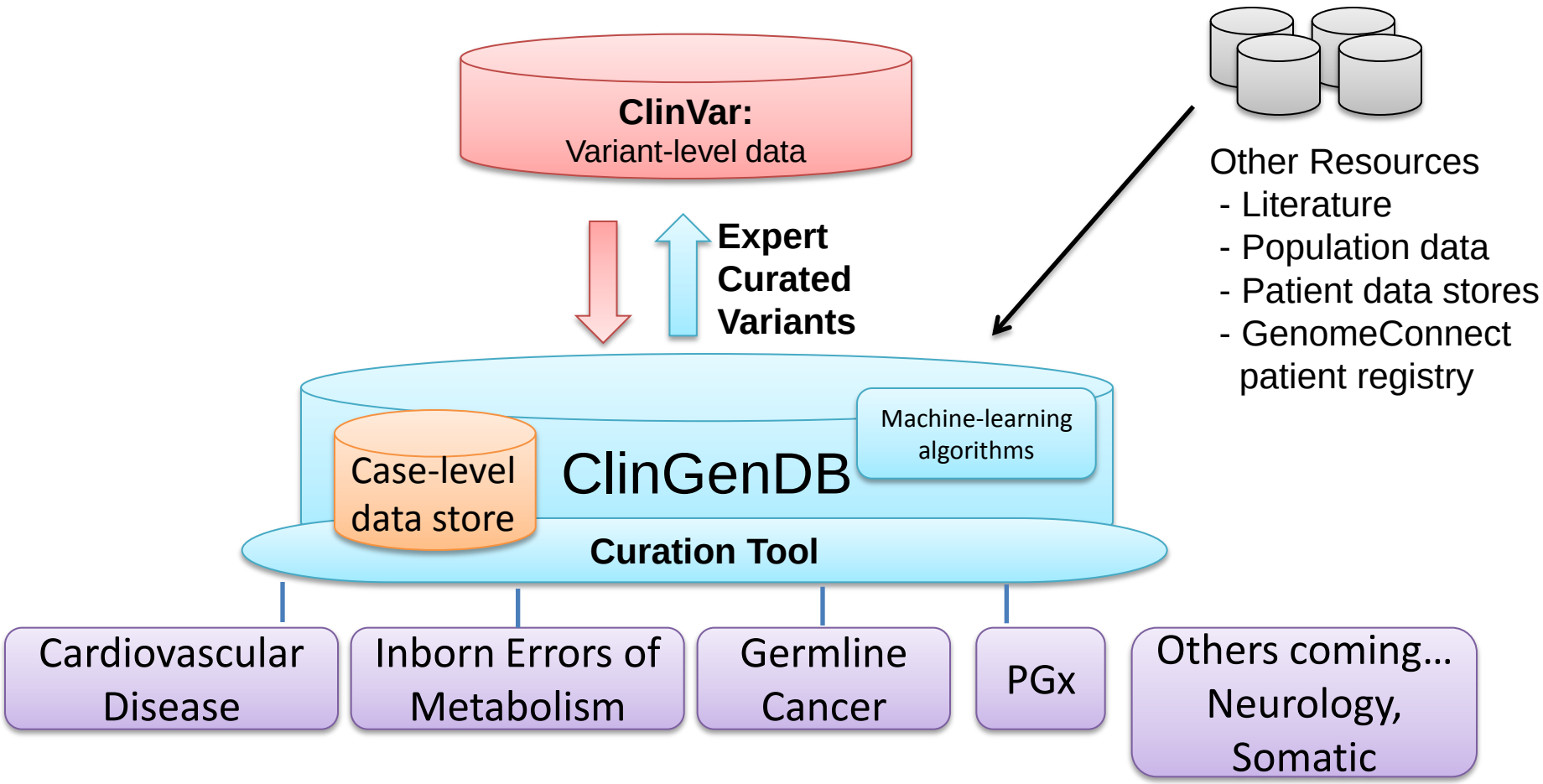
Benign
1 Stand Alone *OR*
≥ 2 Strong

Recommended terms:
- Pathogenic
- Likely pathogenic
- Uncertain significance
- Likely benign
- Benign

Terms modify "variant"
Avoid "mutation" and "polymorphism"'

ACMG/AMP/CAP Draft Guideline for Interpretation of Sequence Variants

ClinGenDB Will Support Gene and Variant Curation



Clinical Domain Workgroups - expert curation/actionability

Diagnostic Case Example

7 yr male with profound sensorineural hearing loss

Lab findings

- GJB2/GJB6 (Cx26/Cx30) testing → Negative
- OtoGenome test (71 genes):
  - Heterozygous c.689_690insA (p.Asn230fs), Exon 3, GJB6
  - Heterozygous c.221A>C (p.Lys74Thr), Exon 3, MYO1A

OtoGenome (71 genes) NGS Panel

ACTG1
ATP6V1
BSND
CCDC50
CLDN1
COCH
COL11A2
CRYM
DFNA5
DIAPH1
ESPN
ESRRB
BOR *EYA1*
EYA4
GIPC3
GJB2
GJB3
GJB6
GPSM2

GRHL2
GRXCR1
HGF
ILDR1
KCNE1
KCNQ1 JLNS
KCNQ4
LHFPL5
LOXHD1
LRTOMT
MARVELD2
MIR96
MSRB3
MTRNR1
MTTS1
MYH14
MYH9
MYO15A
MYO1A

MYO3A
MYO6
OTOA
DFNB59
OTOF AN
POU3F4
POU4F3
PRPS1
RDX
SERPINB6
SLC17A8
Pendred *SLC26A4*
STRC
TECTA
TIMM8A
TJP2
TMC1
TMIE
TMPRSS3

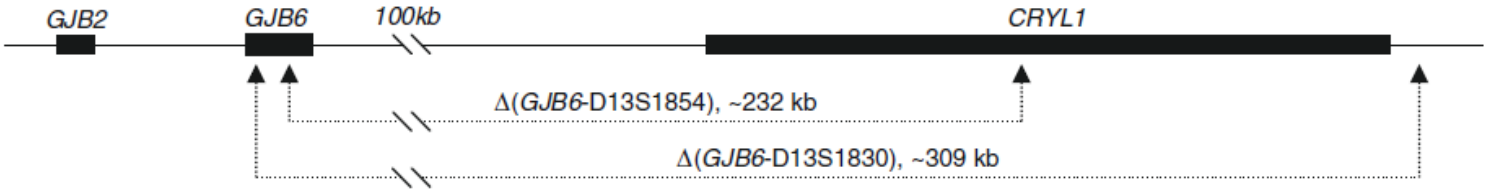
CDH23 Usher
CLRN1
DFNB31
GPR98
MYO7A
PCDH15
USH1C
USH1G
USH2A
TPRN
TRIOBP
WFS1 Wolfram

GJB6 Variants Reported as Pathogenic

Disease	Mutation	Evidence	Ref.
Hidrotic ectodermal dysplasia	Missense (G11R, A88V)	Good	Several
AD hearing loss	Missense (T5M)	Weak	Grifa *et al*. 1999
AD hearing loss	63delG	Weak	Cx Website*
AR hearing loss	**Large deletions**	**Strong**	**Several**

*The Connexin-deafness homepage; Also found in ESP (5/8254 EA and 3/4264 AA).

GJB6 deletions may cause hearing loss through regulatory disruption of Cx26 expression



Rodriqeuz-Paris et al, Biochem Biophys Res Commun, 2009

Conclusion: There is currently no good evidence that point mutations in GJB6 cause hearing loss.

MYO1A

Associated with **autosomal dominant** sensorineural hearing loss in OMIM and GeneReviews.

MYOSIN IA; MYO1A

HGNC Approved Gene Symbol: *MYO1A*

Cytogenetic location: *12q13.3* *Genomic coordinates (GRCh37):* *12:57,422,300 - 57,444,548* (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number
12q13.3	Deafness, autosomal dominant 48	607841

OMIM

Locus Name	Gene	Onset/Decade	Audioprofile
DFNA1	*DIAPH1*	Postlingual/1st	Low frequency progressive
DFNA2	*KCNQ4*	Postlingual/2nd	High frequency progressive
DFNA2B	*GJB3*	Postlingual/4th	High frequency progressive
DFNA3	*GJB2*	Prelingual	High frequency progressive
	GJB6		
DFNA44	*CCDC50*	Postlingual	Low to mild frequencies progressive
DFNA48	*MYO1A*	Postlingual	Progressive
DFNA50	*MIR96*	Postlingual/2nd	Flat progressive

GeneReviews

MYO1A

- Original family used to define the locus was MYO1A negative

Variant	Proband	Segregation	ESP (EA)
R93X	1	**Normal hearing mother**	**0.5% (45/8600)**
349_350insCTT	1	"Maternal family history"	0/8600
V306M	1	**NA**	**1% (83/8600)**
E385D	1	"SNHL Family history"	3/8600
G662E	1	**NA**	**3.8% (324/8600)**
G674D	1	"No family history available"	2/8600
S797F	1	Father had HL	**0.7% (63/8600)**
S910P	1	"Negative family history"	0/8600

Donaudy et al, Am J Hum Genet, 2003

Conclusion: There is currently no evidence that variants in MYO1A cause hearing loss.

BRIEF REPORT

Human Mutation

OFFICIAL JOURNAL

HGVS

HUMAN GENOME VARIATION SOCIETY

www.hgvs.org

Targeted and Genomewide NGS Data Disqualify Mutations in *MYO1A*, the "*DFNA48* Gene", as a Cause of Deafness

Tobias Eisenberger,[1] Nataliya Di Donato,[2] Shahid M. Baig,[3] Christine Neuhaus,[1] Anke Beyer,[2] Eva Decker,[1] Dirk Mürbe,[4] Christian Decker,[1] Carsten Bergmann,[1,5] and Hanno J. Bolz[1,6]*

[1]Center for Human Genetics, Ingelheim, Germany; [2]Institute for Clinical Genetics, Faculty of Medicine Carl Gustav Carus TU Dresden, Dresden, Germany; [3]Human Molecular Genetics Laboratory, Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering (NIBGE), PIEAS, Faisalabad, Pakistan; [4]Division of Phoniatrics and Audiology, Department of Otorhinolaryngology, Technical University of Dresden, Germany; [5]Department of Medicine, Renal Division, University of Freiburg Medical Center, Freiburg, Germany; [6]Institute of Human Genetics, University Hospital of Cologne, Cologne, Germany

Communicated by Haig H. Kazazian, Jr.

Received 22 December 2013; accepted revised manuscript 14 February 2014.
Published online 25 February 2014 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.22532

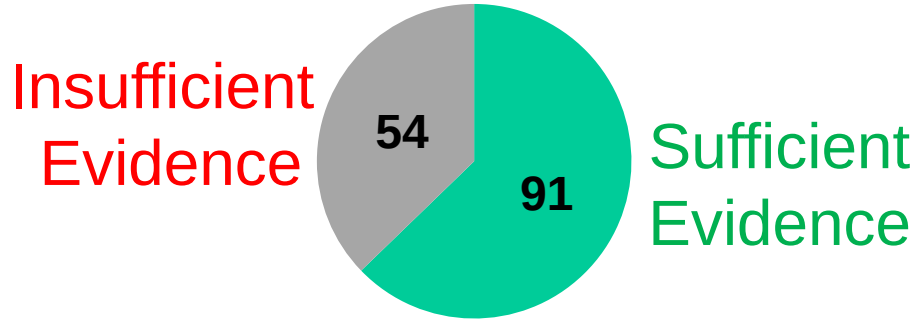
Hearing Loss Gene Assessment

145 genes with published hearing loss associations

Hearing Loss and Related Disorders (Genes)							
Gene	Evid.	Inher.	Mutation Spect.	NonSynd.	Synd.	Phenotype	
						HL	Other
ACTG1	3	AD	M	X^3	X^2	Postlingual, progressive sloping SNHL	Baraitser-Winter syndrome
ATP6V1B1	3	AR	M, LOF		X	Childhood onset, progressive sloping SNHL	Distal renal tubular acidosis
BSND	3	AR	M, LOF	X^1	X^3	Prelingual, severe to profound, flat SNHL	Bartter Syndrome
CABP2	2	AR	LOF	X		Prelingual, moderate to sever, cookie-bite SNHL	
CACNA1D	2	AR	LOF		X	Congenital, severe to profound, flat SNHL	Bradycardia and deafness
CCDC50	2	AD	LOF	X		Postlingual, progressive, moderate to profound SNHL	
CDH23	3	AR	M, LOF	X^3	X^3	Congenital, moderate to profound SNHL	Usher type 1
CEACAM16	2	AD	M	X		Postlingual, progressive, moderate SNHL	
CIB2	3	AR	M	X^3	X^1	Prelingual, severe to profound, flat SNHL	Usher type 1J
CISD2	3	AR	M/LOF		X	Variable onset, progerssive SNHL	WFS2
CLDN14	3	AR	M, LOF	X		Prelingual, flat SNHL (variable progression)	
CLPP	3	AR	M, LOF		X	Congenital, severe to profound, flat SNHL	Perrault Syndrome
CLRN1	3	AR	M, LOF		X	Variable onset, progerssive, moderate to severe SNHL	Usher type 3A
COCH	3	AD	M	X		Postlingual, progressive, profound SNHL	Vestibular impairment
COL11A2	3	AD^3	M, In-frame del	X^3		Congenital, mild to moderately severe cookie-bite SNHL	
					X^3	Childhood/adulthood onset, mild to moderate SNHL	Non-ocular stickler (STL3)
		AR^3	M, LOF	X^{1-2}		Prelingual, profound, flat/cookiee-bite SNHL	
					X^3	Childhood, moderate to profound. Flat SNHL	OSMED
DIABLO	3	AD	M	X		Adulthood onset, progressive, mild to moderate, flat SNHL	
DFNA5	2	AD	Exon 8 skipping	X		Postlingual, progressive SNHL	
DFNB59	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	Auditory neuropathy
DIAPH1	3	AD	M, LOF	X		Postlingual, low frequency progressive SNHL	
EDN3	3	AD/AR	M, LOF		X	Variable HL	Waardenburg type 4B
EDNRB	3	AD/AR	M, LOF		X	Variable HL	Waardenburg type 4B
ESPN	3	AD^1, AR^3	LOF	X		Prelingual, severe to profound, flat SNHL	Vestibular areflexia, in some
ESRRB	3	AR	M*, LOF	X		Early onset, severe to profound, flat/slightly sloping SNHL	
EYA1	3	AD	M, LOF		X	Variable onset, mild to profound SNHL	BOR
EYA4	3	AD	LOF	X		Postlingual, progressive, moderate to profound, flat SNHL	
GIPC3	3	AR	M, LOF	X		Prelingual, mild to profound, flat SNHL	
GJB2	3	AD^3	M	X^{2-3}		Congenital/late onset, mild to profound SNHL	
					X^{2-3}	Childhood onset, moderate to severe, high frequency SNHL	Dermatologic manifestations
		AR^3	M, LOF	X		Congenital/childhood onset, mild to profound SNHL	
GJB6	3	AR	del	X^4		Congenital/childhood onset, mild to profound SNHL	GJB2 dowregulation
		AD	M		X^2	_	Hidrotic Ectodermal dysplasia
			M, LOF	X^1		Variable SNHL	
GPR98	3	AR	M, LOF		X	Prelingual, moderate to profound, sloping SNHL	Usher type 2
GPSM2	3	AR	LOF		X	Prelingual, severe to profound, slightly sloping SNHL	McCullough syndrome
GRHL2	3	AD	LOF	X		Postlingual, progressive, mild to severe SNHL	
GRXCR1	2	AR	M, LOF	X		Congenital, moderate to profound, flat/slightly sloping SNHL	
HARS#	1-2	AR	M		X	Childhood onset, progressive SNHL	Usher type 3B
HARS2	2	AR	M		X	Childhood/teenage onset, progressive, mild to severe, flat SNHL	Perrault Syndrome
HGF	2	AR	Intronic del, splic	X		Prelingual, severe to profound, sloping SNHL	
HSD17B4	2	AR	M, LOF		X	Childhood onset, moderate to severe SNHL	Perrault Syndrome
ILDR1	3	AR	M, LOF*	X		Prelingual, moderate to profound, sloping SNHL	
KARS	3	AR	M	X^2	X^2	Prelingual, moderate to severe, flat SNHL	Peripheral neuropathy
KCNE1	3	AR	M		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ1	3	AR	M, LOF		X	Congenital, severe to profound, flat SNHL	JLNS/Prolonged QT
KCNQ4	3	AD	M, LOF	X		Postlingual, progressive, sloping SNHL	
LARS2	2	AR	M, LOF		X	Childhood onset, progressive, mild to severe, slightly rising SNHL	Perrault Syndrome
LHFPL5	3	AR	M, LOF	X		Prelingual, severe to profound SNHL	
LOXHD1	3	AR	M, LOF*	X^3	X^1	Variable onset, variable SNHL	Fuchs corneal dystrophy
LRTOMT	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	
MARVELD2	3	AR	LOF	X		Prelingual, moderate to profound, flat/sloping SNHL	
MIR96	3	AD	Seed region	X^3	X^1	Postlingual, progressive, flat/sloping SNHL	Vertigo in some
MITF	3	AD	M, LOF		X	Variable HL	Waardenburg type 2
MSRB3	2	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
MTRNR1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	Aminoglycoside exposure
MTTS1	3	Mito.	Point mutat.	X		Variable, progressive SNHL	
MYH14	3	AD	M*, LOF	X^3	X^1	Postlingual, moderate to profound, flat SNHL	Peripheral neuropathy
MYH9	3	AD	M*, LOF	X^2	X^3	Variable onset, progressive SNHL	Macrothrombocytopenia
MYO15A	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	
MYO3A	3	AR	LOF	X		Postlingual, progressive, moderate to severe, sloping SNHL	
MYO6	3	AD^3	M, LOF	X		Postlingual, progressive, moderate to profound sloping SNHL	
		AR^3	LOF	X		Congenital, profound SNHL	Vestibular impairment in some
MYO7A	3	AR	M, LOF		X^3	Congenital, severe to profound, flat SNHL	Usher type 1
			M, LOF	X^3		Congenital, severe to profound, flat SNHL	Vestibular impairment
		AD	M, In-frame del	X^2		Postlingual, mild to severe SNHL	Vestibular impairment
OTOA	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
OTOF	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	Auditory neuropathy
OTOG	2	AR	M, LOF	X		Prelingual/childhood onset, moderate, flat/slightly sloping SNHL	Vestibular impairment in some
OTOGL	3	AR	LOF	X		Congenital, moderate to modertaley severe, sloping SNHL	
P2RX2	3	AD	M	X		Teenage onset, progressive, moderately severe, flat SNHL	High frequency tinnitus
PAX3	3	AD	M, LOF		X	Variable HL	Waardenburg type 1 and 3
PCDH15	3	AR	M, LOF	X^3	X^2	Congenital, profound, flat SNHL	Usher type 1
POU3F4	3	X-linked	M, LOF	X		Cogenital, moderate to profound, flat mixed HL	IAC dilation/Perilymph. Gusher
POU4F3	3	AD	M, LOF	X		Adult onset, progressive, moderate to severe, sloping SNHL	
PRPS1	3	X-linked	M	X^3	X^3	Postlingual, progressive, severe to profound, flat SNHL	PRS-I/Arts/CMT
PTPRQ	3	AR	M, LOF	X		Congenital, moderate to profound, flat SNHL	
RDX	3	AR	M, LOF	X		Prelingual, severe to profound, flat SNHL	
SERPINB6	2	AR	LOF	X		Postlingual, moderate to severe, sloping SNHL	
SIX1	3	AD	M, LOF		X	Variable (3wk-22y) onset, mild to severe, mixed HL	BOR
SLC26A4	3	AR	M, LOF	X^3	X^3	Congenital, progressive, severe to profound, SNHL	Pendred/EVA
SMPX	3	X-linked	LOF	X		Postlingual, progressive, moderate to profound, flat/sloping SNHL	
SNAI2	1-2	AR	del		X	Severe/profound HL	Waardenburg type 2D
SOX10	3	AD	M, LOF		X	Variable HL	Waardenburg types 2E and 4C
STRC	3	AR	M, LOF, del	X^3	X^3	Childhood onset, mild to moderate, sloping SNHL	Deafness Infertility Syndrome
SYNE4	2	AR	LOF	X		pre/postlingual progressive, mild to profound, sloping SNHL	
TBC1D24	3	AR	M	X^2	X^3	Prelingual, profound, flat SNHL	Epilepsy
TECTA	3	AD^3	M	X		Pre/postlingual, progressive (in some), mild to severe SNHL	
		AR^2	LOF	X		Prelingual, moderate to profound, high/mid frequency SNHL	
TIMM8A	3	X-linked	M, LOF*		X	Congenital/early childhood onset, progressive, profound flat SNHL	Mohr-Tranebjaerg syndrome
TMC1	3	AD^3	M	X		Postlingual, progressive SNHL	
		AR^2	LOF	X		Congenital, profound, flat /slightly slopingSNHL	
TMIE	3	AR	M, LOF	X		Congenital, severe to profound, flat SNHL	
TMPRSS3	3	AR	M, LOF	X		Congenital/childhood onset, severe to profound, flat SNHL	
TPRN	3	AR	LOF	X		Prelingual, severe to prfound, flat/slightly sloping SNHL	
TRIOBP	3	AR	LOF	X		Prelingual, severe to profound, flat SNHL	
TSPEAR	2	AR	LOF	X		Congenital, profound, flat SNHL	
USH1C	3	AR	M, LOF	X^3	X^3	Prelingual, severe to profound, flat SNHL	Usher type 1
USH1G	3	AR	M, LOF*		X	Congenital, profound, flat SNHL	Usher type 1
USH2A	3	AR	M, LOF		X	Prelingual, moderate to profound, sloping SNHL	Usher type 2
WFS1	3	AD^3	M	X^3		Congenital, slowly progressive, low frequency SNHL	
					X^2	Childhood onset, progressive, mild to moderate, low-mid freq. SNHL	WFS-like disorder
		AR^3	M, LOF		X^3	Early onset, progressive, high freq. SNHL	Wolfram syndrome
VHRN/DFNB3	3	AR	M, LOF*	X^3	X^3	Prelingual, moderate to profound, sloping SNHL	Usher type 2

Key:
1 - Weak Association
2 - Moderate Association
3 - Definitive Association
* - Most common
# - included on subpanel only

Gene included on Subpanel:
Usher syndrome panel



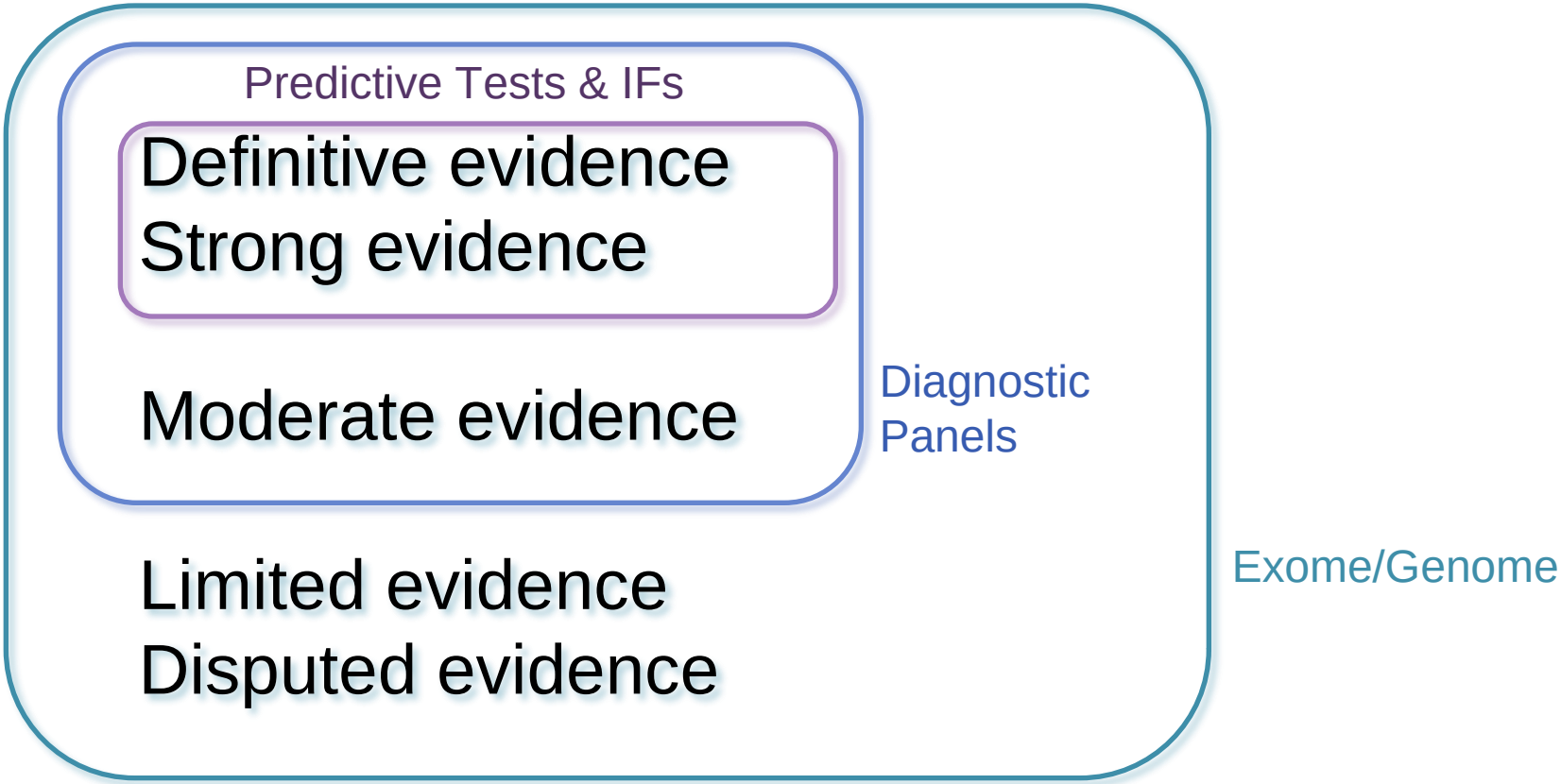
Sami Amr

Ahmad Abou Tayoun

ClinGen Gene-Disease Evidence Levels

Evidence Level	Evidence Description
DEFINITIVE	The role of this gene in this particular disease has been repeatedly demonstrated in both the research and clinical diagnostic settings, and has been upheld over time (in general, at least 3 years). No valid evidence has emerged that contradicts the role of the gene in the specified disease.
STRONG	There is **strong** evidence by at least two independent studies to support a causal role for this gene in this disease, such as: •Strong statistical evidence demonstrating an excess of pathogenic variants[1] in affected individuals as compared to appropriately matched controls •Multiple pathogenic variants[1] within the gene in unrelated probands with several different types of supporting experimental data[2]. The number and type of evidence might vary (eg. fewer variants with stronger supporting data, or more variants with less supporting data) In addition, no valid evidence has emerged that contradicts the role of the gene in the noted disease.
MODERATE	There is **moderate** evidence to support a causal role for this gene in this disease, such as: •At least 3 unrelated probands with pathogenic variants[1] within the gene with some supporting experimental data[2]. The role of this gene in this particular disease may not have been independently reported, but no valid evidence has emerged that contradicts the role of the gene in the noted disease.
LIMITED	There is **limited** evidence to support a causal role for this gene in this disease, such as: •Fewer than three observations of a pathogenic variant[1] within the gene •Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity per 2014 ACMG criteria
NO EVIDENCE	No evidence reported for a causal role in disease.
DISPUTED	Valid evidence of approximate equivalent weight exists both supporting and refuting a role for this gene in this disease.
EVIDENCE AGAINST	Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role.

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



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Well babies

Gene Curation for the Genomic Newborn Sequencing Report

NICU babies

Curating ~3,300 disease-associated genes

Disease association level

ClinGen Criteria

Definitive/Strong	Moderate	Limited

← Well-baby →

← NICU → Specific disease suspected

Inheritance (AD/AR/XL/M/other)

Penetrance

- High
- Moderate
- Low

Age of onset

- Congenital
- Infant-onset (0-2 yrs)
- Childhood-onset (2-10 yrs)
- Adolescent-onset (10-18 yrs)
- Adult-onset (18-50 yrs)
- Advanced age onset (> 50 yrs)

Courtesy Ozge Ceyhan

BabySeq NICU Gene Panels

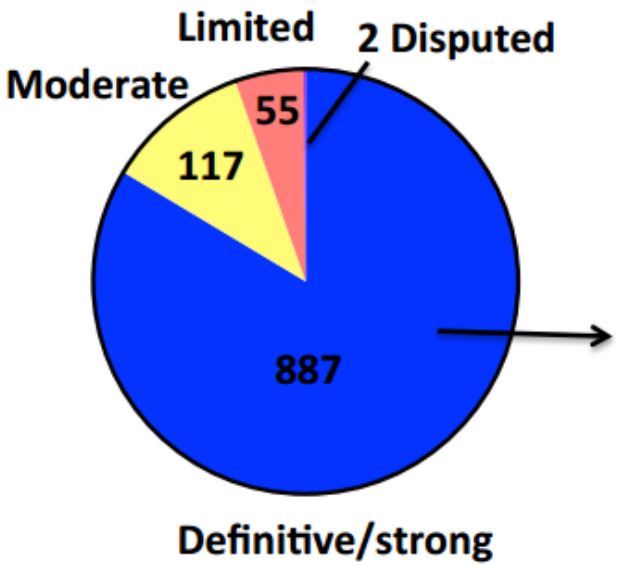
Clinical presentation	% Cases in the NICU (Total)	Number of genes in indication-based panel
Congenital heart disease	9.4	306
Bowel hypomotility / obstruction	5.5	112
Seizures	3.9	667
Hyperbilirubinemia	3.3	103
Hypoglycemia	2.2	70
Hypothyroidism	2	56
Hearing loss	1.9	91
Anemia	1.6	208
Thrombocytopenia	1.6	208
Inborn errors of metabolism	1.1	290
Pulmonary disease	0.8	98
Hypotonia	0.5	699
Renal dysplasia	0.5	238
Neonatal diabetes mellitus	0.2	75
Skeletal dysplasia	0.2	204
Dermatological disorders	0.2	283
Thrombophilia	0.2	37
Multiple anomalies	9.4	N/A
All indications with gene panels prepared in advance	**35.1**	
Total	**44.5**	

Top 20 NICU presentations

Ozge Ceyhan

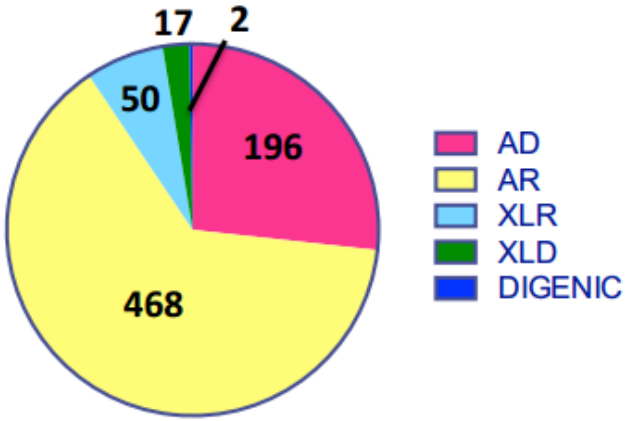
1,063 gene-disease associations curated with ClinGen rules

Evidence level



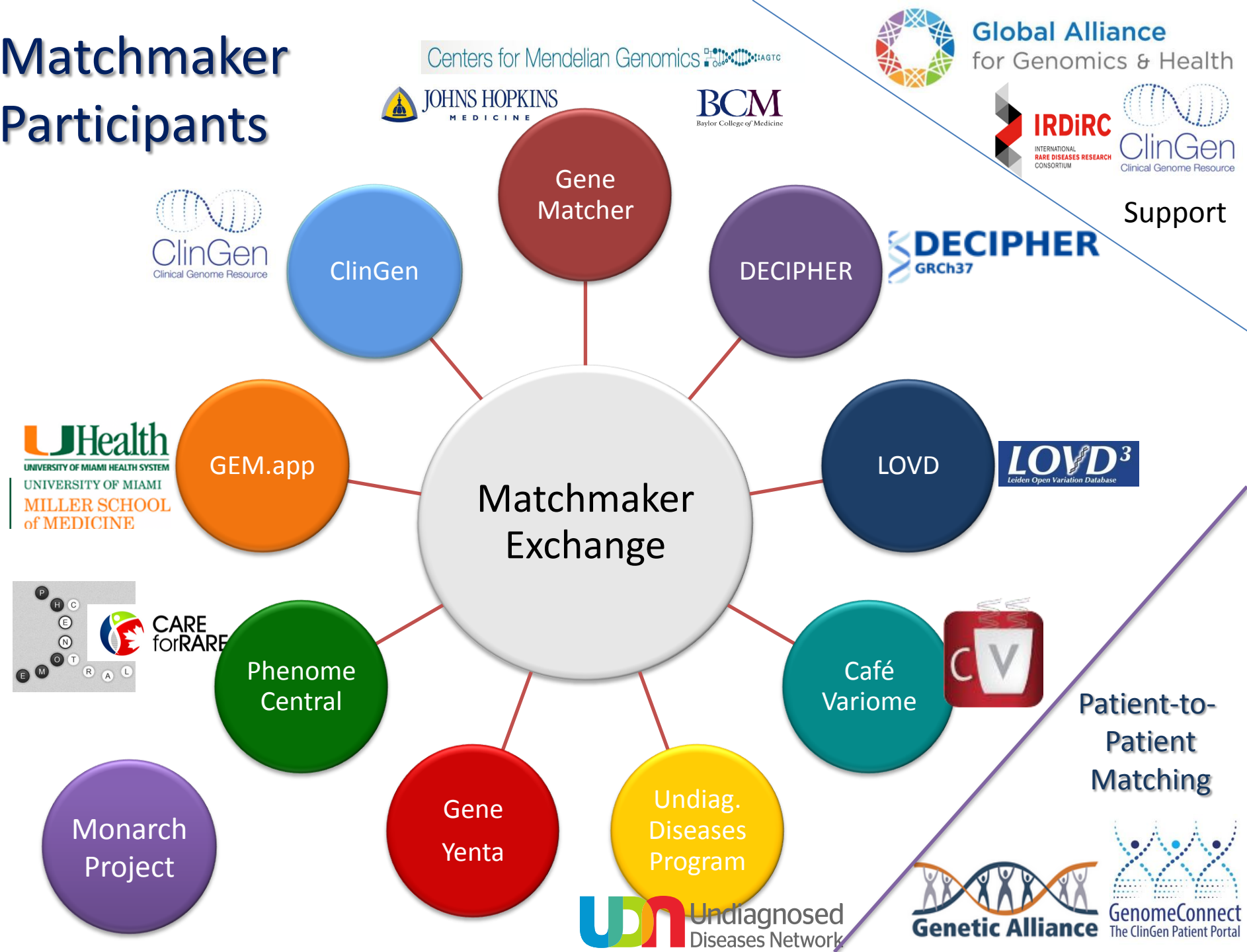
836
Childhood-onset

733
Highly-penetrant



Ozge Ceyhan

Matchmaker Participants



Matchmaker Exchange is a Exemplar Project for the GA4GH

- Success highly dependent on large international effort
- Critical need for standards
- Activity spans multiple workgroups
  1. Data (data format and interfaces)
  2. Regulatory and Ethics (patient consent)
  3. Security (patient privacy)
  4. Clinical (phenotyping and matching algorithms)

www.matchmakerexchange.org

Matchmaker Exchange Acknowledgements

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Sergio Beltran Agullo
Jonathan Berg
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Michael Brudno
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Oriean Buske
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IAGTC

CV

IRDiRC International Rare Diseases Research Consortium

RD Connect

DECIPHER GRCh37

LUMC LOVD3 Leiden Open Variation Database

MedSeq

GenomeBridge

The Human Variome Project

Care for Rare

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