Determining Medical Actionability of Gene/Disease Pairs and Relevance to Newborn Screening

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Next Generation Sequencing

Pipeline Overview

Targeted Sequencing

Patient

DNA sample collected

Library and Sample preparation

NGS platform DNA sequencing

Fastq
Augment, mapping

variant calling

Bioinformatics computing facility

Targeted Analysis

Final consolidated clinical report

Specialist validation and conclusions

Visualization and Analysis

NC NEXUS BINNING COMMITTEE

- Clinical geneticists
- Biochemical geneticists
- Genetic counselors
- Metabolic dietitians
- Molecular geneticists
- Medical genetics resident, fellows, post-docs, graduate students
A semi-quantitative metric is used to score “Medical Actionability” on a 0-3 Point Scale for 5 Criteria:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of Disease</strong></td>
<td>&quot;What is the effect on morbidity/mortality to an individual carrying a pathogenic variant in this gene?&quot;</td>
<td>Modest or No Morbidity</td>
<td>Serious/Chronic Morbidity or Moderate Intellectual Impairment</td>
<td>Possible Death/Severe Intellectual Impairment</td>
<td>Sudden Death or Unavoidable Death in Childhood (&lt;10yo)</td>
</tr>
<tr>
<td><strong>Likelihood of Outcome</strong></td>
<td>&quot;What is the chance that a problem will materialize?&quot;</td>
<td>&lt;1%</td>
<td>1-5%</td>
<td>5-49%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td><strong>Efficacy of Intervention</strong></td>
<td>&quot;How effective are the interventions for preventing harm in a presymptomatic individual?&quot;</td>
<td>No Effective Intervention</td>
<td>Minimally Effective</td>
<td>Modestly Effective</td>
<td>Highly Effective</td>
</tr>
<tr>
<td><strong>Acceptability of Intervention</strong></td>
<td>&quot;How acceptable are the interventions in terms of the burdens or risks placed on the individual?&quot;</td>
<td>No Effective Intervention</td>
<td>Minimally Acceptable</td>
<td>Modestly Acceptable</td>
<td>Highly Acceptable</td>
</tr>
<tr>
<td><strong>Knowledge Base</strong></td>
<td>&quot;What is the evidence base for decisions about the natural history of the disease, and interventions used for preventing serious outcomes?&quot;</td>
<td>Poor</td>
<td>Minimal</td>
<td>Modest</td>
<td>Substantial Evidence and/or Practice Guidelines</td>
</tr>
</tbody>
</table>
Example: PAH (PKU)

- Severity of disease (severe ID) = 2
- Likelihood of disease = 3
- Effectiveness of interventions (diet) = 3
- Acceptability of interventions = 2
- Knowledge base = 3

• TOTAL SCORE of 13
NGS NBS Candidate Condition

• Multiple Endocrine Neoplasia type 2B
  • Medullary thyroid carcinoma in early childhood with high rate of metastases
    • 100% penetrance
  • Pheochromocytoma
    • 50% penetrance
• Mucosal neuromas
• Marfanoid body habitus
Example: RET (MEN2B)

- Severity of disease (possible death) = 2
- Likelihood of a severe outcome = 3
- Effectiveness of interventions = 3
- Acceptability of interventions = 2
- Knowledge base = 3

• TOTAL SCORE of 13
Example: KCNH2 (Long QT syndrome)

- Severity of disease (sudden death) = 3
- Likelihood of a severe outcome = 2
- Effectiveness of interventions = 2
- Acceptability of interventions = 3
- Knowledge base = 3

• TOTAL SCORE of 13
Results

• 15,350 human genes in OMIM database (as of 8/18/2016)

• ~4800 OMIM genes with phenotypic description and molecular basis known

• 790 Gene/Condition pairs scored in NC NEXUS
  • 499 finalized
  • 291 pending further review/binning
307 Pediatric Actionable Conditions
- **Examples**
  - PAH: Phenylketonuria
  - CFTR: Cystic fibrosis
  - RET: Multiple Endocrine Neoplasia IIB
  - APC: Familial adenomatous polyposis
  - WT1: Denys-Drash syndrome/Wilms tumor

174 Pediatric Non-Actionable Conditions
- **Examples**
  - MECP2: Rett syndrome
  - HEXA: Tay Sachs
  - GALC: Krabbe
  - HPD: Tyrosinemia type III

13 Adult Non-Actionable Conditions
- **Examples**
  - HTT: Huntington disease
  - CLN8: Neuronal ceroid lipofuscinosis type 8
  - PSEN1: Early onset Alzheimer disease

31 Adult Actionable Conditions
- **Examples**
  - BRCA1, BRCA2: Hereditary breast and ovarian cancer
  - MSH6/PMS2: Lynch syndrome

Variable Onset Actionable Conditions
- **Examples**
  - KCNH2: Romano-Ward I
  - TPM1: Hypertrophic cardiomyopathy 3

Variable Onset Non-Actionable Conditions
- **Examples**
  - F12: Factor XII deficiency/angioedema
  - CATSPER2: SNHL with male infertility

Gray Zone
- Manual review by committee
NC NEXUS TEAM

Principal Investigators
• Cynthia Powell – PI and Project 2 PI
• Jonathan Berg – PI and Project 1 PI
• Don Bailey – Project 3 PI

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• Pat Roush – Project 2
• Neeta Vora – Project 2
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• Phillips Owen - RENCI

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