Genomics and Population Health Action Collaborative Meeting
Year 1: Recap from the Evidence Working Group

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Evidence Working Group

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- **Dave Dotson**, CDC Office of Public Health Genomics
- **Jim Evans**, University of North Carolina at Chapel Hill
- **Heather Hampel**, Ohio State University
- **George Isham**, HealthPartners
- **Cecile Janssens**, Emory University
- **Muin Khoury**, CDC Office of Public Health Genomics
- **Roger Klein**, Cleveland Clinic
- **Jeanne Mandelblatt**, Georgetown University
- **Doug Campos Outcalt**, Mercy Care Plan
- **Sun Hee Rim**, CDC Division of Cancer Prevention and Control
- **Wendy Rubinstein**, NIH Genetic Testing Registry
- **Sheri Schully**, NIH Office of Disease Prevention
- **Corey Snelson**, Washington State Department of Health
- **Katherine Wilemon**, The FH Foundation
- **Ann Graham Zauber**, Memorial Sloan Kettering Cancer Center
Outline

- Horizon Scanning: the starting point
- Tier I tests
- Case 1: BRCA1&2
  - USPSTF assessment
  - ClinGen assessment
  - Implementation
- Case 2: Lynch syndrome
  - EGAPP Working Group assessment
  - ClinGen assessment
  - Implementation: cascade screening
Outline (cont.)

- Research gaps
  - Implementation (public health support)
- Population health: modeling strategies
- Summary and what’s next
Horizon scanning

- The starting point for genomic test assessment
- Process created with EGAPP and OPHG
- Process implemented by OPHG
- Similar method used by ClinGen
- Fair to large amount of evidence around analytic validity and clinical validity, much less for clinical utility
- Scanning can assist in high-level assignment to tiers:
  - Tier 1: Sufficient evidence to support clinical recommendation
  - Tier 2: Potential clinical utility but evidence insufficient to support clinical guideline
  - Tier 3: Sufficient evidence of no clinical utility, net harm, or no synthesized evidence
Tier I tests

Population (county, state, region, nation) net benefit
  --Modeling
Specific population (health care system) net benefit
  --Health Services research
Family member net benefit
  --Chain of evidence assessment
Individual net benefit
  --RCTs, chain of evidence assessment
Test availability
Tier I tests

- BRCA1&2 --USPSTF, ClinGen
- Lynch syndrome --EGAPP WG, ClinGen
- Familial hyperlipidemia --NICE, ClinGen

- Unlikely that there are more single gene/small cluster of genes that will meet Tier I criteria
  - Perhaps we should retain the chance that a large (lots and lots) of associated SNPs might—supported by analysis via massive computing power—reach the level of sufficient evidence of clinical utility
BRCA1&2: USPSTF assessment

- Systematic Evidence Review
- No RCTs—review depends on evidence chain
  - Sufficient evidence you can determine high risk women via risk assessment
  - Sufficient evidence counseling supports testing decisions
  - Sufficient evidence that intervention in positive patients leads to significant decreased mortality
  - Insufficient evidence about harms, but assessment that harms are no more than small
- Sufficient certainty of sufficient net benefit: B rec
# BRCA1 & 2: ClinGen Assessment

## Final Consensus Scores – Hereditary Breast and Ovarian Cancer

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Outcome/Intervention</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Effectiveness</th>
<th>Nature of the intervention</th>
<th>Total Score</th>
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<td><strong>BRCA1</strong></td>
<td>Breast cancer/surveillance</td>
<td>2</td>
<td>3A</td>
<td>2A</td>
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<tr>
<td></td>
<td>Ovarian cancer/Oophorectomy</td>
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<td>2A</td>
<td>3A</td>
<td>1</td>
<td>8AA</td>
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<tr>
<td><strong>BRCA2</strong></td>
<td>Breast cancer/surveillance</td>
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<td>3A</td>
<td>2A</td>
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</tr>
<tr>
<td></td>
<td>Breast cancer/Mastectomy</td>
<td>2</td>
<td>3A</td>
<td>3A</td>
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<td>9AA</td>
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<tr>
<td></td>
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<td>2</td>
<td>2A</td>
<td>3A</td>
<td>1</td>
<td>8AA</td>
</tr>
</tbody>
</table>
Universal screening (all women)

- **Pros:**
  - Does not require risk assessment
  - Maximizes sensitivity and negative predictive value

- **Cons:**
  - Minimizes specificity and positive predictive value—penetrance in the general population is unknown
  - Costs—test costs will drop, but interpretation and counseling costs and services may not be feasible or equitable
  - Total costs are (likely) maximized
BRCA1&2: strategies

- **Cascade screening**
  - Pros: increases specificity, positive predictive value and cost-effectiveness
  - (Likely) decreases total costs
  - Consistent with current guidelines

- **Cons:**
  - Will miss some positive women who could benefit
  - Difficult to implement outside of organized care systems

- Could be a place for public health support
Lynch syndrome: EWG assessment

- Systematic Evidence Review
- No RCTs—review depends on evidence chain
  - Sufficient evidence you can test for Lynch Syndrome (AV)
  - Sufficient evidence positive tests indicate elevated cancer risk
  - Sufficient evidence that screening in family members who test positive leads to significant decreased mortality
  - Insufficient evidence about harms, but assessment that harms are no more than small
## Lynch syndrome: ClinGen assessment

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Outcome/Intervention</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Effectiveness</th>
<th>Nature of the intervention</th>
<th>Total Score</th>
</tr>
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</tbody>
</table>
Lynch syndrome: strategies

- Identification of high risk individuals (Amsterdam I, II criteria; Bethesda criteria)—largely abandoned for other strategies
- Reflex/universal tumor testing (can guide therapy—may well be standard of care)
- Cascade testing—universal tumor testing with identification, counseling, testing and enhanced screening (or maybe, ASA therapy) for affected family members: most cost effective approach, though test costs will drop
  - Could be a place for public health support
Evidence gaps: Public health support/implementation

- Is there evidence that public health support can improve screening, information sharing, linkage with care (counseling)?
- Five states with CDC grants—stay tuned
- Are there evidence-based learnings from other public health support programs that can provide guidance for public health genomics (Community Task Force on Preventive Services)
Evidence gaps: Population health impact and costs

- No evidence that population-based BRCA1&2 and Lynch syndrome screening improve population health (reduced morbidity/mortality)
- Modeling can provide estimates, with bounds, about what the benefit (and harms) could be based on prevalence, penetrance, effectiveness (effect size), many other factors (compliance, for example)
- Modeling can provide estimates of cost-effectiveness and total costs
- Total costs and population net benefit drive public health decision-making
Summary and what’s next

- There are strategies for using evidence to determine whether public health should pursue genomic medicine support, and for what tests
- There are significant evidence gaps for public health implementation
- We can provide states with information that help them make decisions about whether and how to do public health genomics
- Time to move on to familial hyperlipidemia