Supporting Genomics in the Practice of Medicine

Heidi L. Rehm, PhD, FACMG
Director, Partners Laboratory for Molecular Medicine

Partners Healthcare Personalized Medicine
Department of Pathology, Brigham and Women’s Hospital
Harvard Medical School
Broad Institute of MIT and Harvard
MedSeq WGS Pilot Clinical Trial

100 HCM Patients (10 cardiologists) → Whole Genome Sequencing → 50

100 Healthy Patients (10 PCPs) → Whole Genome Sequencing → 50

Whole Genome Sequencing

- 50
- 50

Standard of Care with Family History

Genome Report

Cardiac Risk Supplement

Compare Outcomes

Genome Report

Cardiac Risk Supplement

Compare Outcomes

Standard of Care with Family History
The Genome Report

GENERAL REPORT

Sex: Male  Specimen: Peripheral Whole Blood  Referring physician: Dr. Martin Solomon  Referring facility: Brigham and Women’s Hospital

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.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrodysplasia punctata (X-linked)</td>
<td>Abnormal bone and cartilage development</td>
<td>ARSE c.440C&gt;G</td>
<td>Uncertain Significance/Favor Pathogenic</td>
</tr>
</tbody>
</table>

CARRIER RISK: 2 VARIANTS IDENTIFIED

This test identified carrier status for 2 autosomal recessive disorders.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylmalonic aciduria and homocystinuria, cbl type C (Autosomal recessive)</td>
<td>Disorder of cobalamin metabolism</td>
<td>MMACHC c.277dupA</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Lobar congenital amaurosis</td>
<td>Retinal dystrophy and blindness</td>
<td>SPATA7 p.27+2T&gt;C</td>
<td>Likely Pathogenic</td>
</tr>
</tbody>
</table>

As a carrier of 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 and dose information. Additional pharmacogenetic results may be requested, but will require additional molecular confirmation prior to disclosure.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Decreased dose requirement</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Typical risk of bleeding and cardiovascular events</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Increased serum concentration of digoxin</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Typical response to methotrexate</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Lower risk of simvastatin-related myopathy</td>
</tr>
</tbody>
</table>

BLOOD GROUPS

This test identified the ABO 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 Genomic Resource Center at GRC@partners.org.

DETAILED VARIANT INFORMATION

MONOGENIC DISEASE RISK

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Gene (Transcript)</th>
<th>Variant (Classification)</th>
<th>Variant Frequency</th>
<th>Disease Prevalence</th>
<th>References (PMID)</th>
<th>Carrier Phenoype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrodysplasia punctata (X-linked)</td>
<td>ARSE (NM_0000474)</td>
<td>c.410C&gt;G</td>
<td>p.Gly137Ala</td>
<td>Hemiwystous (Uncertain Significance)</td>
<td>18729 European American</td>
<td>1500000</td>
</tr>
</tbody>
</table>

VARIANT INTERPRETATION: This OY134A variant in ARSE has previously been identified in 2 individuals with chondrodysplasia punctata. However, this variant was also not seen in a healthy control sample. Variants in a paralogous gene (ARSEB), at the same position have also been identified in an individual with Maroteaux-Lamy syndrome, which also features skeletal deformations (Franco 1995). Functional studies indicate that the OY134A variant leads to decreased ARSE activity (Maito-Matsumoto 2013). In summary, although some data support a disease-causing role, there is currently insufficient evidence for pathogenicity to be assigned to a current classification of uncertain significance.

CARRIER RISK: Chondrodysplasia punctata is typically inherited in an X-linked recessive manner, with primary males being affected. Each child has 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 father.

CARRIER RISK (Simplified Table)

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Gene (Transcript)</th>
<th>Variant (Class)</th>
<th>Variant Frequency</th>
<th>Disease Prevalence</th>
<th>References (PMID)</th>
<th>Carrier Phenoype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA/HCHC</td>
<td>MMACHC (NM_015560.2)</td>
<td>c.277dupA</td>
<td>p.Arg92YfsX14</td>
<td>Pathogenic</td>
<td>1404069</td>
<td>European American</td>
</tr>
</tbody>
</table>

VARIANT INTERPRETATION: The Arg92YfsX14 variant in MMACHC has been identified in homozygosity in 61 individuals and in compound heterozygosity in 86 individuals with methylmalonic aciduria and homocystinuria, cbl type C (Lerner-Bills 2009, Richard 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 at amino acid position 119. This alteration is predicted to lead to a truncated or absent protein. In summary, this variant meets our criteria for pathogenicity. This frameshift variant is predicted to alter the protein’s amino acid sequence beginning at position 91 and lead to a premature termination codon at amino acid position 119. This alteration is predicted to lead to a truncated or absent protein. In summary, this variant meets our criteria for pathogenicity.

The clinical manifestation of disorders of intracranial cobalamin metabolism can be highly variable. The age at clinical recognition of cblC patients can range from birth to 35+ years of age (Shahinian 2008). Some individuals may present with prominent early childhood mental delay, growth retardation, and neurologic signs, including seizures. Other patients may present later in life with less severe neurologic findings. The clinical presentation of cblC patients can range from mild to severe, with some individuals only having mild abnormalities or no symptoms at all. It is important to note that these are only general guidelines and that each patient's presentation may vary. The cblC variant in this report is associated with a high risk of mental retardation and developmental delay, as well as other neurological and physical abnormalities. It is recommended that patients with this variant undergo routine evaluations to monitor for the development of symptoms.

TAPPEL RISK: The TAPPEL/SPATA7 variant in SPATA7 (NM_001140.1) has been previously reported. This variant is located in the S-polymerase region. This variant does not appear to be pathogenic and is not predicted to lead to any significant functional changes in the protein.

VARIANT INTERPRETATION: The C.84+2 T>C variant in SPATA7 (NM_001140.1) has been previously reported. This variant is located within the S-promoter region. This variant does not appear to be pathogenic and is not predicted to lead to any significant functional changes in the protein.
The Genome Report

Monogenic disease risk

Carrier risk

Pharmacogenomics

Blood type

**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.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrodysplasia punctata (X-linked)</td>
<td>Abnormal bone and cartilage development</td>
<td>ARSE c.419C&gt;G</td>
<td>Uncertain Significance: Favor Pathogenic</td>
</tr>
</tbody>
</table>

**CARRIER RISK: 2 VARIANTS IDENTIFIED**

This test identified carrier status for 2 autosomal recessive disorders.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
<th>Carrier Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylmalonic aciduria and homocystinuria, type B (Autosomal recessive)</td>
<td>Disorder of cobalamin metabolism</td>
<td>MMACHC c.277dupA</td>
<td>Pathogenic</td>
<td>None reported</td>
</tr>
<tr>
<td>Leber congenital amaurosis (Autosomal recessive)</td>
<td>Retinal dystrophy and blindness</td>
<td>SPATA7 c.947+1T&gt;A</td>
<td>Likely Pathogenic</td>
<td>None reported</td>
</tr>
</tbody>
</table>

**PHARMACOGENOMIC ASSOCIATIONS**

These associations are based on drug use and dosing. Additional pharmacogenetic results may be requested, but will require additional molecular confirmation prior to disclosure.

**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 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 SRC@partners.org.
Reported findings from analysis of variants in ~4600 genes

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

*2/53 (4%) from ACMG list
Can Primary Care Physicians Understand Genomic Reports?
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
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.”
Patient: “I didn’t have anything monogenic, which I thought was the main thing I would look for.”

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 5.1 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.

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.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene Variant</th>
<th>Classification</th>
<th>Carrier Phenotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1. Hypothyroidism</td>
<td>Underactive thyroid</td>
<td>DUOX2 c.3847+2T&gt;C</td>
<td>Pathogenic</td>
<td>NA</td>
</tr>
</tbody>
</table>

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.

C. 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1. Warfarin</td>
<td>Increased dose requirement</td>
</tr>
</tbody>
</table>
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 5.1 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.

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.

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.”
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.
### Improved Coverage with Medical Exome Enhancement

**Birgit Funke**

#### Medical Exome
- 4,631 genes
- 10.7 Mb
- Fully covered exons (100% ≥ 20x)

**ICE Exome (~200x)**
- 94%

**Agilent v5-PLUS (~200x)**
- 98%

#### Pan Cardio Pnl
- 51 genes
- 262 kb
- Fully covered exons (100% ≥ 20x)

**ICE Exome (~200x)**
- 88%

**Agilent v5-PLUS (~200x)**
- 99%
The development of curated exclusion datasets after 50 cases dramatically reduced variant review.

Not reported variants: 82%
- VUS, Likely Benign, Benign
- False positive variants

Reported variants: 18%
- Pathogenic
- Likely Pathogenic
- VUS-Favor Pathogenic
- Other
- Not reported

Data Set A - Original filters
- >5 million variants
- HGMD
- ClinVar
- >5% variants
- Novel LOF
- Medical exome
- >1% variants

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

Original filters

Curated Exclusion Datasets

>5 million variants

>200-300 variants

>10% in WGS Cases

Gene exclusions

Variant exclusions

~200-300 variants

<60 variants

20-40 variants

10-30 variants

>5 million variants

Variants:
- Pathogenic
- Likely Pathogenic
- VUS-Favor Pathogenic
- Other
- Not reported

Cases:
- HGMD
- ClinVar
- Novel LOF
- Medical exome

Cases:
- >10% MAF WGS Cases
- Excludes common technical FPs
- Common indels wrong nomenclature
- Exceptions FV, HFE, SERPINA1

Exclusions:
- Gene exclusions
- Variant exclusions

Pathogenic
Likely Pathogenic
VUS-Favor Pathogenic
Other
Not reported
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)

68% (1120/1648) percent of pathogenic/likely pathogenic variants are seen only once

96% of variants are seen <10 times
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:

<table>
<thead>
<tr>
<th>NCBI ClinVar</th>
<th>U41 Grant - Partners/Geisinger/UCSF</th>
<th>U01 Grant - UNC/ACMG/Geisinger</th>
<th>U01 Grant - Stanford/Baylor</th>
<th>NIH Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melissa Landrum</td>
<td>David Ledbetter</td>
<td>Jonathan Berg</td>
<td>Carlos Bustamante</td>
<td>Erin Ramos</td>
</tr>
<tr>
<td>Donna Maglott</td>
<td>Christa Martin</td>
<td>Jim Evans</td>
<td>Sharla Plon</td>
<td>Lisa Brooks</td>
</tr>
<tr>
<td>Steve Sherry</td>
<td>Bob Nussbaum</td>
<td>David Ledbetter</td>
<td>Mike Watson</td>
<td>Danuta Krotoski</td>
</tr>
<tr>
<td></td>
<td>Heidi Rehm</td>
<td></td>
<td></td>
<td>Sheri Schully</td>
</tr>
</tbody>
</table>
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
Data Flows in ClinGen
(>200 ClinVar submitters)

Researchers ➔ Clinical Labs ➔ Expert Groups ➔ Clinics ➔ Patients

ClinVar
Variant-level Data

Case-level Data

Sharing Clinical Reports Project
Genome Connect and Free-the-Data

Patient Registries

Unpublished or Literature Citations

Linked Databases
OMIM, CFTR2, BIC, InSiGHT, PharmGKB

ClinVar Review Status
Practice Guideline
Expert Panel
Multi-Source Consistency
Single Source

1. Literature references without assertions
2. Inconsistency in assertions
No stars

>124,000 submissions
>85,000 classified variants
- **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

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

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

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)
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

<table>
<thead>
<tr>
<th>Database</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Information Core (BIC)</td>
<td>3793</td>
</tr>
<tr>
<td>Sharing Clinical Reports Project (SCRP)</td>
<td>2148</td>
</tr>
<tr>
<td>Invitae</td>
<td>4220</td>
</tr>
<tr>
<td>Ambry Genetics</td>
<td>1318</td>
</tr>
<tr>
<td>GeneDx</td>
<td>286</td>
</tr>
<tr>
<td>Counsyl</td>
<td>112</td>
</tr>
<tr>
<td>OMIM</td>
<td>81</td>
</tr>
</tbody>
</table>

LOVD: 3262 variants

UMD (France): 3913 variants

A=ClinVar  B=LOVD  C=UMD

Courtesy of Xin Feng

LSDB Updates
BRCA1 and BRCA2 Variants in ClinVar

Conflicting interpretations: 465
- Benign/Likely benign: 254
- Uncertain significance: 2035
- Pathogenic/likely pathogenic: 2105
- Not provided: 1127

Total: 5986

Not provided: 19%
Uncertain significance: 34%
Pathogenic/likely pathogenic: 35%
Benign/Likely benign: 4%
Conflicting: 8%

Data from ClinVar August 7, 2014

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

BRCA1/2 Conflicts:
- P/LP vs. B/LB: 5
- P/LP vs. VUS: 59
- VUS vs. B/LB: 395
22 variants (Confidence differences)

60 variants (3-Level)

14 variants (3-Level)

8 variants (Confidence differences)

43 variants consistent

17 variants still discrepant

11 variants still discrepant

3 variants consistent

1/82 variants need expert panel input

Reasons for discrepancies:

• Novel silent: LB vs VUS
• Missense (freq cut-offs; MOI)

Discussion between labs
<table>
<thead>
<tr>
<th>Population Data</th>
<th>Computational Data</th>
<th>Functional Data</th>
<th>Segregation Data</th>
<th>De novo Data</th>
<th>Allelic Data</th>
<th>Other Database</th>
<th>Other Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAF frequency is too high for disorder OR observation inconsistent with disease penetrance⁶</td>
<td>Multiple lines of computational evidence suggest no impact on gene /gene product⁹</td>
<td>Well-established functional studies show no deleterious effect⁴</td>
<td>Non-segregation with disease⁵</td>
<td>De novo (without paternity &amp; maternity confirmed)³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type of variant does not fit known mechanism of disease</td>
<td>In-frame indels in a repetitive region without a known function⁷</td>
<td>Co-segregation with disease in multiple affecteds in multiple families⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before²</td>
<td>Missense in gene with low rate of benign missense variation and pathogenic missenses common</td>
<td>De novo (without paternity &amp; maternity confirmed)³</td>
<td>For recessive disorders, detected in trans with a pathogenic variant¹¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Located in a mutational hot spot and/or known functional domain⁷</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For recessive disorders, detected in trans with a pathogenic variant¹¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

---

**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

2. 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
ClinGenDB Will Support Gene and Variant Curation

ClinVar:
- Variant-level data

Other Resources:
- Literature
- Population data
- Patient data stores
- GenomeConnect patient registry

Expert Curation of Variants

Case-level data store

ClinGenDB Curation Tool

ClinVar: Variant-level data

Clinical Domain Workgroups - expert curation/actionability

Cardiovascular Disease
Inborn Errors of Metabolism
Germline Cancer
PGx
Others coming... Neurology, Somatic

Machine-learning algorithms
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
EYA1
EYA4
GIPC3
GJB2
GJB3
GJB6
GPSM2
GRHL2
GRXCR1
HGF
ILDR1
KCNE1
KCNE4
KCNE4
LHFPL5
LOXHD1
LRTOMT
MARVELD2
MIR96
MSRB3
MTRNR1
MTTS1
MYH14
MYH9
MYO15A
MYO1A
MYO3A
MYO6
OTOA
DFNB59
OTOF
POU3F4
POU4F3
PRPS1
RDX
SERPINB6
SLC17A8
SLC26A4
STRC
TECTA
TIMM8A
TJP2
TMC1
TMIE
TMPRSS3
CDH23
CLRN1
DFNB31
GPR98
MYO7A
PCDH15
USH1C
USH1G
USH2A
TPRN
TRIOBP
WFS1

BOR
JLNS
AN
Pendred
Usher
Wolfram
## GJB6 Variants Reported as Pathogenic

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidrotic ectodermal dysplasia</td>
<td>Missense (G11R, A88V)</td>
<td>Good</td>
<td>Several</td>
</tr>
<tr>
<td>AD hearing loss</td>
<td>Missense (T5M)</td>
<td>Weak</td>
<td>Grifa et al. 1999</td>
</tr>
<tr>
<td>AD hearing loss</td>
<td>63delG</td>
<td>Weak</td>
<td>Cx Website*</td>
</tr>
<tr>
<td>AR hearing loss</td>
<td>Large deletions</td>
<td>Strong</td>
<td>Several</td>
</tr>
</tbody>
</table>

*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.

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 NCI)

**Gene-Phenotype Relationships**

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>12q13.3</td>
<td>Deafness, autosomal dominant 48</td>
<td>607841</td>
</tr>
</tbody>
</table>

**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/2\textsuperscript{nd} | Flat progressive
**MYO1A**

> Original family used to define the locus was MYO1A negative

<table>
<thead>
<tr>
<th>Variant</th>
<th>Proband</th>
<th>Segregation</th>
<th>ESP (EA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R93X</td>
<td>1</td>
<td>Normal hearing mother</td>
<td>0.5% (45/8600)</td>
</tr>
<tr>
<td>349_350insCTT</td>
<td>1</td>
<td>“Maternal family history”</td>
<td>0/8600</td>
</tr>
<tr>
<td>V306M</td>
<td>1</td>
<td>NA</td>
<td>1% (83/8600)</td>
</tr>
<tr>
<td>E385D</td>
<td>1</td>
<td>“SNHL Family history”</td>
<td>3/8600</td>
</tr>
<tr>
<td>G662E</td>
<td>1</td>
<td>NA</td>
<td>3.8% (324/8600)</td>
</tr>
<tr>
<td>G674D</td>
<td>1</td>
<td>“No family history available”</td>
<td>2/8600</td>
</tr>
<tr>
<td>S797F</td>
<td>1</td>
<td>Father had HL</td>
<td>0.7% (63/8600)</td>
</tr>
<tr>
<td>S910P</td>
<td>1</td>
<td>“Negative family history”</td>
<td>0/8600</td>
</tr>
</tbody>
</table>

_Donaudy et al, Am J Hum Genet, 2003_

**Conclusion:** There is currently no evidence that variants in MYO1A cause hearing loss.
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. Bolz¹,6

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

#### Insufficient Evidence
- **54** genes

#### Sufficient Evidence
- **91** genes

---

**Sami Amr**

**Ahmad Abou Tayoun**
## ClinGen Gene-Disease Evidence Levels

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Evidence Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITIVE</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
| **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?

- Definitive evidence
- Strong evidence
- Moderate evidence
- Limited evidence
- Disputed evidence
The BabySeq Project

Leadership Team:

Alan Beggs
Robert Green
Pankaj Agrawal
Ingrid Holm
Amy McGuire
Richard Parad
Peter Park
Heidi Rehm
Tim Yu
Gene Curation for the Genomic Newborn Sequencing Report

Curating ~3,300 disease-associated genes

### Disease association level

<table>
<thead>
<tr>
<th>Definitive/Strong</th>
<th>Moderate</th>
<th>Limited</th>
</tr>
</thead>
</table>

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

#### Top 20 NICU presentations

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

Ozge Ceyhan
1,063 gene-disease associations curated with ClinGen rules

Evidence level

- Definitive/strong: 887
- Limited: 117
- Moderate: 55
- Disputed: 2

836 Childhood-onset
733 Highly-penetrant

Ozge Ceyhan
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)

170 organizations from 25 countries so far......
www.matchmakerexchange.org
### Matchmaker Exchange Acknowledgements

<table>
<thead>
<tr>
<th>S Balasubramanian</th>
<th>Jan Friedman</th>
<th>Danielle Metterville</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mike Bamshad</td>
<td>Richard Gibbs</td>
<td>Debbie Nickerson</td>
</tr>
<tr>
<td>Sergio Beltran Agullo</td>
<td>Marta Girdea</td>
<td>Woong-Yan Park</td>
</tr>
<tr>
<td>Jonathan Berg</td>
<td>Robert Green</td>
<td>Justin Paschall</td>
</tr>
<tr>
<td>Kym Boycott</td>
<td>Matt Hurles</td>
<td>Anthony Philippakis</td>
</tr>
<tr>
<td>Anthony Brookes</td>
<td>Ada Hamosh</td>
<td>Heidi Rehm</td>
</tr>
<tr>
<td>Michael Brudno</td>
<td>Ekta Khurana</td>
<td>Peter Robinson</td>
</tr>
<tr>
<td>Han Brunner</td>
<td>Sebastian Kohler</td>
<td>Francois Schiettecatte</td>
</tr>
<tr>
<td>Oriean Buske</td>
<td>Joel Krier</td>
<td>Rolf Sijmons</td>
</tr>
<tr>
<td>Deanna Church</td>
<td>Owen Lancaster</td>
<td>Nara Sobreira</td>
</tr>
<tr>
<td>Raymond Dalgliesh</td>
<td>Melissa Landrum</td>
<td>Jawahar Swaminathan</td>
</tr>
<tr>
<td>Andrew Devereau</td>
<td>Paul Lasko</td>
<td>Morris Swertz</td>
</tr>
<tr>
<td>Johan den Dunnen</td>
<td>Rick Lifton</td>
<td>Rachel Thompson</td>
</tr>
<tr>
<td>Helen Firth</td>
<td>Daniel MacArthur</td>
<td>Stephan Zuchner</td>
</tr>
<tr>
<td>Paul Flicek</td>
<td>Alex MacKenzie</td>
<td></td>
</tr>
</tbody>
</table>

---

**Logos:**
- **ClinGen**
- **NCBI**
- **EMBL-EBI**
- **Centers for Mendelian Genomics**
- **Global Alliance for Genomics & Health**
- **IRDiRC**
- **RD Connect**
- **DECIPHER**
- **GRCh37**
- **LOVD3**
- **UMC**
- **UCSC**
- **MedSeq**
- **GenomeBridge**
- **THE HUMAN VARIOME PROJECT**

---

**Logos:**
- **CARE for RARE**
- **FORGE Canada Consortium**
- **UHealth**
- **University of Miami Miller School of Medicine**
- **HGVS**
- **BCM**
- **Johns Hopkins Medicine**
MedSeq Project Collaborators

Project Leadership
Robert Green, MD, MPH
Zak Kohane, MD, PhD
Calum MacRae, MD, PhD
Amy McGuire, JD, PhD
Michael Murray, MD
Heidi Rehm, PhD
Christine Seidman, MD
Jason Vassy, MD, MPH, SM

Project Manager
Denise Lautenbach, MS, CGC

Project Personnel
Sandy Aronson, ALM, MA
Stewart Alexander, PhD
David Bates, MD
Jennifer Blumenthal-Barby, PhD
Ozge Ceyhan-Birsoy, PhD
Kurt Christensen, MPH, PhD
Allison Cirino, MS, CGC
Lauren Conner
Kelly Davis
Jake Duggan
Lindsay Feuerman, MPH
Siva Gowrisankar, PhD
Carolyn Ho, MD
Leila Jamal, ScM, CGC
Peter Kraft, PhD
Joel Krier, MD
Sek Won Kong, MD
William Lane, MD, PhD
Matt Lebo, PhD
Lisa Lehmann, MD, PhD, MSc
In-Hee Lee, PhD
Ignat Leschiner, PhD
Christina Liu
Phillip Lupo, PhD, MPH
Kalotina Machini, PhD, MS
David Margulies, MD
Heather McLaughlin, PhD
Danielle Metterville, MS, CGC
Rachel Miller Kroouze, MA
Sarah Panchang
Julie Robinson, MA
Melody Slashinski, MPH, PhD
Sarita Panchang
Melody Slashinski, MPH, PhD
Shamil Sunyaev, PhD
Peter Ubel, MD
Scott Weiss, MD

External Advisory Board
Katrina Armstrong, MD
David Bentley, DPhil
Robert Cook-Deegan, MD
Muin Khoury, MD, PhD
Bruce Korf, MD, PhD (Chair)
Jim Lupski, MD, PhD
Kathryn Phillips, PhD
Lisa Salberg
Maren Scheuner, MD, MPH
Sue Siegel, MS
Sharon Terry, MA

Consultants
Les Biesecker, MD
George Church, PhD
Geoffrey Ginsburg, MD, PhD
Tina Hambuch, PhD
J. Scott Roberts, PhD
David Veenstra, PharmD, PhD

Protocol Monitoring Committee
Judy Garber, MD, MPH
David Miller, MD, PhD
Cynthia Morton, PhD
BabySeq Project Team

Leadership
Alan H. Beggs, PhD (joint PI)
Robert C. Green, MD, MPH (joint PI)
Peter J. Park, PhD
Heidi L. Rehm, PhD
Tim Yu, MD, PhD
Pankaj B. Agrawal, MD, MMSC
Richard B. Parad, MD, MPH
Ingrid A. Holm, MD, MPH
Amy L. McGuire, JD, PhD

Project Managers
Sarah Kalia, ScM, CGC
Meghan Towne, MS, CGC

Co-Investigators
Ozge Ceyhan-Birsoy, PhD
Kurt Christensen, PhD
Leslie Frankel, PhD
Anne Hansen, MD, MPH
Lise Johnson, MD
Joel Krier, MD
Harvey Levy, MD
Philip Lupo, PhD
David Miller, MD, PhD
Patrice Milos, PhD
Ann Poduri, MD
Steve Ringer, MD, PhD
Amy Roberts, MD
Jason Vassy, MD, MPH
Susan Waisbren, PhD
Louise Wilkins-Haug, MD, PhD

Co-Investigators, continued
Harvey Levy, MD
Philip Lupo, PhD
David Miller, MD, PhD
Patrice Milos, PhD
Ann Poduri, MD
Steve Ringer, MD, PhD
Amy Roberts, MD
Jason Vassy, MD, MPH
Susan Waisbren, PhD
Louise Wilkins-Haug, MD, PhD

Advisory Board
Bruce Korf, MD, PhD (Chair)
Les Biesecker, MD
Steve Cederbaum, MD
Alex Kemper, MD, MPH
Zak Kohane, MD, PhD
Lou Kunkel, PhD
Jim Lupski, MD, PhD
Sharon Terry, MA
Chris Walsh, MD, PhD

Consultants
George Church, PhD
Lisa Diller, MD
Dmitry Dukhovny, MD, MPH
Steve Joffe, MD, MPH
Peter Kraft, PhD
Michelle Lewis, MD, JD
David Margulies, MD, PhD
Neela Sahai, MD

Staff
Lindsay Feuerman
Christina Liu
Ali Noorbaksh
Jill Robinson, MA

Boston Children’s Hospital
Brigham and Women’s Hospital
Harvard Medical School
Baylor College of Medicine
ClinGen Acknowledgements

Jonathan Berg
Lisa Brooks
Carlos Bustamante
Jim Evans
Melissa Landrum
David Ledbetter
Donna Maglott
Christa Martin
Robert Nussbaum
Sharon Plon
Erin Ramos
Heidi Rehm
Steve Sherry
Michael Watson

Erica Anderson
Swaroop Arahdya
Sandy Aronson
Euan Ashley
Larry Babb
Erin Baldwin
Sherri Bale
Louisa Baroudi
Les Biesecker
Chris Bizon
David Borland
Rhonda Brandon
Michael Brudno
Damien Bruno
Atul Butte
Hailin Chen
Mike Cherry
Eugene Clark

Soma Das
Johan den Dunnen
Edwin Dodson
Karen Eilbeck
Marni Falk
Andy Faucett
Xin Feng
Mike Feolo
Matthew Ferber
Penelope Freire
Birgit Funke
Monica Giovani
Katrina Goddard
Robert Green
Marc Greenblatt
Robert Greenes
Ada Hamosh
Bret Heale
Madhuri Hegde
Ray Hershberger
Lucia Hindorff
Sibel Kantarci
Hutton Kearney
Melissa Kelly
Muin Khoury
Eric Klee
Patti Krautschaid
Joel Krier
Danuta Krotoski
Shashi Kulkarni
Matthew Lebo
Jennifer Lee
Elaine Lyon
Subha Madhavan
Teri Manolio
Rong Mao
Daniel Masys
Peter McGarvey
Dominic McMullan
Danielle Metterville
Laura Milko
David Miller
Aleksander Milosavljevic
Rosario Monge
Stephen Montgomery
Michael Murray
Rakesh Nagarajan
Preetha Nandi
Teja Nelakuditi
Annie Niehaus
Elke Norwig-Eastaugh
Brendon O’Fallon
Kelly Ormond
Daniel Pineda-Alvaraz
Darlene Reithmaier
Erin Riggs
George Riley
Peter Robinson
Wendy Rubinstein
Shawn Rynearson
Cody Sam
Avni Santani
Neil Sarkar
Melissa Savage
Jeffery Schloss
Charles Schmitt
Sheri Schully
Alan Scott
Chad Shaw
Weronika Sikora-Wohlfeld
Bethanny Smith Packard
Tam Sneddon
Sarah South
Marsha Speevak
Justin Starren
Jim Stavropoulos
Greer Stephens
Christopher Tan
Peter Tarczy-Hornoch
Erik Thorland
Stuart Tinker
David Valle
Steven Van Vooren
Matthew Varughese
Yekaterina Vaydylevich
Lisa Vincent
Karen Wain
Meredith Weaver
Kirk Wilhelmsen
Patrick Willems
Marc Williams
Eli Williams

ACMG
Baylor College of Medicine
Geisinger
Harvard Medical School
NCBI
NC VN
National Human Genome Research Institute
UCSF
University of Miami
The University of Chicago
THV
University of Miami Miller School of Medicine
University of North Carolina at Chapel Hill
Stanford University
American College of Medical Genetics and Genomics
Baycrest Health Sciences
Johns Hopkins Medicine
The Children’s Hospital of Philadelphia
Charité
Emory University
GeneDx
Genetic Testing Lab
HGS
Institute of Human Genetics
IRDiRC
LOVD
Mayo Clinic
University of Miami Miller School of Medicine
Partners Healthcare
UCSF
University of Chicago Genetic Services
University of Miami Miller School of Medicine
University of North Carolina at Chapel Hill
Stanford University
UCSF
SAVE THE DATE!

2015 ClinGen/DECIPHERER Conference

May 27-28, 2015 • Washington, DC

Advancing Genomic Medicine through Collaboration and Data Sharing

Who should attend? Clinical molecular and cytogenetic lab directors, researchers, clinicians, genetic counselors, and others.

Formal meeting announcement to follow

www.clinicalgenome.org
decipher.sanger.ac.uk/