Primary Provider “Just in Time” Education That Supports Screening Healthy Volunteers with Genomics

Inter-Society Coordinating Committee for Practitioner Education in Genomics
Bethesda, MD

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10:45 - 11:20

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No CME Conflicts of Interest

Disclosure: Geisinger has a collaboration with Regeneron Pharmaceutical Company
Problem:

- Pathogenic Variants in BRCA 1 and 2 result in dramatic increases in Breast and Ovarian Cancer Risk
- For over 15 years methods for identifying individuals with this risk have existed

- Teach providers to identify risk and order appropriate testing
Problem:

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• For over 15 years methods for identifying individuals with this risk have existed
• Most individuals with this risk are not aware of it
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Educational Solution:

- Teach providers to identify risk and order appropriate testing
Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility, along with the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is included in the evidence synthesis available through the USPSTF Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse (www.guideline.gov).

For author affiliation, see end of text.

Individuals who wish to cite this recommendation statement should use the following format: U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. Ann Intern Med. 2005;143:355-61.

*For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.
USPSTF expects this kind of analysis

Scenario One – patient concerned

USPSTF screen negative
Should not be referred or tested

Scenario Two – patient not concerned

USPSTF screen positive
Should be referred for possible testing
Is it an educational failure that the majority of the estimated 250,000 to 415,000 adult US women with pathogenic variants in BRCA1 or 2 are not aware of it?

• Simple Answer is no.
Is it an educational failure that the majority of the estimated 250,000 to 415,000 adult US women with pathogenic variants in BRCA1 or 2 are not aware of it?

- 50% of families found to harbor BRCA1 or BRCA2 mutations had no history of breast or ovarian cancer that would have triggered clinical attention.

Principle:
• Targeted testing

Education:
• Who to test
• How to test
• What to do with negative
• What to do with positive
Genomics Education: past and future

**Principle:**
- Targeted testing

**Education:**
- Who to test
- How to test
- What to do with negative
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**Principle:**
- Population is tested

**Education:**
- What to do with positive
Primary Provider “Just in Time” Education That Supports Screening Healthy Volunteers with Genomics

Describe:

• GenomeFIRST CME Modules
• GenomeFIRST Clinical Guidance
Primary Provider “Just in Time” Education That Supports Screening Healthy Volunteers with Genomics

Describe:

• Geisinger Health System
• MyCode Community Health Initiative
• GenomeFIRST Return of Results Project
• GenomeFIRST CME Modules
• GenomeFIRST Clinical Guidance
Geisinger’s GenomeFIRST Program

Return of Results

The prompt for the clinical encounter is the DNA variant
Our Return of Incidental Findings Flips the Care Model within Geisinger’s HealthCare System

- **Genotype First** – is the use of DNA sequence information as the trigger for clinical evaluation and management.

- **Phenotype First** – is the use of clinical clues as the trigger for clinical evaluation and management.
Geisinger’s MyCode® Biobank is carrying out an unselected recruitment of patient participants from across the healthcare system.

Patients consented for both research and potential return of results.

Samples from approximately 50,000 patient participants have undergone WES for discovery research.
We have initiated a return of secondary findings to participants with pathogenic/likely pathogenic findings in the “Geisinger 76” (i.e. the ACMG 56 plus 20 genes).

Anticipate 1 in 50 patients will receive a result.

Half of the results returned will be linked to just three conditions.
GenomicFIRST™ Return of Results

Geisinger Incidental Findings List (The Geisinger 76)
- Focus on 27 conditions (76 genes)
- Builds on the ACMG Incidental Findings List (published 2013)
- Cancer predisposition (e.g. BRCA 1 and BRCA 2 mutations)
- Cardiovascular disease (e.g. Hypertrophic Cardiomyopathy)
- Malignant Hyperthermia (leads to anesthesia complications)
- Hereditary Hemorrhagic Telangiectasia (risk for visceral arteriovenous malformations)
- Ornithine transcarbamylase (OTC) deficiency (hyperammonemia, coma)

Return of Results
- Patients with genomic findings that warrant return for clinical management will receive that result (initially ~ 2%).
- Infrastructure and decision support to be developed to support patients and providers.
MyCode® Participants

- Goal Enrollment: 250,000
- Current Enrollment: 95,000+
- Current WES: 60,000+
- Current QC’d Cases: 53,000

WES = Whole Exome Sequence
<table>
<thead>
<tr>
<th>Study</th>
<th>ClinSeq 2012-2013</th>
<th>Univ Wash 2013</th>
<th>Univ Wash 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>870 *</td>
<td>1000</td>
<td>6500</td>
</tr>
<tr>
<td>Demographics</td>
<td>96% EA</td>
<td>50% EA</td>
<td>~ 66% EA</td>
</tr>
<tr>
<td></td>
<td>50% AA</td>
<td>50% AA</td>
<td>~ 33% AA</td>
</tr>
<tr>
<td>Gene List</td>
<td>80</td>
<td>114</td>
<td>112</td>
</tr>
<tr>
<td>Percent Returnable</td>
<td>2.3%</td>
<td>3.4% EA</td>
<td>~ 2% EA</td>
</tr>
</tbody>
</table>
In Geisinger’s GenomeFIRST we anticipate that: 9 genes (BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, LDLR, APOB, PCSK9) associated with 3 conditions will drive half of the return of results.

<table>
<thead>
<tr>
<th>GENOMIC CONDITION</th>
<th>POPULATION PREVALENCE</th>
<th>CLINICAL RISK</th>
<th>DISEASE-ALTERING INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome</td>
<td>~1 in 400</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</td>
<td>~1 in 400</td>
<td>Early-onset Colon and Uterine Cancers</td>
<td>Targeted screening and management of pre-cancerous changes</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>~1 in 200</td>
<td>Early-onset Coronary Artery Disease and Stroke</td>
<td>Targeted screening and aggressive medical management</td>
</tr>
<tr>
<td>TOTAL</td>
<td>~1 in 100</td>
<td>Multiple Cancers and Cardiovascular Diseases</td>
<td>Life-saving screening and intervention before development of disease</td>
</tr>
</tbody>
</table>
**Predicted Clinical Volume for Return of Results**

<table>
<thead>
<tr>
<th>Patients Identified</th>
<th>MyCode Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100,000</td>
</tr>
<tr>
<td>Participants with pathogenic variants from Geisinger 76</td>
<td>2,000</td>
</tr>
<tr>
<td><strong>Relatives identified with same variant</strong></td>
<td>6,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8,000</td>
</tr>
</tbody>
</table>

**Estimated average 3 per participant with variant, and 3 who will test negative for risk variant**
Genomics Education: past and future

**Principle:**
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Supporting tools in Return of Results

• Provider and patient support for all results returned

  • **Provider support** include:
    – [1] “Just in Time” Continuing Medical Education
    – [2] condition specific standardized phenotyping
    – [3] opportunity to consult clinical genomics and other specialists

  – **Patient support** plan which includes opportunities to have queries answered and for counseling
Provider Education in Return of Results

- Over 1000 practitioners are the immediate target audience
- They are motivated by desire to manage their patient
- Principles:
  - Start with the result
  - Don’t try to create 1000+ Genetics Experts
  - Offer Repetitive Opportunities to Learn Content
  - Motivate by offering CME Credit
  - Make it available to External Audience
GenomeFIRST™ CME for Practitioners

- The educational modules
  - 30 free-standing CME modules (30 minute duration)
  - Electronically hosted on internal website
  - Pre- and post-test evaluation
- Providers receiving medically actionable clinical result will receive a hyperlink to condition specific module
- Participation is optional
Course #9
Genomics Learning Objectives

Describe clinical features common to individuals with a pathogenic germline variant in \textit{RET}

Describe management considerations for patients with a pathogenic germline variant in \textit{RET}

Review basics of \textbf{autosomal dominant} inheritance

Understand the concepts of \textbf{penetrance} and \textbf{variable expressivity}

Understand the concept of \textbf{pleiotropy}

Understand the importance of identifying at-risk family members
Multiple Endocrine Neoplasia Type 2

Synonyms: MEN 2, MEN2 Syndrome

Jessica Marquard, MS, LGC and Charis Eng, MD, PhD, FACP.


Summary

Clinical characteristics. Multiple endocrine neoplasia type 2 (MEN 2) is classified into three subtypes: MEN 2A, FMTC (familial medullary thyroid carcinoma), and MEN 2B. All three subtypes involve high risk for development of medullary carcinoma of the thyroid (MTC); MEN 2A and MEN 2B have an increased risk for pheochromocytoma; MEN 2A has an increased risk for parathyroid adenoma or hyperplasia. Additional features in MEN 2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, and a ‘marfanoid’ habitus. MTC typically occurs in early childhood in MEN 2B, early adulthood in MEN 2A, and middle age in FMTC.
Penetrance = an individual carrying a particular variant of a gene (genotype) also expresses an associated trait (phenotype, shown as shaded dark purple).

Penetrance of MEN2 is high – nearly all individuals with pathogenic variants will develop medullary thyroid cancer without prophylactic thyroidectomy.
Clinical Follow-Up

- **In your patient** - A “likely pathogenic” DNA variant identified through genomic sequencing warrants clinical follow-up in the patient, similar to incidental findings on radiology studies.

- **In family members** - A “likely pathogenic” DNA variant warrants follow-up in the patient’s family.

New Diagnosis or Unifying Diagnosis

- DNA findings alone do not constitute a diagnosis.

- However, in the clinical context of other supportive findings, these DNA findings can lead to a new diagnosis or a unifying diagnosis.
Problem Listing

• When DNA findings do not lead to a diagnosis, the DNA variant should be listed on the patient’s EHR “problem list” to allow re-evaluation should relevant clinical signs or symptoms develop in the future.

Available Tools

• The GenomeFIRST™ team has developed a list of relevant signs and symptoms for each of the 27 conditions in our return of results program.

• The GenomeFIRST™ team has developed explanatory letters for patients and doctors to share with those outside the family or the clinical care team.
In Geisinger’s GenomeFIRST we anticipate that: Patients receiving secondary results will fall into one of five diagnostic groups.
Technology to Power the Healthcare Quality Enterprise

Serving over 1.2 million healthcare professionals, 5,000 practices and 100 professional organizations in partnership to improve the health of over 50 million patients

CONTACT US
## 15 Positive Results Delivered

<table>
<thead>
<tr>
<th></th>
<th>Pathogenic variant identified</th>
<th>Laboratory confirmed P/PL</th>
<th>Clinical Report Generated and Entered into EHR</th>
<th>Report Pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC (BRCA1/2)</td>
<td>57</td>
<td>11</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia (FH)</td>
<td>52</td>
<td>1</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Lynch</td>
<td>42</td>
<td>2</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Final Revised Report (non-pathogenic final)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>161</strong></td>
<td><strong>14</strong></td>
<td><strong>15</strong></td>
<td><strong>146</strong></td>
</tr>
</tbody>
</table>
Thank you.