Translation of Genomics for Patient Care and Research: The Clinical End-User

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Institute of Medicine Roundtable on Translating Genomic-Based Research for Health: Genomics-Enabled Learning Health Care Systems

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Question

What information do clinical end-users need to successfully make decisions about health?
Physicians report unpreparedness for genomic medicine

**Barriers to using genomic medicine in clinical practice:**

- Lack of genomics knowledge and low self-efficacy
- Electronic health records not equipped to incorporate genomic information
- Lack of evidence for clinical utility

Klitzman, et al. J Genet Couns 2013
Selkirk, et al. Genet Test Mol
The MedSeq Project (U01 HG 006500)

- Integrating whole-genome sequencing into the clinical care of:
  - Generally healthy adult primary care patients
  - Patients with cardiomyopathy
- Physicians and patients are all study participants

Principal investigators
Robert Green, Heidi Rehm, and Amy McGuire
Disclosure visit

Disease Specific Genomic Medicine
Cardiology

Standard of care + Family history review + Traditional HCM/DCM genetic testing + Genome report

Family history report +/- genome report sent to physicians

Physician support: Genome Resource Center (GRC)

Disclosure visit

DATA COLLECTION

Physician baseline surveys and interviews

GRC logbook
Audio recording

10 PCPs and 100 of their healthy middle-aged patients

10 cardiologists and 100 of their patients with HCM or DCM

Standard of care + Family history review

Standard of care + Family history review + Genome report
Genome Report

Result Summary
Sequencing of this individual's genome was performed and covered 95.7% of all positions at 6X coverage or higher, resulting in over 5.2 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

Monogenic Disease Risk
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>Gene Transcript</th>
<th>Zygosity Variant</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrodysplasia punctata X-linked</td>
<td>ARSE NM_000047.2</td>
<td>Hemiyygous c.410G&gt;C p.Gly137Ala</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

Carrier Status: 2 Variants Identified
This test identified carrier status for 2 autosomal recessive disorders.

<table>
<thead>
<tr>
<th>Disease Inheritance</th>
<th>Gene Transcript</th>
<th>Zygosity Variant</th>
<th>Classification</th>
<th>Carrier Phenotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis Autosomal Recessive</td>
<td>CFTR NM_000042.3</td>
<td>Heterozygous c.3840G&gt;A p.Trp1282X</td>
<td>Pathogenic</td>
<td>None reported</td>
</tr>
<tr>
<td>Glycogen storage disease 7 Autosomal recessive</td>
<td>PFKM NM_000289.5</td>
<td>Heterozygous c.237+1G&gt;A</td>
<td>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 also would need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

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>Warfarin</td>
<td>Increased dose requirement</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Typical response to clopidogrel</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Intermediate metabolism and serum concentration of digoxin</td>
</tr>
<tr>
<td>Metformin</td>
<td>Decreased glycemic response to metformin</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Typical risk of simvastatin-related myopathy</td>
</tr>
</tbody>
</table>

Red Blood Cell and Platelet Antigens
This test identified the ABO Rh blood type as AB Negative. Based on their results, this person is a very desirable universally compatible platelet donor. Additional RBC and platelet antigen 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.
## Genomics Education for Physicians

<table>
<thead>
<tr>
<th>Case #</th>
<th>Clinical Content Area</th>
<th>Genomic Concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Familial Hypercholesterolemia</td>
<td>- Autosomal dominant and recessive&lt;br&gt;- Modifying genes and penetrance</td>
</tr>
<tr>
<td>2</td>
<td>MODY (Maturity Onset Diabetes of the Young)</td>
<td>- Family history and pedigree analysis&lt;br&gt;- Monogenic forms of common disease</td>
</tr>
<tr>
<td>3</td>
<td>Myotonic Dystrophy</td>
<td>- Expansion repeat disease and anticipation&lt;br&gt;- Variable expressivity</td>
</tr>
<tr>
<td>4</td>
<td>BRCA-related Disease</td>
<td>- Monogenic forms of common disease&lt;br&gt;- Deletion as a mutation mechanism</td>
</tr>
<tr>
<td>5</td>
<td>Alzheimer's Disease</td>
<td>- Monogenic forms of common disease&lt;br&gt;- Non-Mendelian genetic risk for common disease</td>
</tr>
<tr>
<td>6</td>
<td>Cystic Fibrosis</td>
<td>- Autosomal recessive carrier state&lt;br&gt;- Incidental diagnosis of mild disease</td>
</tr>
<tr>
<td>7</td>
<td>Hypertrophic Cardiomyopathy</td>
<td>- Variants of Unknown significance&lt;br&gt;- Database variability</td>
</tr>
<tr>
<td>8</td>
<td>Clopidogrel Pharmacogenomics</td>
<td>- Cytochrome p450 genetics&lt;br&gt;- Splice inducing mutations</td>
</tr>
<tr>
<td>9</td>
<td>Vascular Ehlers-Danlos Syndrome</td>
<td>- Ethical, legal and social implications of genomic information&lt;br&gt;- GINA and MA genetic privacy law</td>
</tr>
<tr>
<td>10</td>
<td>Age-related Macular Degeneration</td>
<td>- Genome Wide Association Studies (GWAS) and risk</td>
</tr>
<tr>
<td>11</td>
<td>Atrial Fibrillation</td>
<td>- Management advice in the setting of pre-symptomatic risk</td>
</tr>
<tr>
<td>12</td>
<td>Thoracic Aortic Aneurysm</td>
<td>- Syndromic vs. non-syndromic disease</td>
</tr>
</tbody>
</table>

Courtesy: Michael Murray
First 10 “healthy” genomes

- Monogenic disease risk in 3 patients:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Variant classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHX4</td>
<td>Combined pituitary hormone deficiency</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>Romano-Ward syndrome (long QT)</td>
<td>Likely pathogenic</td>
</tr>
<tr>
<td>ARSE</td>
<td>Chondrodysplasia punctata</td>
<td>VUS: Favor pathogenic</td>
</tr>
</tbody>
</table>

- Carrier variants in all 10 patients (mean 2.2 variants/patient)
What questions are physicians asking?

Are there standard recommendations for counseling patients concerning the significance of their carrier status for their children?

Would Ehlers-Danlos syndrome have come up on the WGS screen? There is a question of this in my patient’s family.

Given that my patient’s directed screening for HCM genes was negative, are there standard recommendations on the frequency and means for subsequent genetic reassessments?
<table>
<thead>
<tr>
<th>Patient's Result</th>
<th>Test Ordered</th>
</tr>
</thead>
</table>
| **Monogenic Result**  
KCNQ1 c.826delT: Likely Pathogenic Romano-Ward syndrome | EKG  
Referral to Cardiovascular Geneticist |
| **Carrier Status**  
HFE c.845G>A: Pathogenic Hereditary hemochromatosis | Iron/ferritin studies |
How are physicians talking about the results with their patients?
“Negative” Finding

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

“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.”

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.”
<table>
<thead>
<tr>
<th>Theme</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contextualization</strong></td>
<td>Physicians use additional patient information to interpret the validity or significance of a WGS result (e.g. age, family history, physical examination)</td>
</tr>
<tr>
<td></td>
<td>Additional information may be concordant, discordant or uninformative with a WGS result</td>
</tr>
<tr>
<td><strong>Limitations of WGS and WGS results</strong></td>
<td>Interpretation of a WGS result may be limited by technical deficiencies of sequencing or by limited scientific understanding</td>
</tr>
<tr>
<td></td>
<td>Even a valid WGS result may have no impact on clinical decision-making</td>
</tr>
<tr>
<td><strong>Emphasizing or de-emphasizing a WGS result</strong></td>
<td>The physician indicates whether a WGS result is important or not important for the patient</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td>The physician recommends a clinical action to the patient</td>
</tr>
</tbody>
</table>
What information do clinical end-users need to successfully make decisions about health?

- Genetic non-exceptionalism
- Just-in-time information:
  - Test characteristics: limitations, the “denominator”
  - Guidelines or expert recommendations for decision-making
  - Time limits on the validity of the information
- Demonstration of clinical utility
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