Systematic Evidence Gathering and Actionability Determination

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PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

HARVARD MEDICAL SCHOOL

Areas of Evidence Analysis for Genomics

Gene-Disease Association Evidence

>4300 gene-disease associations but many do not have sufficient data to support a definitive relationship

Informs content for tests and genomic interpretations

Variant Pathogenicity Evidence

>50 million variants have been found in the human genome and many are unique to an individual

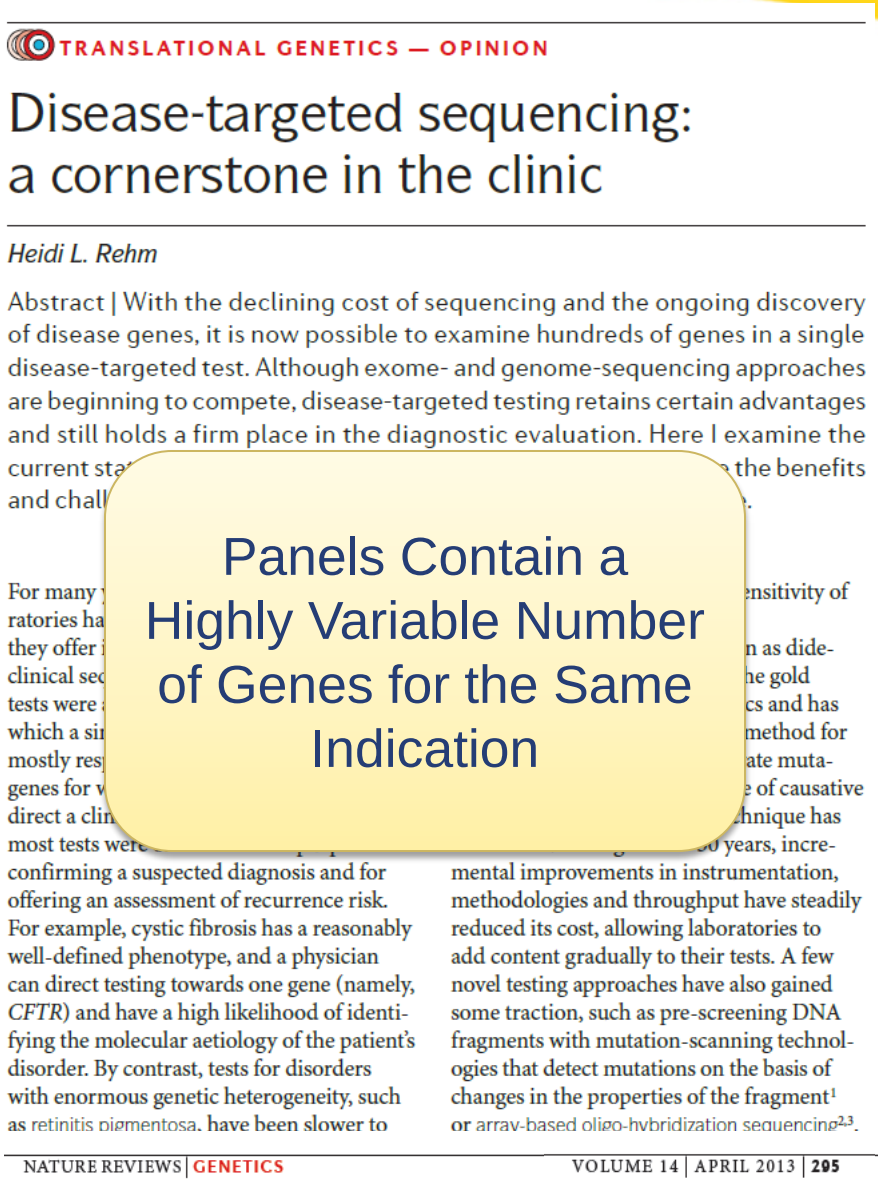
Misinterpretation can impact clinical care and study outcomes

Evidence for an Outcome

- Phenotype or prognosis prediction
- Therapeutic response prediction
- Adverse event avoidance

Disease-Targeted NGS Tests on the Market

Disease area	Genes
Cancer	
Hereditary cancers (e.g. breast, colon, ovarian)	10-50
Cardiac diseases	
Cardiomyopathies	50-70
Arrhythmias (e.g. LongQT)	10-30
Aortopathies (e.g. Marfan)	10
Immune disorders	
Severe combined immunodeficiency syndrome	18
Periodic fever	7
Neurological/Neuromuscular/Metabolic	
Ataxia	40
Cellular Energetics/Metabolism	656
Congenital disorders of glycosylation	23-28
Dementia (e.g. Parkinson, Alzheimer)	32
Developmental Delay/Autism/ID	30-150
Epilepsy	53-130
Hereditary neuropathy	34
Microcephaly	11
Mitochondrial disorders	37-450
Muscular dystrophy	12-45
Sensory	
Eye disease (e.g. retinitis pigmentosa)	66-140
Hearing loss and related syndromes	23-72
Other	
Rasopathies (e.g. Noonan)	10
Pulmonary disorders (e.g. cystic fibrosis)	12-40
Ciliopathies	94
Short stature	12



TRANSLATIONAL GENETICS — OPINION

Disease-targeted sequencing: a cornerstone in the clinic

Heidi L. Rehm

Abstract | With the declining cost of sequencing and the ongoing discovery of disease genes, it is now possible to examine hundreds of genes in a single disease-targeted test. Although exome- and genome-sequencing approaches are beginning to compete, disease-targeted testing retains certain advantages and still holds a firm place in the diagnostic evaluation. Here I examine the current sta… the benefits and chall….

For many … ratories ha… they offer … clinical se… tests were … which a si… mostly res… genes for v… direct a cli… most tests were … confirming a suspected diagnosis and for offering an assessment of recurrence risk. For example, cystic fibrosis has a reasonably well-defined phenotype, and a physician can direct testing towards one gene (namely, *CFTR*) and have a high likelihood of identifying the molecular aetiology of the patient's disorder. By contrast, tests for disorders with enormous genetic heterogeneity, such as retinitis pigmentosa, have been slower to … mental improvements in instrumentation, methodologies and throughput have steadily reduced its cost, allowing laboratories to add content gradually to their tests. A few novel testing approaches have also gained some traction, such as pre-screening DNA fragments with mutation-scanning technologies that detect mutations on the basis of changes in the properties of the fragment[1] or array-based oligo-hybridization sequencing[2,3].

…nsitivity of … as dide… …he gold …cs and has …method for …ate muta… …e of causative …hnique has … years, incre…

NATURE REVIEWS | GENETICS VOLUME 14 | APRIL 2013 | 295

Panels Contain a Highly Variable Number of Genes for the Same Indication

AGMG NGS Guideline

ACMG PRACTICE GUIDELINES | Genetics inMedicine

ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD[1,2], Sherri J. Bale, PhD[3], Pinar Bayrak-Toydemir, MD, PhD[4], Jonathan S. Berg, MD[5], Kerry K. Brown, PhD[6], Joshua L. Deignan, PhD[7], Michael J. Friez, PhD[8], Birgit H. Funke, PhD[1,2], Madhuri R. Hegde, PhD[9] and Elaine Lyon, PhD[4]; for the Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

Disclaimer: These American College of Medical Genetics and Genomics Standards and Guidelines are developed primarily as an educational resource for clinical laboratory geneticists to help them provide quality clinical laboratory genetic services. Adherence to these standards and guidelines is voluntary and does not necessarily assure a successful medical outcome. These Standards and Guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinical laboratory geneticist should apply his or her own professional judgment to the specific circumstances presented by the individual patient or specimen. Clinical laboratory geneticists are encouraged to document in the patient's record the rationale for the use of a particular procedure or test, whether or not it is in conformance with these Standards and Guidelines. They also are advised to take notice of the date any particular guideline was adopted and to consider other relevant medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

ACMG (www.acmg.net) > Publications > Laboratory Standards and Guidelines > NGS

Evaluating Evidence for Gene-Disease Associations

AMA CPT coding subpanel for hearing loss:

- Gathered lists of all genes in all clinically available hearing loss test panels

37% (53/145) of genes available in clinical hearing loss tests do not have sufficient evidence for a definitive disease-association

Ahmad Abou Tayoun

Rating System for Gene Dosage

Highest -- 3, 2, 1, 0, unlikely dosage sensitive -- Lowest

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2012: 81: 403–412
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CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2011.01818.x

Review

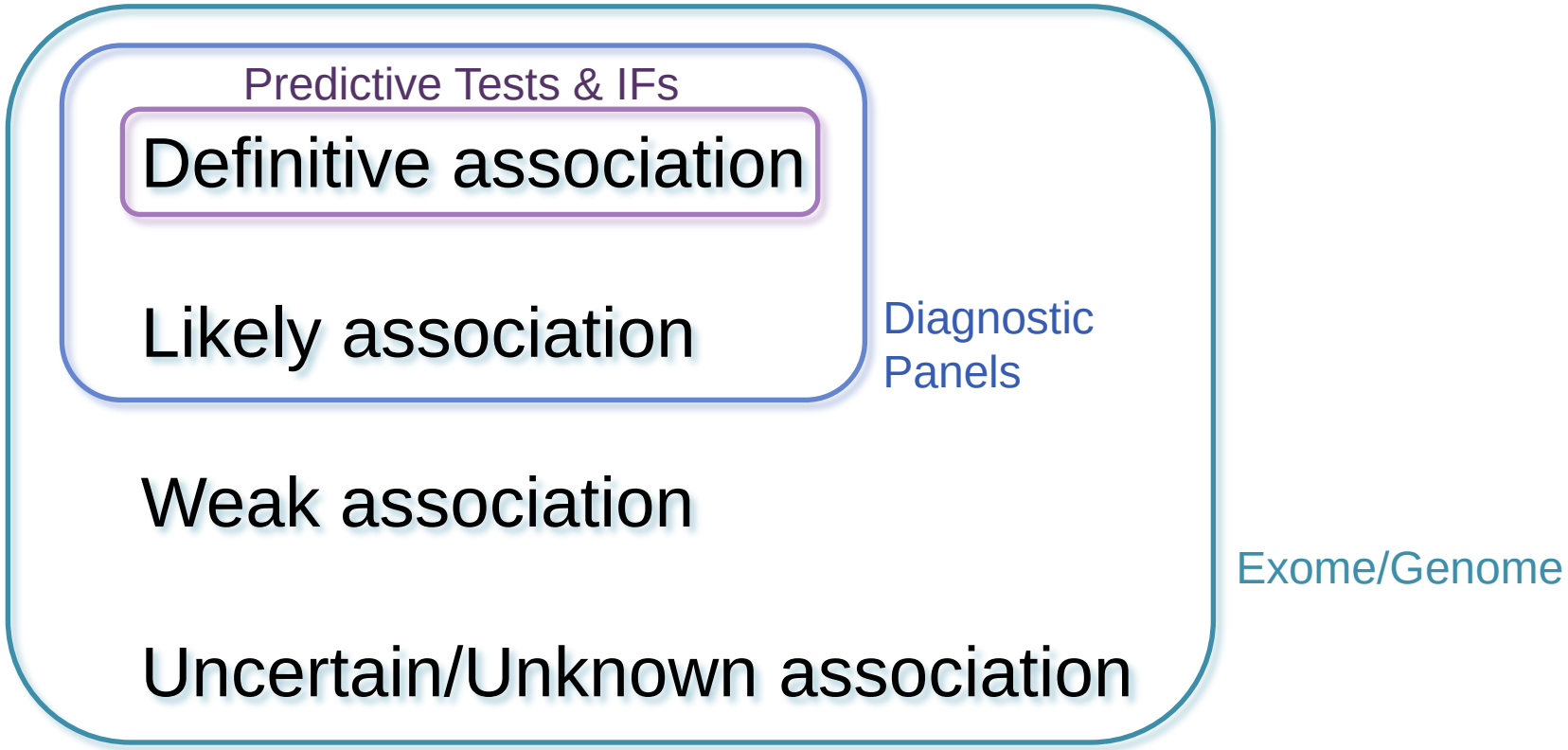
Towards an evidence-based process for the clinical interpretation of copy number variation

Riggs ER, Church DM, Hanson K, Horner VL, Kaminsky EB, Kuhn RM, Wain KE, Williams ES, Aradhya S, Kearney HM, Ledbetter DH, South ST, Thorland EC, Martin CL. Towards an evidence-based process for the clinical interpretation of copy number variation.
Clin Genet 2012: 81: 403–412. © John Wiley & Sons A/S, 2011

The evidence-based review (EBR) process has been widely used to develop standards for medical decision-making and to explore complex

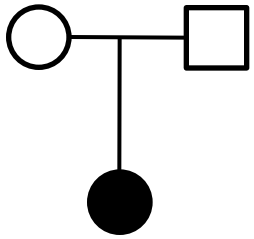
ER Riggs[a], DM Church[b], K Hanson[c*], VL Horner[a], EB Kaminsky[a], RM Kuhn[d], KE Wain[e], ES Williams[a], S Aradhya[f], HM Kearney[g], DH Ledbetter[h], ST South[i], EC Thorland[g] and CL Martin[a,*]

What Evidence is Required to Include a Gene In a Panel?



Level 3	**Definitive association**
Level 2	**Likely association**
Level 1	**Weak association**
Level 0	**Uncertain association**
Level -1	**No association**

Clinical Exome/Genome Sequencing: A New Challenge in Evidence Generation



Distal Arthrogryposis Type 5

- Disease is known to be AD and to occur *de novo*
- No known genes for DA5

Clinical features:

Skeletal	Spine stiffness, Hunched anteverted shoulders, Pectus excavatum, Limited forearm rotation and wrist extension, Bilateral club feet, Congenital finger contractures, Long fingers, Absent phalangeal creases, Poorly formed palmar creases, Camptodactyly, Dimples over large joints
Muscle	Decreased muscle mass (especially in lower limbs), Firm muscles
Face	Triangular face, Decreased facial expression
Ears	Prominent ears
Eyes	Ophthalmoplegia, Deep-set eyes, Epicanthal folds, Ptosis, Duane anomaly, Keratoglobus, Keratoconus, Macular retinal folds, Strabismus, Astigmatism, Abnormal electroretinogram, Abnormal retinal pigmentation

Case from
Michael Murray, MD

WGS Case: Distal Arthrogryposis Type 5

Two de novo mutations in exonic sequence:

ACSM4 – acyl-CoA synthetase medium-chain family member 4
5 nonsense variants identified in ESP; 1 with 6.4% MAF;

PIEZO2: mechanosensitive ion channel


Shamil Sunyeav

Great candidate, but how to we prove causality for a novel gene-disease association?

Then came serendipity……

Second DA5 family with *PIEZO2* mutation was found

Gain-of-function mutations in the mechanically activated ion channel PIEZO2 cause Distal Arthrogryposis Type 5

Bertrand Coste1,†*, Gunnar Houge2,3*, Michael F. Murray4*, Nathan O. Stitziel4,§,Michael Bandell5, Monica A. Giovanni4, Anthony A. Philippakis4, Alexander Hoischen2,6,Gunnar Riemer7, Unni Steen7, Vidar M. Steen2,3, Jayanti Mathur5, James J. Cox8,Matthew S. Lebo9, Heidi L. Rehm9, Scott T. Weiss9, John N. Wood8, Richard L. Maas4,Shamil R. Sunyaev4**, and Ardem Patapoutian1,5**

Genomic Matchmaker

Joel Krier

Patient #1
Clinical Geneticist #1

Patient #2
Clinical Geneticist #2

Genotypic Data	**Phenotypic Data**
Gene A	**Feature 1**
Gene B	Feature 2
Gene C	**Feature 3**
Gene D	**Feature 4**
Gene E	Feature 5
Gene F	
Gene G	

Genomic Matchmaker

Genotypic Data	**Phenotypic Data**
Gene D	**Feature 1**
Gene H	**Feature 3**
Gene I	**Feature 4**
	Feature 6
	Feature 7

- Gene Matcher/PhenoDB (Ada Hamosh)
- LOVD (Johan den Dunnen)
- DECIPHER (Matt Hurles and Helen Firth)
- PhenomeCentral/Care4Rare (Michael Brudno)
- Café Variome (Anthony Brookes)
- GEM.app (Stephan Zuchner)

Defining Content for Genomic Newborn Screening

Disease association evidence level	3
	2
	1
	0
	-1
Age of onset	< 5 yrs
	5-18 yrs
	> 18 yrs
Inheritance	AR
	AD
	XLR
	XLD
	Mitochondrial
Penetrance	Full penetrance
	High penetrance
	Moderate penetrance
	Low penetrance
	Age-dependent penetrance
Phenotype category	Disease
	Susceptibility to disease
	Pharmacogenetic
	Disease risk modifier
Clinically tested?	Offered as a clinical test (Lab?)

Data collected for each gene-phenotype association

Data is used to determine return of results for BabySeq Study

673 genes done, ~3000 to go

Working with Jonathan Berg on adding actionability measures

Ozge Birsoy Ceyhan

The Medical Exome Project and ClinGen Resource

Medical Exome Project Founders

Emory Genetics Laboratory – *Madhuri Hegde*

Harvard/Partners Lab for Molecular Medicine – *Birgit Funke*

Children's Hospital of Philadelphia – *Avni Santani*

1: define medically relevant genes + develop framework for iterative curation

4631 genes

2: develop a **"**medically enhanced exome**"** capture kit (all clinically significant genes adequately covered)

Community Collaboration for the Evidence-Based Review of Gene-Disease Associations

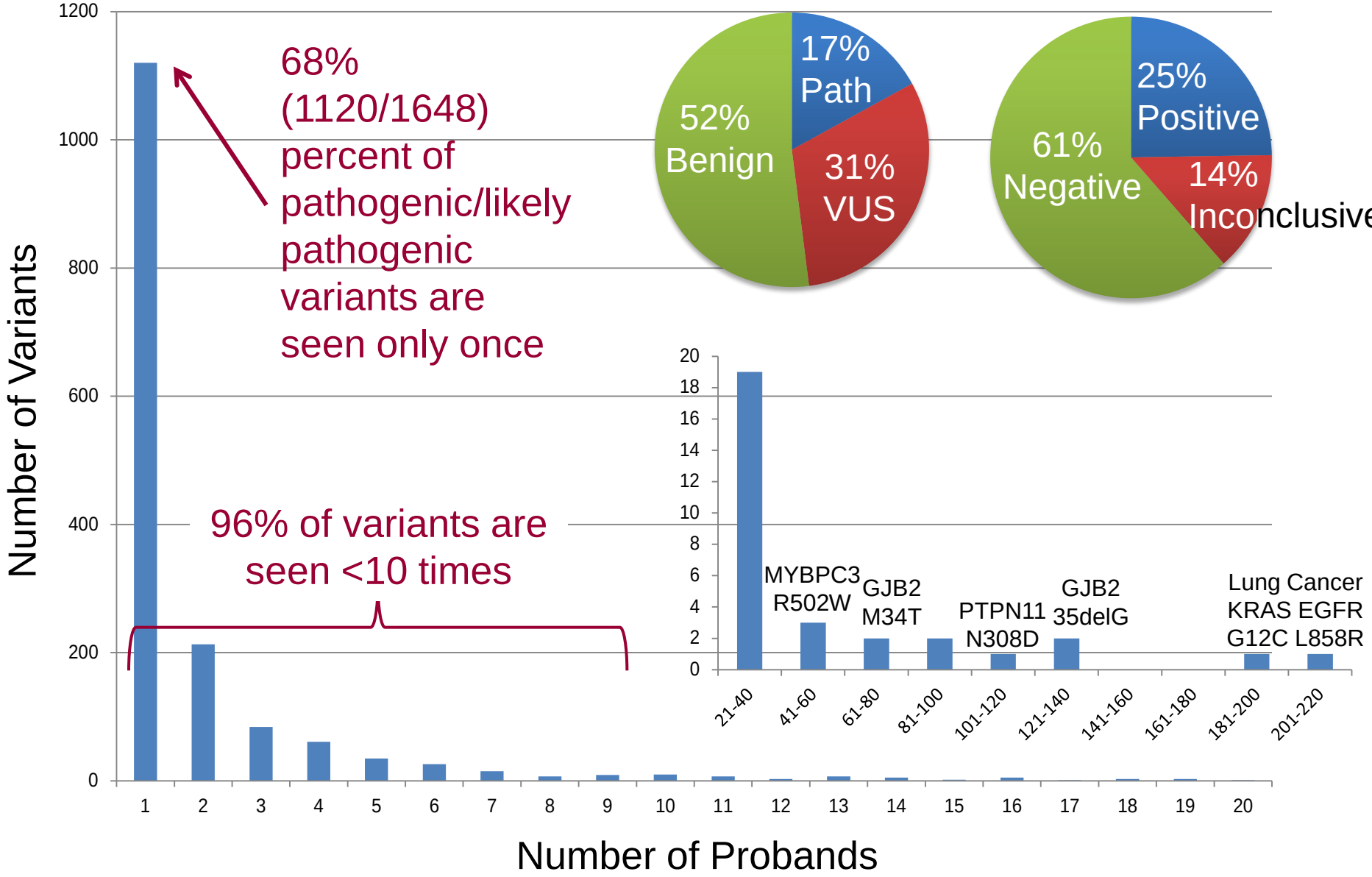
- *Medical Exome Project*
- *Ledbetter/Martin/Nussbaum/Rehm* (U41)
- *Berg/Evans/Ledbetter/Watson* (U01)
- *Bustamante/Plon* (U01)
- *ClinVar Database* (NCBI)

Clinical Genome Resource Program

Level 3	**Definitive association**
Level 2	**Likely association**
Level 1	**Weak association**
Level 0	**Uncertain association**
Level -1	**No association**

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)



Variant Analysis for the Genome Report

3-5 million variants

Genes

~20,000 Coding/Splice Variants

Published as Disease-Causing

<1%

Pharmacogenetics

20-40 "Pathogenic" Variants

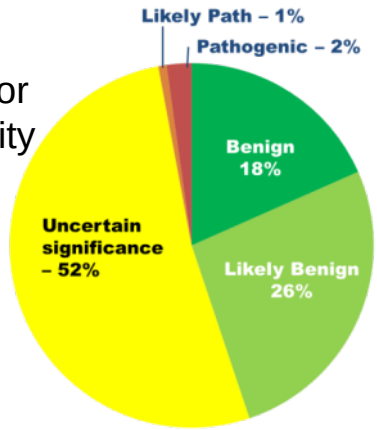
Rare CDS/Splice Variants

5-10 Variants

LOF in Disease Associated Genes

30-50 Variants

Review evidence for variant pathogenicity



97% Excluded

Review evidence for gene-disease association and LOF role

94% Excluded

ACMG Lab QA Committee on the Interpretation of Sequence Variants

ACMG
Sue Richards (chair), Heidi Rehm (co-chair)
Sherri Bale, David Bick, Soma Das, Wayne Grody, Madhuri Hegde, Elaine Spector

AMP
Julie Gastier-Foster, Elaine Lyon

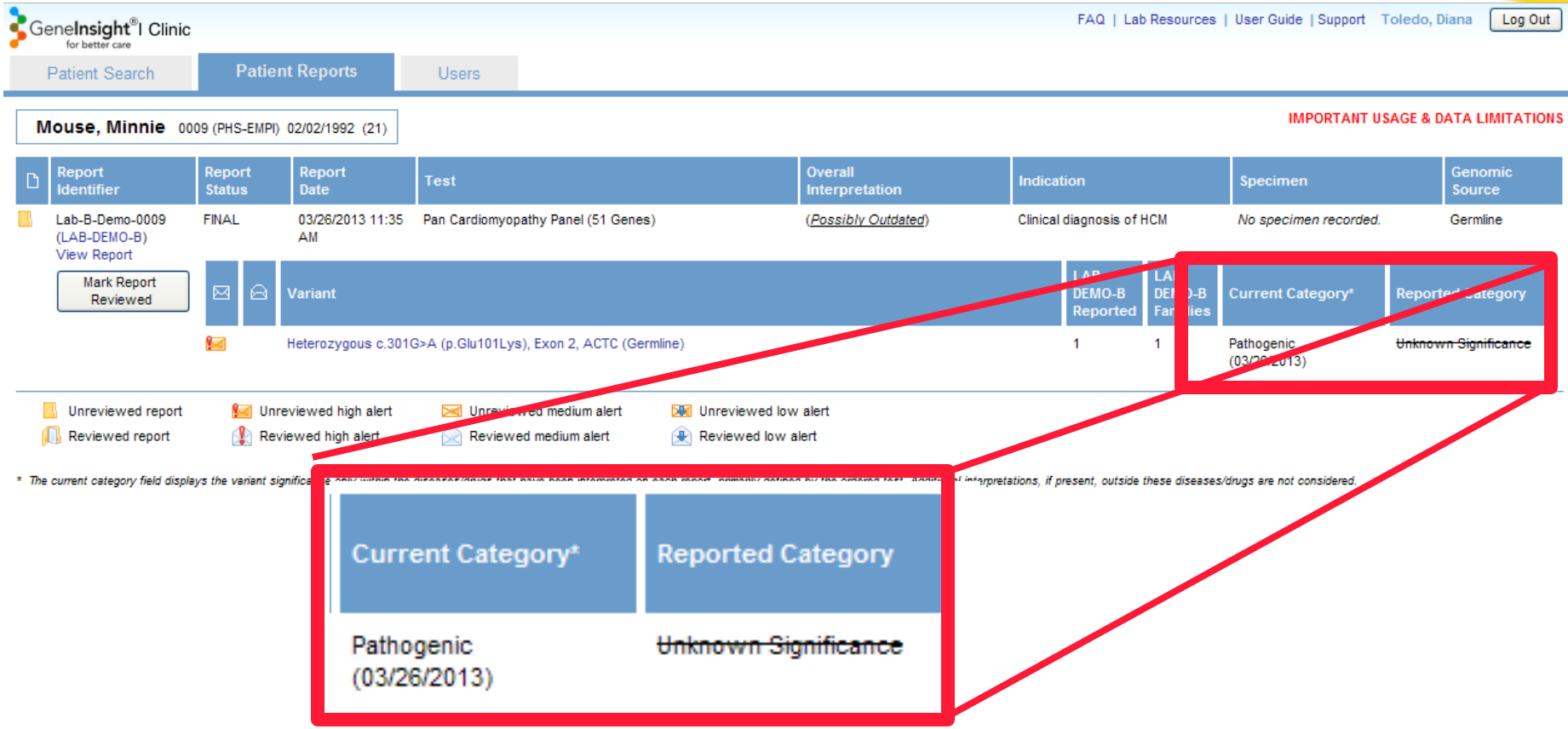
CAP
Nazneen Aziz, Karl Voelkerding

ACMG
American College of Medical Genetics and Genomics

AMP Association for Molecular Pathology

cap

GeneInsight Clinic EHR Integration



Electronic interface to laboratory variant database
Automatically updates patient record in EHR and sends alert to ordering physician

Acknowledgements

The ClinGen Resource

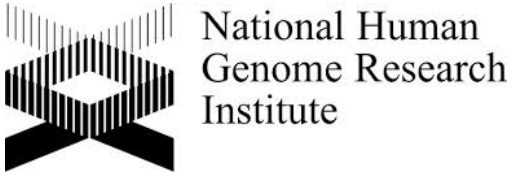
National Human Genome Research Institute

U41 - BWH/Geisinger/UCSF

U01 – UNC/ACMG/Geisinger

U01 – Stanford/Baylor

NCBI ClinVar



International Collaboration for Clinical Genomics

The MedSeq Project

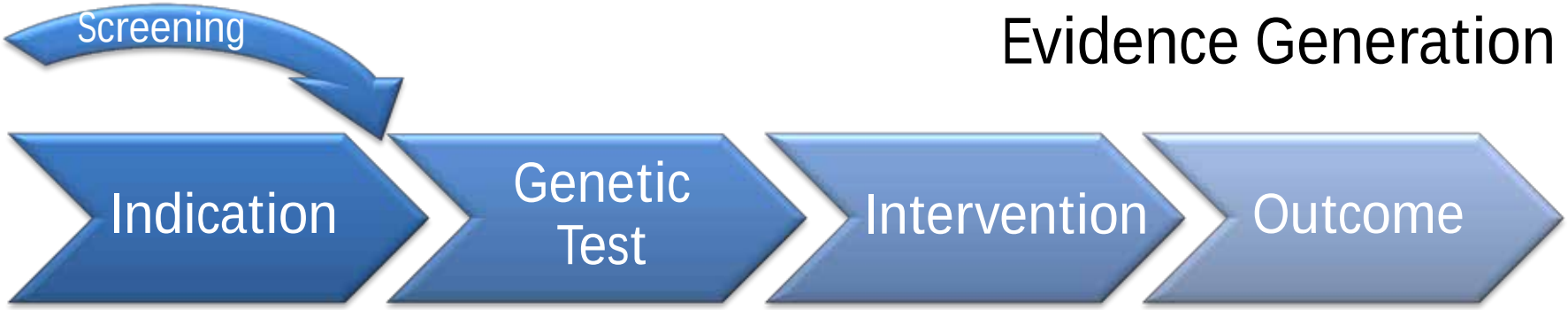
American College of Medical Genetics

The GeneInsight Team

Laboratory for Molecular Medicine

Extra Slides

Evidence Generation



Outcomes dependent on phenotyping

- Need to develop standards for phenotyping and tools to aid in collection*
  - ICHPT
  - GA4GH
  - ClinGen
  - EHR
  - Others…

Outcomes dependent on test content and interpretation

- Need method standards
  - ACMG, CAP, CDC, NIST
  - CMGS, EBMG, EuroGenTest
- Need guidelines for the evidence-based assessment of genes and variants
  - ACMG
  - ClinGen
  - Others…
- Need experts to evaluate genes and variants for medical use
  - ClinGen

Health Improvements +/- Economic Savings

- Randomized Control Trials
- Comparative Effectiveness Research
- "Sound Arguments"
- Rarity of phenotypes and variants may require aggregation of studies by gene, disease, category of disease
- Need EHR tools to collect outcomes

*ICHPT: International Consortium for Human Phenotype Terminologies (HPO, PhenoDB, Orphanet, SNOMed-CT, Elements of Morphology); GA4GH: Global Alliance for Genomic Health; ClinGen: The Clinical Genome Resource

ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

Inherited Cancer Disorders
Hereditary Breast and Ovarian Cancer
Li-Fraumeni Syndrome
Peutz-Jeghers Syndrome
Lynch Syndrome, FAP, MYH-Associated Polyposis
Von Hippel Lindau syndrome
Multiple Endocrine Neoplasia Types 1 & 2
Familial Medullary Thyroid Cancer (FMTC)
PTEN Hamartoma Tumor Syndrome
Retinoblastoma
Hereditary Paraganglioma-Pheochromocytoma Syndrome
WT1-related Wilms tumor
Neurofibromatosis type 2
Tuberous Sclerosis Complex

56 Genes

Cardiac Disorders
Ehlers Danlos Syndrome - vascular type
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms
Hypertrophic, Dilated, and ARV cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Romano-Ward Long QT Syndromes Types 1, 2, and 3 and Brugada Syndrome
Familial hypercholesterolemia

Other: Malignant hyperthermia susceptibility

Incidental Findings Rates:

ClinSeq 2% (ACMG list of 56 genes)

U Wash 2.3% (23/1000) from 114 genes

Baylor 4.6% (55/1200) or (2.6% from ACMG list)

GeneDx 20% (10/50) from ACMG list

mendations, and the background and rationale for these recommen-

on penetrance and clinical utility to fully support these recom-
dations, and we encourage the creation of an ongoing process
pdating these recommendations at least annually as further data
ollected.

t Med 2013:15(7):565–574

Words: genome; genomic medicine; incidental findings; per-
lized medicine; secondary findings; sequencing; whole exome;
whole genome

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:

MEDSEQ™

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PARTNERS HEALTHCARE
CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

Name:
DOB:
Sex: Male
Race:

Accession ID:
MRN:
Specimen:
Received:

Family #:
Referring physician:
Referring facility: MEDSEQ

GENERAL GENOME REPORT

RESULT SUMMARY

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 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)	Classification
A1. X-linked recessive chondrodysplasia punctata (X-linked)	Abnormal bone and cartilage development	ARSE (c.410G>C p.Gly137Ala)	Uncertain Significance: Favor pathogenic

B. CARRIER RISK: 2 VARIANTS IDENTIFIED

This test identified carrier status for 2 autosomal recessive disorders.

Disease (Inheritance)	Phenotype	Gene (Variant)	Classification	Carrier Phenotype*
B1. Methylmalonic aciduria and homocystinuria,cblC type (Autosomal recessive)	Disorder of cobalamin metabolism	MMACHC (c.271_272insA p.Arg91LysfsX14)	Pathogenic	None Reported
B2. 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 future children to be affected, the partner of this individual would also need to be tested for these variants. 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	Decreased dose requirement
C2. Clopidogrel	Typical response to clopidogrel
C3. Digoxin	Intermediate metabolism and serum concentration of digoxin
C4. Metformin	Intermediate glycemic response to metformin
C5. Simvastatin	Typical risk of simvastatin-related myopathy

D. 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 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.

Monogenic Disease and Carrier Risk

Detailed Variant Information

Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence	References
A1. X-linked recessive chondrodysplasia punctata (X-linked)	ARSE (NM_000047.2)	c.410G>C p.Gly137Ala hemizygous (Uncertain Significance)	1/6728 European American	1:500,000	Sheffield 1998, Nino 2008, Franco 1995, Matos-Miranda 2013

VARIANT INTERPRETATION: The Gly137Ala variant in ARSE has been previously identified in 2 males with chondrodysplasia punctata; however, this variant was also identified in one unaffected male 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: X-Linked chondrodysplasia punctata is 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.

“Evidence Generation” session at Global Leaders in Genomic Medicine Meeting

Priorities areas of focus to enable genomic medicine implementation

1. Need definitions of evidence (gene, variant, test, treatment)
2. Develop standards for a test (method, content, interpretation, risk prediction)
3. Catalog evidence generating projects – IGNITE?
    - Define status of projects to decide which to implement elsewhere, which could benefit from larger datasets and which should not be prioritized elsewhere due to poor evidence for effect
4. Encourage adoption of genomic medicine applications with existing evidence
    - Identify areas of economic benefit
    - Engage physicians in identifying areas of opportunity for genomic implementation
    - Stimulate development of society practice guidelines
    - Intersociety coordinating committee – competencies in residency training
5. Discuss areas of overlap with activities of other organizations
6. Identify countries/systems willing to enable access to patient data
    - Share evidence generated in those systems
7. Need systems to capture evidence - Facilitate a federated network and standardized APIs to share data – GA4GH?

Returning Results from Large Panels and Genomic Tests

Key Questions:

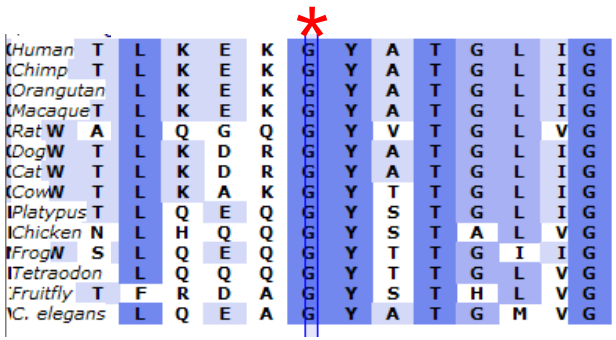
Is there strong evidence for the gene's role in disease?

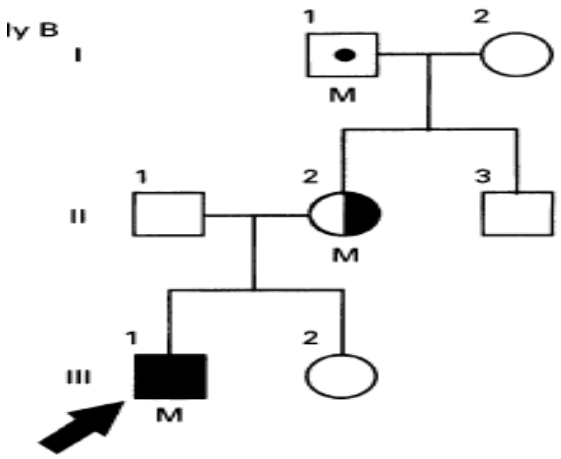
Is there strong evidence for variant pathogenicity?

Does this result explain the indication for testing?
OR
Should I return the result as an Incidental Finding?

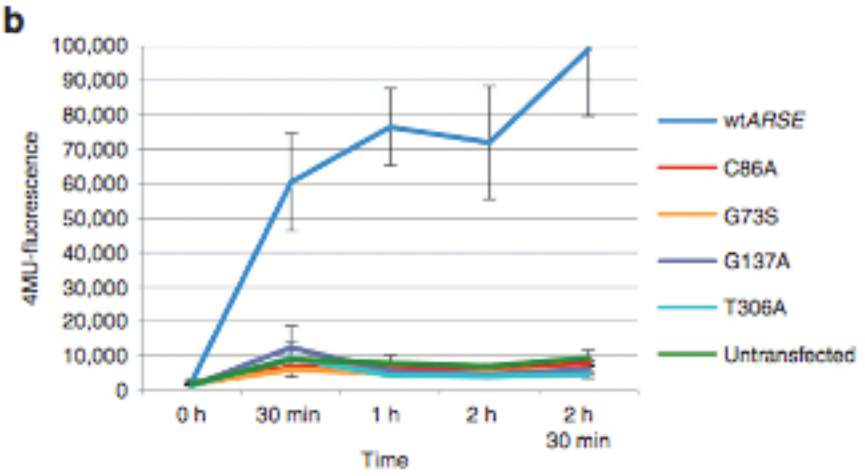
ARSE p.Gly137Ala – Reported Pathogenic

- Strong evidence for ARSE role in XLR chondrodysplasia punctata 1
- Variants identified in 2 males with CDPX1, one severe, one mild
- 1/6728 female EA ESP; 1 asymptomatic male
- Pathogenic by PolyPhen, SIFT, AlignGVGD
- Functional studies show reduced ARSE activity after expressing the mutant *ARSE* cDNA in mammalian COS1 cells and measuring ARSE activity using 4MU sulfate





Sheffield, et al. J Med Genet 1998



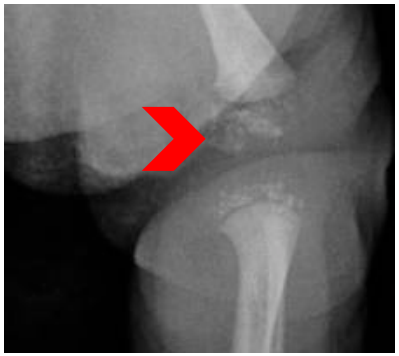
Matose-Miranda, et al. Genet Med 2013

MedSeq Case – Adult Male

ARSE c.410G>C (p.Gly137Ala) Hemizygous

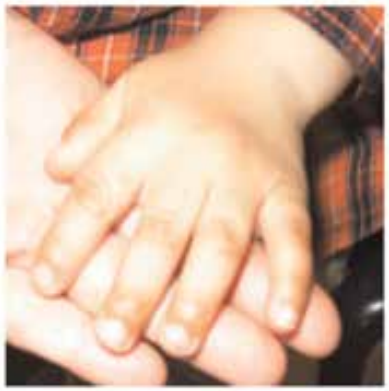
Pathogenic ARSE variants à XLR chrondodysplasia punctata 1 (CDPX1)

- Most males have mild disease that improves by adulthood
- Variable intrafamilial disease expression



Epiphyseal stippling (100%)
Brachytelephalangy (68%)
Nasomaxillary hypoplasia (58%)

Minimal morbidity



Severe morbidity
Respiratory disease (32%)
Cervical spine stenosis (19%)
Hearing loss (26%)
Cognitive delay (16%)
Eye abnls (16%)
Cardiac abnls (13%)
Infant demise (13%)

TOR1A: c.726del (p.Ser243fs)

- Novel variant, Not present in EVS or 1000Genomes
- Predicted loss of 116 amino acids (third of protein); predicted NMD
- No other truncating mutations in ESP cohorts
- No other splice forms of gene described

TOR1A strongly associated with Early-Onset Primary Dystonia (DYT1)

- Typically presents in childhood or adolescence, range 4-64 years
- Dystonic muscle contractions causing posturing of a foot, leg, or arm are most common
- Autosomal dominant with incomplete penetrance (30%) and variable expressivity
- Disease prevalence: AJ population 1/3000 – 1/9000
  Europe: 1/200,000-330,000
- Clinical testing available
- Actionability: Oral medications and surgical intervention to prevent contractures of the joints and deformities of the spine

TOR1A: c.726del (p.Ser243fs)

- Common mutation: c.907_909delGAG

- Mechanism of variant pathogenicity not well established
  - Gain-of function?
  - Loss-of-function with haploinsufficiency?

- Tor1A knockdown mice expressing reduced levels of torsin A exhibit deficits in motor control and alterations similar to those displayed by KI heterozygous mice

<u>Other variants:</u>

- 3 other putative pathogenic variants, all non-truncating, all insufficient evidence
  - Phe205Ile, Arg288Gln, Phe323_Tyr328del
- 1 loss of function variant found in an anonymous blood donor specimen:
  - Arg312fs