Clinical ⇔ Research Enterprises
A Virtuous Cycle
The Concept of Evidence

**Experimental Discovery**
“The perfect experiment”
p-values
Replication
Prior expectation

**Hum Gen Discovery**
p-values entrenched
1 (patent) vs a lot
(e.g. ExAC)
Replication
Prior expectation

**Translation**
Clinical impression entrenched
Professional standards (experts and societies)
Does not like contradictory data
# Evaluating the Clinical Validity of Gene-Based Associations

Strande et al. AJHG, 2017

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive</strong></td>
<td>≥2 independent studies with: • Multiple pathogenic variants in unrelated probands • AND • Several different types of supporting experimental data • OR • Excess of pathogenic variants in cases vs. controls • No convincing contradictory evidence</td>
</tr>
<tr>
<td><strong>Strong</strong></td>
<td>≥1 independent study with: • Several unrelated probands with pathogenic variants • Some supporting experimental data • No convincing contradictory evidence</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>≥1 independent study with: • &lt;3 unrelated probands with pathogenic variants • OR • Multiple variants reported in unrelated probands but <em>without</em> sufficient evidence for pathogenicity • No convincing contradictory evidence</td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td>No evidence reported for a causal role in disease (candidate genes, etc.), therefore no pathogenic variants have been identified in humans to date.</td>
</tr>
<tr>
<td><strong>No Evidence Reported</strong></td>
<td>Convinced evidence disputing a role for this gene in this disease has arisen • Disputing evidence need not outweigh existing evidence supporting the gene:disease association</td>
</tr>
<tr>
<td><strong>Refuted</strong></td>
<td>Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role • Applied at the discretion of clinical domain experts after thorough review of available evidence</td>
</tr>
</tbody>
</table>
Clinical Genome Resource

ClinGen’s Critical Questions

Is this gene associated with a disease?  *Clinical Validity*

Is this variant causative?  *Pathogenicity*

Is this information actionable?  *Clinical Utility*

Curated Genomic Knowledge Base  *ClinVar & Other Resources*

Improved Patient Care

Rehm et al.  
ClinGen.  
NEJM 2015

www.clinicalgenome.org
### ClinGen Scoring System(s)

<table>
<thead>
<tr>
<th>Assertion criteria</th>
<th>Genetic Evidence (0-12 points)</th>
<th>Experimental Evidence (0-6 points)</th>
<th>Total Points (0-18)</th>
<th>Replication Over Time (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Case-level, family segregation, or case-control data that support the gene-disease association</td>
<td>Gene-level experimental evidence that support the gene-disease association</td>
<td>Sum of Genetic &amp; Experimental Evidence</td>
<td>&gt; 2 pubs w/ convincing evidence over time (&gt;3 yrs)</td>
</tr>
</tbody>
</table>

#### Assigned Points

<table>
<thead>
<tr>
<th>CALCULATED CLASSIFICATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LIMITED</td>
<td>1-6</td>
</tr>
<tr>
<td>MODERATE</td>
<td>7-11</td>
</tr>
<tr>
<td>STRONG</td>
<td>12-18</td>
</tr>
<tr>
<td>DEFINITIVE</td>
<td>12-18 AND replication over time</td>
</tr>
</tbody>
</table>
Some comments about “actionability”

Hunter et al. (2016) Genetics in Med: Severity, Effectiveness, Nature of Intervention

What is the action?
        Usually considered modified treatment or preventive measure applied to the patient.
        Reporting is, by itself, an action. The patient’s family? Family planning?

What is the evidence above and beyond traditional evidence (e.g. risk factors)?
        e.g. Cholesterol levels vs LDLR mutation
        Do we treat the genotype or the phenotype?

What is the risk/harm of a misapplied action?
        It is assumed to be high, but it may be quite low in some cases
What we have seen so far is great, but......

WHY WORRY ABOUT THE FUTURE WHEN THE PRESENT IS MORE THAN MOST OF US CAN HANDLE!
.... it doesn’t scale.
NIH Sequencing Efforts

- **TOPMed**
  - CVD Cohorts
  - >130K WGS
  - Multi-omics

- **CCDG**
  - LSAC Evolved
  - 22K WGS Freeze
  - Multiple Cohorts

- **emerge network**
  - 15K Custom Panel
  - Clinical Signout
  - HGSC-cl

- **adsp**
  - 1K Family WGS
  - 11K Case/Control WES

- **CHARGE CONSORTIUM**
  - Cohorts for Heart & Aging Research in Genomic Epidemiology

- **T2D-GENES**
Neptune: Automated Clinical Reporting

- Genes of Interest
- Variant Calling
- Knowledge Base
- Automated Report
- Manual Review
- Final Report

- Raw VCFs
- VIP Filter
- Known Positive
- Negative Pre-Report
- VIP Variants
- Novel Positive
- Novel Clinical Significance

- Gene List
- Mercury
- Sample Data
- Clinical DBs

- BluePrint
- Phenotypes of Interest

- Neptune
- Signout Portal
- Review Portal

- Negative Report
- Positive Report

- Automated Clinical Reporting
BAYLOR HGSC STATUS UPDATE: Interpretation & Reporting
ALL sites, n = 2,417, Variable phenotypes

Indication based
Returnable results

Non indication based
Consensus returnable results

Non indication based
Site-specific returnable results

<table>
<thead>
<tr>
<th>Indications</th>
<th>Total</th>
<th>Pos.</th>
<th>Neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Arrhythmia</td>
<td>31</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Hyperlipidemia a</td>
<td>637</td>
<td>16</td>
<td>621</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>279</td>
<td>2</td>
<td>277</td>
</tr>
<tr>
<td>Breast/Ovarian Cancer b</td>
<td>72</td>
<td>16</td>
<td>56</td>
</tr>
</tbody>
</table>

Hyperlipidemia includes FH, hypertriglyceridemia, hyperlipidemia and coronary artery disease indications.

All returned genes belong to the 68 consensus except for CHEK2 in a breast cancer patient

Path and Lpath variants in NU specific returned

<table>
<thead>
<tr>
<th>Genes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>24</td>
</tr>
<tr>
<td>ATM</td>
<td>7</td>
</tr>
<tr>
<td>SERPINA1</td>
<td>2</td>
</tr>
<tr>
<td>MC4R</td>
<td>3</td>
</tr>
<tr>
<td>KCNE1</td>
<td>6</td>
</tr>
<tr>
<td>F11, FLG, KCNE2 (x1)</td>
<td>3</td>
</tr>
</tbody>
</table>

a 1 patient had 2 variants

a 3 patients not included with indication based results

n = 1,020
n = 2,417
n = 1,209
Neptune: Automated Clinical Reporting

Neptune

- Knowledge Base
- VIP Filter
- VIP Variants

Automated Report

Manual Review

Final Report

Negative Pre-Report

Known Positive

Novel Positive

Negative Report

Positive Report

Signout Portal

Review Portal

Novel Clinical Significance

Clinical DBs

Neptune:

- Automated Clinical Reporting
How can expert curation be scaled?

Developing national healthcare services with crowdsourcing

Paradigm shift we’ve been waiting for?