Genomics in Public Health

Vision and Goals for the Cascade Screening Working Group

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Cascade Screening Working Group Vision

• Identify gaps in research and barriers to implementation of cascade screening in the US
• Identify and enable public health / healthcare interfaces to accelerate cascade screening for all Tier 1 conditions.
• Meaningful, demonstrated pilot results within 1 year!

“….the concept of “cascade” testing, in which at-risk family members of those with pathogenic mutations undergo screening, can be seen as a ‘bridge’ to inform population screening.”

Jim Evans & Sun Hee Rim
Our Collective Goal: Cascade Screening for All Tier 1 Hereditary Conditions

Cancer (HBOC, Lynch Syndrome)

“Advantages to this approach [Cascade Screening] include limiting the number of individuals that need to be tested, and the identification of a specific cancer-causing mutation that family members can then be tested for as cost saving measures.”

Approaches To Identifying BRCA1 and BRCA2 Mutations, Corey Snelson

Cardiovascular (FH)

“Because of the high prevalence of FH among family members, cascade screening has been shown to be a cost-effective method of identifying people with FH. Early detection and treatment with statins have been shown to reduce morbidity and mortality among those with heterozygous FH”.

Cascade Screening for Familial Hypercholesterolemia, Ned & Sijbrands
Cascade Screening Rationale

• Once an individual is diagnosed with an actionable autosomal dominant adult-onset condition:
  • 50% of their FDRs will also be affected
  • 25% of their SDRs will also be affected
  • 12.5% of their TDRs will also be affected

• Cascade screening: Most effective in identifying large numbers of individuals affected with Tier 1 hereditary conditions

• Optimizing cascade screening is important
  • This approach will be needed whether we are screening affected individuals first (with the undesirable “signal”) or whether we are performing population screening

• Population screening now on all 18 year olds in the US, we still have millions of people who wouldn’t be screened
  • Will take years to get full “saturation”
  • In the meantime, we still need cascade testing
Value Proposition

• Cascade testing is the key to cost-effectiveness of universal screening programs

• Most screening programs involve substantial up front costs
  • Have to test a lot of people to identify probands with the condition of interest
  • Cascade screening optimizes the efficiency of using genetic testing for prevention

• The more at-risk relatives that can be tested, the more cost-effective and **life-saving** the entire screening program
Screening + Earlier Intervention = Better Outcomes

Coronary disease & death before age 20

Homozygous FH

Threshold for CHD

Start high dose statin

Start low dose statin

Without FH

Untreated coronary disease before age 55/60

Heterozygous FH

Female sex

Smoking
Hypertension
Diabetes
↑Triglycerides
↓HDL-C
↑Lipoprotein(a)

Nordestgaard BG et al. Eur Heart J 2013;34:3478–3490a

Coronary disease & death before age 20

Without FH

Cumulative LDL-C (mmol)
Research Gaps and Implementation Barriers Requiring Attention

• Review and summarize the evidence base for cascade testing in FH and HBOC
  • LS was completed as part of the GPHAC Evidence Working Group

• Review and summarize the cost-effectiveness evidence
  • Isolate and study where additional research is needed

• Review and summarize data regarding life years saved

• Review and summarize current impediments to contacting at-risk relatives directly pertaining to:
  • Legal issues
  • Acceptability
  • Evaluate making Tier One Conditions reportable
Developing FH Evidence & Tracking Measures

Child–parent screening was feasible in primary care practices at routine child immunization visits. For every 1000 children screened, 8 persons (4 children and 4 parents) were identified as having positive screening results for familial hypercholesterolemia...

National FH Registry: family screening offered to 4,000 families. FH Foundation USA

Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

Amit V. Khera, MD, Hong-Hee Won, PhD, Gina M. Peloso, PhD, Traci M. Bartz, MS, Xuan Deng, MSc, Elisabeth M. van Leeuwen, Pradeep Natarajan, MMSc, Connor A. Emdin, HBSc, Alexander G. Bick, PhD, Alanna C. Morrison, PhD, Jennifer A. Brody, BA, Namrata Gupta, PhD, Akhilo Nomura, MD, Thorsten Kessler, MD, Stefano Duga, PhD, Joshua G. Bis, PhD, Cornelia M. van Duijn, PhD, L. Adrienne Cupples, PhD, Bruce Psaty, MD, PhD, Daniel J. Rader, MD, John Danesh, PhD, Heribert Schunkert, MD, Ruth McPherson, MD, Martin Farrall, MD, Hugh Watkins, MD, PhD, Eric Lander, PhD, James G. Wilson, MD, Adolfo Correa, MD, PhD, Eric Boerwinkle, PhD, Piera Angelica Merlini, MD, Diego Ardissino, MD, Danish Saleheen, MBBS, PhD, Stacey Gabriel, PhD, Sekar Kathiresan, MD.
# Lynch Syndrome Cost Effectiveness

<table>
<thead>
<tr>
<th>Strategy</th>
<th>6 relatives tested per proband</th>
<th>12 relatives tested per proband</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC, BRAF testing &amp; sequencing</td>
<td>$22,552</td>
<td>$12,332</td>
</tr>
<tr>
<td>IHC testing &amp; sequencing</td>
<td>$23,321</td>
<td>$12,663</td>
</tr>
<tr>
<td>MSI testing &amp; sequencing</td>
<td>$41,511</td>
<td>$20,470</td>
</tr>
<tr>
<td>Genetic sequencing for 4 genes</td>
<td>$142,289</td>
<td>$63,773</td>
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More Evidence Needed On Other Tier 1 Conditions
## FH Cost Effectiveness Indicators

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number needed to treat</td>
<td>222*</td>
</tr>
<tr>
<td>Cascade Screening (Yield of family members found per proband)</td>
<td>8**</td>
</tr>
<tr>
<td>Reverse Cascade screening (Child-parent screening yield)</td>
<td>8 persons per 1000 screened***</td>
</tr>
</tbody>
</table>
| Proband vs. family testing gene sequencing costs | ~$1,200 Proband  
~ $500 Each Family Member |

*Number of individuals needed to treat with statins to prevent 1 death from FH per year (Knowles, JACC 2016)

**Data from Dutch national screening program (Umans-Eckenshausen et al., Lancet, 2001)

***4 children, 4 parents (Wald et al. *NEJM* 2016.)
Operating Model for Cascade Screening

Central coordination of genetic counselors at state, regional (e.g., health system) or national level (e.g., disease nonprofit) to whom probands would be reported and who would be in charge of cascading for the family.

Advantages:
• Solutions largely generalizable to all tier 1 conditions
• Not affected by how probands are identified (lipid screening, universal tumor screening, general population germline panel testing, etc.)
• Can refer out-of-state relatives to the cascade screening genetic counselor in the appropriate state
• Compare numbers of relatives tested prior-to-implementation to post-implementation
• Use existing infrastructure of cancer state registries and national disease registries
Approaches to Optimize Uptake

• Data showing that having a local person responsible for cascade testing reaching out to at risk relatives directly is more successful than relying on the proband to make referrals for relatives

  • LS – 6 relatives counseled/tested per proband identified in a research setting with 3 mutation+ compared to 3.6 relatives counseled/tested per proband with 1 mutation+ in normal clinical scenario

  • FH – Netherlands 25 relatives counseled/tested per proband identified compared to 4 relatives counseled/tested per proband in Norway using referral modality

• Overall effort should be centrally coordinated but the "reach out” needs to be from an known person
Privacy and HIPPA Considerations

• Covered entities versus Non-Covered Entities (e.g., Disease Nonprofit)
• Research Studies versus Clinical Care
• Federal and State Laws
• PHI, Genetic, and Consumer Protections
• Infectious disease analogs
Should Tier 1 Conditions be Reportable?

“Public health control of infectious outbreaks has achieved great success through a process of index patient identification followed by contact elicitation to identify, evaluate, and treat exposed individuals. ... 

... ‘Cascade’ genetic screening uses an analogous approach of proband identification and family member contacting, evaluation, and management. **In essence, the family is the ‘outbreak,’ but the transmission is genetic, not infectious. “**

LYNCH SYNDROME CASCADE SCREENING AND PUBLIC HEALTH

Author: Wendy Rubinstein
Ideas for Action

**Public Policy**
Example: Tier 1 Conditions Reportable

**Genetic Counseling Model**
Example: State, Regional, National or Tele-health Delivery

**Public / Private Partnership**
Example: National registry with bidirectional reporting

**Benefits**
- Consent to share health information for benefit of at-risk population
- Expand utilization of GC’s despite fragmented hc delivery & dispersed families
- Innovative use of multiple stakeholder assets