SYSTEMATIC ASSESSMENT OF CLINICAL ACTIONABILITY ASSOCIATED WITH GENOMIC VARIATION

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Center for Health Research
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E. Andy Rivera
Clinical Genome Resource (ClinGen)

- NIH-funded program launched Sept. 2013
  - Co-funding from the NHGRI, NICHD, and NCI
  - Collaboration with NCBI’s ClinVar
  - > 250 researchers & clinicians from >75 institutions

- **Purpose:** Create authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research.
ClinGen’s Critical Questions

- Is this gene associated with a disease? *Clinical Validity*
- Is this variant causative? *Pathogenicity*
- Is this information actionable? *Clinical Utility*

Building a Genomic Knowledge Base
*ClinVar & Other Resources*

Improved Patient Care Through Genomic Medicine
ClinGen Actionability Working Group:
Develop a framework to provide a transparent and systematic evidence base for prioritizing genes based on their clinical actionability.
Clinical Context

- Adult with an incidental or secondary finding via genome-scale sequencing
- Strong or definitive association with disease
- Not previously diagnosed with the genetic condition
- May have signs or symptoms of disease, but not diagnosed
Clinical Actionability

- Well established clinical interventions
- Specific to the genetic disorder under consideration
- Lead to disease prevention or delayed onset, lowered clinical burden, or improved clinical outcomes
Qualitative Evidence Synthesis

- Standardized
- Reproducible
- Feasible

Semi-Quantitative Metric

- Quantify
- Prioritize
- Compare

Knowledge Synthesis Team

Actionability Working Group
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Stage II: Evidence Synthesis

Evidence Sources

Standardized search:
- Systematic reviews, clinical practice guidelines, and meta-analyses
- OMIM, GeneReview, and OrphaNet entries
- Clinical Utility Gene Cards
- EXCLUDED: Narrative reviews and primary literature excluded

Highest Tier of Evidence

Tier 1: Systematic review, meta-analysis or practice guideline based on systematic review
Tier 2: Practice guideline or expert consensus
Tier 3: Non-systematic evidence review with citations (e.g., GeneReview, OMIM)
Tier 4: Non-systematic evidence review with no citations (e.g., OrphaNet)
Stage II: Evidence Synthesis

Limited (high quality), feasible

Comprehensive, impractical
Stage II: Evidence Synthesis

Evidence Sources

Highest Tier of Evidence

Summary Report

Evidence compiled into written summary
May be supplemented with evidence from a Tier 5 (non-systematically identified) sources as needed
Tier 5: sources may include primary literature
## Domains of Clinical Actionability

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- Standardized
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Semi-Quantitative Metric

- Quantify
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| **LIKELIHOOD**                    |                |
| What is the chance a serious outcome will materialize given a deleterious variant? | 3 = > 40% chance  
2 = 5 - 39% chance  
1 = 1 - 4% chance  
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<td>B = Moderate evidence (Tier 2)</td>
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<td></td>
<td>C = Minimal evidence (Tier 3 or 4)</td>
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<td>D = Poor evidence, or missing</td>
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<td>E = Expert contributions (Tier 5)</td>
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Scoring Outcome-Intervention Pairs

- Breast Cancer + Surveillance: 10AA
- Breast Cancer + Mastectomy: 9AA
  - ↑ Effectiveness
  - ↓ Nature of the intervention
- Ovarian Cancer + Oophorectomy: 8AA
  - ↑ Effectiveness
  - ↓ Penetrance
  - ↓ Nature of the intervention
Scoring Outcome-Intervention Pairs

*MUTYH*-Associated Polyposis

Outcomes

- Colorectal cancer

Interventions

- Colonoscopy

Additional outcomes and interventions:

- Breast cancer
- Ovarian cancer
- Sarcomas
- CNS Tumors
- Adrenocortical tumors

Risk reducing surgery

Avoidance of radiotherapy

MUTYH-Associated Polyposis

Li Fraumeni Syndrome
Scoring Process

- Preliminary Score
- Discussion
- Final Score

Consensus Score
A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation

Jessica Ezzell Hunter, MS, PhD1, Stephanie A. Irving, MHS1, Leslie G. Biesecker, MD2, Adam Buchanan, MS, MPH3, Brian Jensen, MD4, Kristy Lee, MS5, Christa Lese Martin, PhD6, Laura Milko, PhD5, Kristin Muessig, MS1, Annie D. Niehaus, BA7, Julianne O’Daniel, MS8, Margaret A. Piper, PhD, MPH8, Erin M. Ramos, MPH, PhD8, Sheri D. Schully, PhD8, Alan F. Scott, PhD8, Anne Slavotinek, MBBS, PhD9, Nara Sobreira, MD, PhD9, Natasha Strande, PhD9, Meredith Weaver, ScM, PhD10, Elizabeth M. Webber, MS1, Marc S. Williams, MD11, Jonathan S. Berg, MD, PhD5, James P. Evans, MD, PhD5, Katrina A.B. Goddard, PhD1; on behalf of the ClinGen Resource
Perfect 12s

- 4 pairs have received perfect scores
- All genes currently on ACMG list (*FBN1, TGFBR1, TGFBR2, SMAD3*)
- Loeys-Dietz syndrome 1 and Marfan syndrome
  - Beta-blockers for prevention of aortic dilation progression
  - Surveillance for aortic aneurysms
Distribution of scores for all Outcome-Intervention Pairs

To date:
66 topics, 166 pairs scored
Average score: 9.3
ACMG and non-ACMG topics

• ACMG: Average- 9.5
  • Range: 8-12
    • 8: APC (FAP)
      • Nature of the intervention scores low for colectomy

• Non-ACMG: Average- 8.8
  • Range: 6-11
    • 6: MEFV (Autosomal dominant familial Mediterranean fever)
      • No evidence on penetrance in AD form, less severe phenotype
      • Autosomal recessive form scores higher
High scores not on ACMG list

4 genes have scored 11

- **SERPINA1** (Alpha-1 Antitrypsin Deficiency)
  - Smoking cessation
  - Serum A1AT monitoring

- **BTD** (Biotinidase deficiency)
  - Biotin therapy

- **HNF1A** (Maturity Onset Diabetes of the Young, Type 3)
  - Sulfonylureas for diabetic control

- **ENG** (Hereditary Hemorrhagic Telangiectasia)
  - Echocardiography to detect pulmonary arteriovenous malformations
Extrapolation

• Lack of effectiveness data for some interventions specific to population
• Example: LFS
Familial Breast Cancer

Clinical guideline 164
Familial breast cancer, 2013 (Tier 1)

- Tier 1: Evidence-based
- BRCA1/BRCA2: HBOC
- TP53: LFS
- Breast cancer rec’s by risk category:
  - Risk reducing surgery
  - Surveillance
- High risk rec’s based on BRCA populations

<table>
<thead>
<tr>
<th>Breast cancer risk category</th>
<th>Near population risk</th>
<th>Moderate risk</th>
<th>High risk¹</th>
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<tbody>
<tr>
<td>Lifetime risk from age 20</td>
<td>Less than 17%</td>
<td>Greater than 17% but less than 30%</td>
<td>30% or greater</td>
</tr>
<tr>
<td>Risk between ages 40 and 50</td>
<td>Less than 3%</td>
<td>3–8%</td>
<td>Greater than 8%</td>
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¹This group includes known BRCA1, BRCA2 and TP53 mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11), Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).

Effectiveness of the Intervention Scores

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<tr>
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<th>Risk Reducing Surgery</th>
<th>Surveillance</th>
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<tr>
<td>HBOC</td>
<td>3A</td>
<td>2A</td>
</tr>
<tr>
<td>LFS</td>
<td>3B*</td>
<td>2B*</td>
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Wilson Disease

“Unknown” Penetrance

- No penetrance estimates in literature
- Segregation analysis → Autosomal recessive inheritance
- Penetrance of at least some clinical characteristics would need to be high

Penetrance = 3D

3 = High (>40%)
D = Poor evidence/Missing
## Hemophilia A and B
### Disorders with (mostly) Childhood Onset

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<tr>
<th>Severity</th>
<th>Factor Level</th>
<th>Age</th>
<th>Spontaneous Bleeding</th>
<th>Bleeding with trauma</th>
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<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>&lt;2 yrs</td>
<td>+++</td>
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<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>&lt;5-6 yrs</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Mild</td>
<td>6-40%</td>
<td>Later in life</td>
<td>-</td>
<td>+</td>
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### SEVERITY

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<td>Scorer 2</td>
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<td>Scorer 3</td>
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- **SEVERITY**
  - 3 = Sudden death
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  - 0 = Minimal or no morbidity
How do you interpret a 9CB?
Going Forward

- Evidence summaries and scores publically available: www.clinicalgenome.org
- Additional topics
- Expand protocol to address sequencing in children
- Visualization of scores
Questions?
Genes and Disorders Assessed
ACMG 56

- Arrhythmogenic right-ventricular cardiomyopathy
- Brugada syndrome*
- Catecholaminergic polymorphic ventricular tachycardia
- Dilated cardiomyopathy
- Ehlers Danlos syndrome, type 4
- Fabry disease
- Familial adenomatous polyposis
- Familial hypercholesterolemia
- Familial thoracic aortic aneurysms and dissections
- Hereditary breast and ovarian cancer
- Hereditary paraganglioma-pheochromocytoma syndrome
- Hypertrophic cardiomyopathy
- Li-Fraumeni syndrome
- Loeys-Dietz syndrome
- Lynch syndrome
- Malignant hyperthermia susceptibility
- Marfan syndrome
- Multiple endocrine neoplasia, type 1
- Multiple endocrine neoplasia, type 2B
- MUTYH-associated polyposis
- Neurofibromatosis, type 2
- Peutz Jeghers syndrome
- PTEN hamartoma tumor syndrome
- Retinoblastoma*
- Romano-Ward long QT syndrome
- Tuberous sclerosis complex
- Von Hippel-Lindau syndrome
- WT1-related Wilms tumor*

*Did not pass Stage I

Hunter et al. 2016 Genetics in Medicine
Genes and Disorders Assessed Beyond the ACMG 56

- Acute intermittent porphyria
- Alpha-1 antitrypsin deficiency
- Alzheimer disease*
- Basal cell nevus syndrome
- Biotinidase deficiency
- Birt-Hogg-Dube syndrome
- BRCA2-Pancreatic cancer*
- CADASIL
- Charcot-Marie-Tooth, type 1
- Congenital disorders of glycosylation, type Ia*
- Cystic fibrosis*
- Factor V leiden
- Familial atrial fibrillation*
- Familial Mediterranean Fever
- Gaucher
- Gastrointestinal stromal tumor*
- Hemophilia A and B
- Hemochromatosis
- Hereditary diffuse gastric cancer
- Hereditary hemochromatosis, type 1
- Hereditary hemorrhagic telangiectasia
- Hereditary neuropathy with liability to pressure palsies
- Homocystinuria
- Juvenile polyposis syndrome
- Leiomyomatosis and renal cell cancer
- Maturity onset diabetes of the young, type 3
- Methylmalonic acidemia
- Ornithine transcarbamylase deficiency
- Parkinson disease*
- PALB2-Breast cancer
- Phenylketonuria
- Polycystic kidney disease
- Pompe disease
- Wilson disease

*Did not pass Stage I
| ACTIONABILITY | • Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?  
• Does the practice guideline or systematic review indicate that the result is actionable?  
• Is the result actionable in an undiagnosed adult with the genetic condition? |
| PENETRANCE | • Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population? |
| SIGNIFICANCE/BURDEN OF DISEASE | • Is this an important health problem? |
Examples of topics that did not pass Stage 1

- Childhood onset:
  - Retinoblastoma
  - WT1-related Wilms tumor

- Penetrance:
  - Brugada syndrome: exception made

- Lack of guidelines:
  - Cystic fibrosis
  - KCNE2 (familial atrial fib)
  - KIT/PDGFRA (GISTs)
Highest Score for Each Topic

The bar chart shows the highest score for each topic, with scores ranging from 0 to 0.5. The topics are labeled as 1 to 12, with the highest score being observed for topic 10.
Familial Breast Cancer

Extrapolation of Evidence

- PALB2 Penetrance
  - 14% by age 50
  - 35% by age 70

Effectiveness of the Intervention Scores

<table>
<thead>
<tr>
<th></th>
<th>Risk Reducing Surgery</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td>3A</td>
<td>2A</td>
</tr>
<tr>
<td>LFS</td>
<td>3B*</td>
<td>2B*</td>
</tr>
<tr>
<td>PALB2</td>
<td>3B*</td>
<td>2B*</td>
</tr>
</tbody>
</table>

1. This group includes known BRCA1, BRCA2 and TP53 mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11), Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).
While no breast cancer screening recommendations were identified for PALB2 mutation carriers, breast cancer screening guidelines agree that women at an increased risk level corresponding to the lifetime risk of a PALB2 mutation carrier should receive earlier breast cancer screening than the general population. However, recommendations for age to start, frequency, and the use of mammography versus MRI vary between guidelines.