Genomics in Public Health

Vision and Goals for the Population Screening Working Group

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Jim Evans
Co-chairs; IOM Action Collaborative

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Washington DC
Intent of IOM Action Collaborative

1. Convene those with interest and expertise in public health genomics
2. Identify important research questions that remain unanswered and are critical to implementation of genomic public health efforts
3. Develop a “framework” to help guide those wishing to implement public health genomics programs
   • Main target audience: state public health departments
4. Prompt/facilitate the launch of 2 or more pilot studies
5. Generate interest by potential funders to study PHG
Framework

• Rationale for general population screening of adults via targeted sequencing of carefully selected genes
  – 1-2% of general population harbors pathogenic variants conferring high risk of serious - but preventable disease
  – Technology now exists to enable affordable identification of such at-risk individuals
  – Cascade screening, even if applied in an optimal manner, will miss >50% of cases
    • And relies on an undesirable “signal” – death and/or disease in an individual and/or family to trigger tumor screening

We screen newborns, don’t we?
Where is Appropriate “Locus” for Policy Recommendations?

• For ongoing deliberation and recommendations regarding:
  – Appropriate genes for adult screening
  – Appropriate nature of variants that constitute “positives”
  – Appropriate recommendations for preventive action
  – etc.

• Difficult to envision dedicated advisory committee akin to SACHDNC

• American College of Genetics & Genomics (ACMG) would be an appropriate locus
  – Leads efforts in closely related endeavor of opportunistic screening (the “ACMG List”)
Nuts and Bolts of Screening

• What constitutes appropriate analytic approach?
  – Likely focus first on massively parallel sequencing only
    • del/dup analysis possible/necessary?

• Must have a very high threshold for reporting of positive results given low prior probability of disease in those screened
  – Only report KP/LP
  – No reporting of VUSs
  – Thresholds for reporting are likely to eventually be gene specific, hinging on parameters such as
    • Availability of good f/u test
    • Low burden/risk to preventive modalities
      – e.g., contrast CDH1 vs. HFE
Return of Results

Those who screen negative

• Negative results (~99% of those screened) will need to be returned in a way that emphasizes caveats of any screening test
  – e.g. FHx is important to identify those who, in spite of negative screen, require enhanced surveillance, genetic counseling, etc.
    • Necessitates acquisition of targeted FHx as part of intake protocol

• Develop “boiler plate” for negative ROR as part of Action Collaborative?
Return of Results

*Those who screen positive*

- Positive results must be returned with specific guidelines for recommended actions, e.g.:
  - Frequency of colonoscopy in Lynch cases
  - Rx protocols for FH
  - Recommendations for those screening + for HBOC?
    - Must take into account lack of certainty regarding penetrance in those ascertained via population screening (likely inflation of existing estimates)
      - Likely necessitates adjusting recommendations to be less aggressive
      - Uncertainties must be relayed to those screen positive
    - Address facilitation of family communication so at-risk FMs stand best chance of notification
- Develop “boiler plate” for positive ROR as part of Action Collaborative?
Locus of Implementation

• Dedicated public health effort like NBS not feasible
• Rather, part of routine care by general physicians who offer recommended screening
  – At the same time acquire targeted FHx
    • Components of FHx will need to be specified
    • “Script” (e.g. web based teaching tool?) to educate patients upon uptake of screening
    • Need involvement/back up by geneticists and appropriate specialists as resource for enrolling physicians
  – Initial implementation within integrated health systems appealing due to lack of fragmentation, better ability to f/u outcomes
Research Gaps Requiring Attention in Initial Trials

Need to implement and study

- Penetrance of pathogenic variants in such genes in unselected populations
- Prevalence of pathogenic variants
- Understanding by participants of negative and positive results
- Adherence to recommendations by those screening positive and negative
- Health outcomes following screening
- Family communication of results
- Economic impact
  - Upfront & downstream costs to calculate utility
  - Necessary for eventual uptake by third-party payors
Identify Funding Mechanisms for Pilots

• Will not be inexpensive
  – Similar to many clinical trials; less expensive than most drug trials
• Will need to:
  – Generate sufficient numbers of those screening positive
  – f/u adherence, understanding, costs
  – Establish infrastructure for long term f/u to document outcomes/utility
• Will likely require >20,000 individuals
Genomic Conditions of Interest

• Must meet following criteria (similar to Wilson & Jungner NBS criteria)
  – When mutated result in high risk of disease (high penetrance)
  – Predispose to serious disease
  – Availability of well-established preventive modalities
  – Sufficient population prevalence to justify screening
  – Asymptomatic until it is too late to prevent morbidity or mortality
  – High level of knowledge and experience regarding each gene, condition and prevention
Leading Contenders

• Familial Hypercholesterolemia
  – Need to determine # of FH genes meeting prior criteria

• Lynch Syndrome
  – 5 genes (MLH1, MSH2, EPCAM, MSH6, PMS2)

• Hereditary Breast & Ovarian Cancer
  – BRCA1/2

• Consider well understood, highly penetrant, focus of previous consideration by IOM PH Genomics
### Three Tier One CONDITIONS

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>CLINICAL RISK</th>
<th>DISEASE-ALTERING INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia (FH)</td>
<td>Early-onset Coronary Artery Disease and Stroke</td>
<td>Targeted screening and medical management</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome (HBOC)</td>
<td>Early-onset Breast, Ovarian, and Prostate Cancers</td>
<td>Targeted screening with prophylactic medical and surgical intervention</td>
</tr>
<tr>
<td>Lynch Syndrome (LS)</td>
<td>Early-onset Colon and Uterine Cancers</td>
<td>Targeted screening and management of pre-cancerous changes</td>
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</table>

### SOME PRELIMINARY INSIGHTS REGARDING ASCERTAINMENT THROUGH THIS APPROACH

<table>
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<tr>
<th>CONDITION</th>
<th>NUMBER OF VARIANT CARRIERS</th>
<th>PREVALENCE OF “GENOMIC SCREEN” POSITIVE</th>
<th>PUBLISHED PREVALENCE ESTIMATES</th>
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<tbody>
<tr>
<td>FH</td>
<td>229</td>
<td>1:222</td>
<td>1:500</td>
</tr>
<tr>
<td>HBOC</td>
<td>248</td>
<td>1:205</td>
<td>1:400</td>
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<tr>
<td>LS</td>
<td>173</td>
<td>1:293</td>
<td>1:440</td>
</tr>
<tr>
<td>TOTAL</td>
<td>650</td>
<td>1:78 (1.28%)</td>
<td>1:148</td>
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NBS is 1:800 screen positive
Note:
1. Variant Screening identifies cases with significant risk.
2. These cases are otherwise not always distinct and identifiable using cholesterol measures alone.
3. Even at lower cholesterol levels the risk of CAD (coronary artery disease) is significantly elevated.
4. Risk can be managed however 54% of patients at Geisinger undertreated prior to genomic identification.
# Diagnostic Groups in Incidental BRCA1 BRCA2 Cases from Genomic Screening

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<th>BRCA ROR from MyCode</th>
<th>N = 81 (%)</th>
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<td>Group 1 - previous genetic test</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Group 2 - previous cancer diagnosis</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Group 3 - new cancer dx prompted by initial evaluation</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Group 4/5 - ongoing screening recommended</td>
<td>60 (74%)</td>
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**Note:**
- Group 3 includes one asymptomatic case each of: Breast CA, Ovarian CA, Prostate CA
- Half the recipients are men
- Cascade testing of relatives will identify 2-3X number of cases
## Questions to Answer Prior to Broad Public Health Application

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