Genomic Testing: Actionability, Validation, and Standards for Lab Reports

Reaction: Heidi Rehm, PhD FACMG

eMERGE Consortium Meeting
1/22/2014
Actionability

- **Goal:** Define/discover clinically useful content that can be implemented into the practice of medicine to improve patient outcomes and/or save healthcare costs

- **Observation:** Large focus of eMERGE to date has been on genotypes (PGx, GWAS, PheWAS)

- **Suggestion:** Expand focus to gene - phenotype pairs instead of genotype - phenotype pairs

**Opportunity for Collaboration**
ClinGen: The Clinical Genome Resource Program

**Purpose:** Create a centralized repository and interconnected resources of clinically annotated genes and variants to improve our understanding of genomic variation and optimize its use in genomic medicine.

Collaboration between:

- **NHGRI U41 Genomic Resource Grant**
  - PIs: Ledbetter (Geisinger), Martin (Geisinger), Nussbaum (UCSF), Mitchell (Utah), Rehm (Partners/Harvard)

- **NHGRI U01 “Clinically Relevant Variant Resource” Grants**
  - Grant 1 PIs: Berg (UNC), Evans (UNC), Ledbetter (Geisinger), Watson (ACMG)
  - Grant 2 PIs: Bustamante (Stanford), Plon (Baylor)

- **NCBI**
  - ClinVar
THE MEDICAL EXOME INITIATIVE

POSTER # 1585 (Thursday)

FOUNDERS

• Harvard/Partners Lab for Molecular Medicine – Birgit Funke
• Emory Genetics Laboratory – Madhuri Hegde
• Children’s Hospital of Philadelphia – Avni Santani

HELP STANDARDIZE MEDICAL EXOME SEQUENCING

• 1: define medically relevant genes + develop framework for iterative curation
• 2: develop a “medically enhanced exome” capture kit (all clinically significant genes adequately covered)
• 3: support evidence-based curation by community experts
  • Ledbetter/Martin/Nussbaum/Rehm (U41)
  • Berg/Evans/Ledbetter/Watson (U01)
  • Bustamante/Plon (U01)
  • ClinVar Database (NCBI)

ClinGen Resource

4631 genes

Level 3  Definitive association
Level 2  Likely association
Level 1  Weak association
Level 0  Uncertain association
Level -1  No association
# Evidenced-based Review of Gene-Disease Associations

## Disease association evidence level

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>

## Age of onset

<table>
<thead>
<tr>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 yrs</td>
<td></td>
</tr>
<tr>
<td>5-18 yrs</td>
<td></td>
</tr>
<tr>
<td>&gt; 18 yrs</td>
<td></td>
</tr>
</tbody>
</table>

## Inheritance

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>XLR</td>
<td></td>
</tr>
<tr>
<td>XLD</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial</td>
<td></td>
</tr>
</tbody>
</table>

## Carrier phenotype

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely</td>
<td>(phenotype)</td>
</tr>
<tr>
<td>Possible</td>
<td>(phenotype)</td>
</tr>
<tr>
<td>Unlikely</td>
<td></td>
</tr>
</tbody>
</table>

## Penetrance

<table>
<thead>
<tr>
<th>Penetrance Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full penetrance</td>
<td></td>
</tr>
<tr>
<td>High penetrance</td>
<td></td>
</tr>
<tr>
<td>Moderate penetrance</td>
<td></td>
</tr>
<tr>
<td>Low penetrance</td>
<td></td>
</tr>
<tr>
<td>Age-dependent penetrance</td>
<td></td>
</tr>
</tbody>
</table>

## Phenotype category

<table>
<thead>
<tr>
<th>Phenotype Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>Susceptibility to disease</td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic</td>
<td></td>
</tr>
<tr>
<td>Disease risk modifier</td>
<td></td>
</tr>
</tbody>
</table>

## Actionability

<table>
<thead>
<tr>
<th>Actionability Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of disease</td>
<td>Severe outcome</td>
</tr>
<tr>
<td>Likelihood of severe outcome</td>
<td></td>
</tr>
<tr>
<td>Effectiveness of interventions</td>
<td></td>
</tr>
<tr>
<td>Acceptability of interventions</td>
<td></td>
</tr>
</tbody>
</table>

## Clinically tested?

- Offered as a clinical test (Lab?)

## Estimate of certainty (added to each classification score)

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
ClinGen Grant #2

- U01: Berg (UNC), Evans (UNC), Ledbetter (Geisinger), McLeod (UNC), Watson (ACMG) co-PIs
  - Focus on gene-based clinical actionability
  - Emphasis on expert curation
  - Informatics largely to support curation activities
  - ACMG: logistical/meeting coordination
  - Geisinger: EHR integration pilot project
Developing a Semi-Quantitative “Actionability” Scale

An informatics approach to analyzing the incidentalome

Jonathan S. Berg, MD, PhD1-3, Michael Adams, MS1, Nassib Nassar, PhD4, Chris Bizon, PhD4, Kristy Lee, MS1, Charles P. Schmitt, PhD4, Kirk C. Wilhelmsen, MD, PhD1,3,4 and James P. Evans, MD, PhD1-3

Purpose: Next-generation sequencing has transformed genetic research and is poised to revolutionize clinical diagnosis. However, the vast amount of data and inevitable discovery of incidental findings require novel analytic approaches. We therefore implemented for the first time a strategy that utilizes an a priori structured framework and a conservative threshold for selecting clinically relevant incidental findings.

Methods: We categorized 2,016 genes linked with Mendelian diseases into “bins” based on clinical utility and validity, and used a computational algorithm to analyze 80 whole-genome sequences in order to explore the use of such an approach in a simulated real-world setting.

Results: The algorithm effectively reduced the number of variants requiring human review and identified incidental variants with likely clinical relevance. Incorporation of the Human Gene Mutation Database improved the yield for missense mutations but also revealed that a substantial proportion of purported disease-causing mutations were misleading.

Conclusion: This approach is adaptable to any clinically relevant bin structure, scalable to the demands of a clinical laboratory workflow, and flexible with respect to advances in genomics. We anticipate that application of this strategy will facilitate pretest informed consent, laboratory analysis, and posttest return of results in a clinical context.

Key Words: clinical informatics; incidental findings; secondary findings; whole-exome sequencing; whole-genome sequencing
Semi-Quantitative “Actionability” Scale

- 5 key parameters of “medical actionability” when considering the case of genomic incidental findings
  - Severity of disease
  - Likelihood of a severe outcome (akin to penetrance)
  - Effectiveness of interventions (for prevention or amelioration of disease prior to developing symptoms)
  - Acceptability of interventions (considering hazards of intervention in an asymptomatic individual)
  - Knowledge base

- These parameters are then scored on a 0-3 scale to yield a final “actionability score”

- EGAPP formalized this concept for an evidence-based method to determine actionability
  - Katrina Goddard’s group has a subcontract to generate the streamlined evidence review and provide curations for scoring by experts

*Modified from Jonathan Berg*
ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD,1,2 Sherri J. Bale, PhD,3 Pınar 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 Birgıt H. Funke, PhD,9 Madhuri R. Hegde, PhD,10 and Elaine Lyon, PhD,4 for the Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

Test Validation

Figure 2  Next-generation sequencing test development and validation process. CNV, copy-number variant; in/dels, insertions and deletions; sample prep, sample preparation.
Validation (cont.)

• Validation must cover all types of rare variants being reported and address homologous regions

• For common variants, validation should be variant-specific

• Orthogonal confirmation may not be necessary if sufficient validation has been performed, quality metrics are high (coverage, mapping quality, etc) and workflow has low-risk for sample swaps
Variant Calling

• Traditional pipelines perform alignment and variant calling to generate a complete vcf file.

• Genotyping accuracy can be improved through joint calling (batching many cases) but this is challenging for clinical TATs.

• Improved accuracy can also be achieved through targeted “genotype” calling on raw NGS data – more amenable to clinical workflows.
Standards for Lab Reports and EHR Deposition

Covers:
G.1. Turnaround times
G.2. Data interpretation
G.3. Reporting of incidental findings
G.4. Written report
    Supplement contains samples reports for NGS panels and Exome
G.5. Data reanalysis

EHR Recommendations:
Restriction to variants with analytical and clinical validity
Variants in structured form for CDS (full report can be pdf)
Reports Contain Structured Variants

### DNA Variants:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Classification</th>
<th>Parental Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTN</td>
<td>c.37112-1G&gt;A (p.?)</td>
<td>Pathogenic</td>
<td>Maternal</td>
</tr>
<tr>
<td>TTN</td>
<td>c.32854G&gt;C (p.?)</td>
<td>Likely Pathogenic</td>
<td>Paternal</td>
</tr>
<tr>
<td>CLIP1</td>
<td>c.3258G&gt;T (p.Gln1086His)</td>
<td>Uncertain</td>
<td>de novo</td>
</tr>
</tbody>
</table>

**Overall Results:** Positive, Negative, Inconclusive

Variants
Structured to enable clinical decision support
Comprehensive (gene, HGVS nomenclature, zygosity, parent of origin)
Variants classified according to a 5 tier system
### GeneInsight Clinic (EHR Integration)

**Report Details:**
- **Report Identifier:** Lab-B Demo-0009 (LAB-DEMO-B)
- **Report Status:** FINAL
- **Report Date:** 03/26/2013 11:35 AM
- **Test:** Pan Cardiomyopathy Panel (51 Genes)
- **Overall Interpretation:** Possibly Cytodinated
- **Indication:** Clinical diagnosis of HCM
- **Specimen:** No specimen recorded
- **Genomic Source:** Germine

**Variant Information:**
- **ID:** 1
- **Current Category:** Pathogenic (03/26/2013)
- **Reported Category:** Unknown Significance

**Additional Notes:**
*The current category field displays the variant significance for the disease. *Pathogenic* variants are those that are recurrent in families with the disease and are found in patients with the disease, indicating a causal role in disease development. *Unknown Significance* variants have no established correlation with the disease.*
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:

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.

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Phenotype</th>
<th>Gene (Variant)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL, X-linked recessive chondrodysplasia punctata (X-linked)</td>
<td>Abnormal bone and cartilage development</td>
<td>ARSE (c.410G&gt;C p.Gly137Ala)</td>
<td>Uncertain Significance: Favor pathogenic</td>
</tr>
</tbody>
</table>

B. 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>BL, Methylmalonic aciduria and homocystinuria,cb/cb type (Autosomal recessive)</td>
<td>Disorder of cobalamin metabolism</td>
<td>MMACHC (c.271_272insA p.Arg91lysfsX14)</td>
<td>Pathogenic</td>
<td>None Reported</td>
</tr>
<tr>
<td>B2, Leber congenital amaurosis (Autosomal recessive)</td>
<td>Retinal dystrophy and blindness</td>
<td>SPATA7 (c.94+2T&gt;C)</td>
<td>Likely Pathogenic</td>
<td>None Reported</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1. Warfarin</td>
<td>Decreased dose requirement</td>
</tr>
<tr>
<td>C2. Clopidogrel</td>
<td>Typical response to clopidogrel</td>
</tr>
<tr>
<td>C3. Digoxin</td>
<td>Intermediate metabolism and serum concentration of digoxin</td>
</tr>
<tr>
<td>C4. Metformin</td>
<td>Intermediate glycemic response to metformin</td>
</tr>
<tr>
<td>C5. Simvastatin</td>
<td>Typical risk of simvastatin-related myopathy</td>
</tr>
</tbody>
</table>

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

<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</th>
</tr>
</thead>
</table>

**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 Maroteaux-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.
Pharmacogenomic Associations

<table>
<thead>
<tr>
<th>C2. Clopidogrel (Anti-coagulation)</th>
<th>Typical response to clopidogrel</th>
<th>CYP2C19 Genotype Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 rs12248560 rs4244285 rs4986893</td>
<td>Patients with the CYP2C19 *1/*1 genotype may have extensive (typical) metabolism of clopidogrel as well as typical response to clopidogrel as compared to ultrarapid or poor clopidogrel metabolizers. Additional information and dosing recommendations for this result can be found at: <a href="http://www.pharmgkb.org/drug/PA449053">http://www.pharmgkb.org/drug/PA449053</a>.</td>
<td><strong>CYP2C19 GENOTYPE FREQUENCIES</strong></td>
</tr>
<tr>
<td>Genotype: *1/*1 c.[-806C();681G();636G]; c.[-806C();681G();636G]</td>
<td></td>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td></td>
<td>Ultrarapid</td>
<td>*1/*17, *17/*17</td>
</tr>
<tr>
<td></td>
<td>Extensive</td>
<td>*1/*1</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>*1/*2, *1/*3</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
</tbody>
</table>
Cardiac Risk Supplement

D. ALLELES CONFOURING SMALL-MODERATE RISK MODIFICATION FOR EIGHT CARDIOVASCULAR PHENOTYPES

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Contextual Data</th>
<th>Patient Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population Prevalence of Phenotype for Age 56</td>
<td>Proportion of Variation in Phenotype Liability Explained by Common Genetic Variants</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>6%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>13%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Obesity</td>
<td>37%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Unknown</td>
<td>5-10%</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>Unknown</td>
<td>7%</td>
</tr>
</tbody>
</table>

* # of total possible risk alleles = # risk loci x 2 alleles per loci.
** As data utilized in this analysis were derived from non-longitudinal association studies, “Relative Risk from Common Genetic Variation” pertains to near-term risk of developing a phenotype (e.g. approximately 5 year risk), not lifetime risk. “Relative Risk from Common Genetic Variation” and “Percentile Rank of Relative Risk from Common Genetic Variation” values have been estimated using the 1000 Genomes European cohort.

- Polygenic Predicted Fasting Lipid Profile
- Alleles Conferring Small-Moderate Risk for Cardiovascular Traits
ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

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\textbf{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

\textbf{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

\textbf{Other: Malignant hyperthermia susceptibility}

\textbf{56 Genes}

\textbf{Incidental Findings Rates:}
- ClinSeq 2\% (ACMG list of 56 genes)
- Baylor 4.6\% (55/1200) or (2.6\% from ACMG list)
- U Wash 2.3\% (23/1000) from 114 genes
- GeneDx 20\% (10/50) from ACMG list
Variant Analysis for the Genome Report

3-5 million variants

Genes

~20,000 Coding/Splice Variants

Published as Disease-Causing

20-40 “Pathogenic” Variants

Review evidence for variant pathogenicity

97% Excluded

<1%

Pharmacogenetics

Rare CDS/Splice Variants

LOF in Disease Associated Genes

5-10 Variants

30-50 Variants

Review evidence for gene-disease association and LOF role

94% Excluded
Acknowledgements

The MedSeq and BabySeq Projects

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

American College of Medical Genetics

The GeneInsight Team

Laboratory for Molecular Medicine
Genome >>> Report Steps

- Identifies reported pathogenic and rare loss-of-function in disease genes
- Generates >100 fields of data on each variant for dashboard view

Primary Variant Review
- Typically PhD fellow
- Quick exclusions based upon prior exclusions, frequency data, etc
- More thorough review of rare variants identified from filters
- Summarize data for variants and genes using Variant Assessment Tool and Gene Assessment Tool

Secondary Variant Review
- ABMG-boarded geneticist
- Final decision to report and/or bring to committee for discussion

MedSeq Committee
- Lab geneticists, physicians, researchers/biofx, GCs, ethicists
- Review diseases/genes/variants under debate
- Decisions to report/not report are made

Report Draft
- Typically genetic counselor or fellow
- Writes summaries of variant evidence, disease phenotypes and familial risk
- Creates report in standard format

Report Sign-Out
- ABMG-boarded geneticist

1. Is there strong evidence for the gene's role in disease?
2. Is there strong evidence for variant pathogenicity?
3. Should I return this result to the patient?