Patient-Centered Precision Health In A Learning Health Care System: Geisinger’s Genomic Medicine Experience

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Overview

• Define terms in common use and provide background for GenomeFIRST

• Describe the opportunity for synthesis between genomics/precision health and the learning healthcare system

• Present the Geisinger experience with implementation of a genomic medicine program in the context of an integrated system
53 year old woman enrolled in MyCode Community Health Initiative
History of a basal cell carcinoma removed at age 33
Currently treated for Crohn’s disease
Receives regular medical care, but has declined mammography for the last 5 years
Primary caregiver for her grandchildren
Healthcare delivery is increasingly influenced by two emerging concepts: Precision medicine (health) and the learning healthcare system.
PRECISION HEALTH

meaning, definition, explanation...
Genomic Medicine

• Includes
  o Traditional single gene disorders (genetics)
  o Analysis of the whole genome (genomics)
  o Analysis of subsets of the whole genome
    ▪ Exome sequencing
    ▪ Pharmacogenomics
  o Family History
Genomic Medicine ≠ Personalized Medicine

“Personalized medicine is the practice of clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual’s state as is available.”

Precision Medicine

• Currently--Intuitive medicine
  o Care for conditions that can be diagnosed only by their symptoms and only treated with therapies whose efficacy is uncertain and watching for empiric response.
  o Empiric ‘trial and error’

• Future—Precision medicine
  o The provision of care for diseases that can be precisely diagnosed, whose causes are understood, and which consequently can be treated with rules-based therapies that are predictably effective.
  o Expect genomics to play a key role in this

Adapted from The Innovator’s Prescription A Disruptive Solution for Healthcare. Christensen, Grossman and Hwang, 2009
Precision Health

• Emphasizes prevention while encompassing the interventions inherent in precision medicine
• We view our project as a population precision health effort, and have renamed it the MyCode Community Health Initiative to distinguish it from the biorepository
• Inherent in this are educational efforts directed at participants, providers, payers, administrators and other stakeholders
• This is endorsed at the highest level of the organization as a strategic initiative
What is a Learning Healthcare System?

The Institute of Medicine has defined this as a healthcare system:

- ‘that is designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider;
- to drive the process of discovery as a natural outgrowth of patient care;
- and to ensure innovation, quality, safety, and value in health care.’
“Science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”
“A health care system in which an infrastructure supports complete learning cycles that encompass both the analysis of data to produce results, and the use of those results to develop changes in clinical practices is a system that will allow for optimal learning.” (Friedman)
Source: KP Washington Health Research Institute
Geneticists know how to do this
Genomics at scale
GenomeFIRST™ Return of Results

• 250,000 Geisinger Patients Will Have Their Exomes Sequenced.

• We will Look For Medically Actionable Results In That Data And Then Return Results To Patients And Providers.

• We will support the patients and providers in the follow-up to the results and long term management planning.

• We will be Operationalizing A Scalable Genomic Return Of Results Infrastructure In A Large Integrated Healthcare System
High Level Process

Consenting and sample collection

Sequence interpretation, confirmation and reporting

Reporting results to participants and family

Measuring outcomes attributable to reporting
Sequencing, confirmation, and reporting - In theory

1. Eligible MyCode® samples sent for exome sequencing
2. Exome sequences undergo bioinformatic analysis of Geisinger genes
3. Reportable Result?
   - Yes: Variant Confirmation in CAP/CLIA certified clinical laboratory
     - Report issued to Geisinger
   - No: Save exome sequences for future bioinformatic analysis
Sequence Analysis-in practice
Reporting Results to Participants and Families
Primary care provider (PCP) management

Genomic Screening and Counseling Program (GSP)

Result sent to PCP

PCP encounter scheduled 5 days*

GSP sends EHR message/letters to patient

5-10 days*

GSP calls patient

No contact x 3

1. Letters & result to patient
2. No-contact documented in EHR

If patient responds

1. Disclosure phone script
2. Family hx ID assigned

Result & support materials mailed to patient

Patient may follow up\(^a\) with PCP, GSP or both

Patient follows up with PCP

Targeted follow-up w/PCP & condition-specific specialists

GSP assists w/referral from PCP

Patient follows up with GSP

*Business; \(^a\)Follow-up includes genetic counseling & medical evaluation
Measuring Outcomes Attributable to Reporting
Secondary or Incidental Finding of a PATHOGENIC/LIKELY PATHOGENIC VARIANT

GENE SPECIFIC EVALUATION
Including history, exam, testing, consultation

DIAGNOSIS OF GENOMIC SYNDROME WITH TESTING AND INITIAL EVALUATION
Both Genotype and Phenotype Present

GROUP 1
Existing Genomic Syndrome Diagnosis Confirmed
Previous genotype and phenotype documented

GROUP 2
Unifying Genomic Syndrome Diagnosis
Previously documented phenotype and new genotype

GROUP 3
New Genomic Syndrome Diagnosis Achieved
Sub-clinical phenotype revealed thru evaluation

GROUP 4
No Genomic Syndrome Diagnosis Achieved Initially
Phenotype Emerges over time

GROUP 5
No Genomic Syndrome Diagnosis Achieved Initially
Phenotype Does Not Emerge

GENOMIC SYNDROME DIAGNOSED
Both Genotype and Phenotype

NO DIAGNOSIS OF GENOMIC SYNDROME WHEN TESTED
Genotype without Phenotype

<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>Familial Hypercholesterolemia (LDLR, APOB, PCSK9)</td>
<td>1 in 222</td>
<td>Early-onset Coronary Artery Disease and Stroke</td>
<td>Targeted screening and aggressive medical management</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome (BRCA1, BRCA2)</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 (MLH1, MSH2, MSH6, PMS2)</td>
<td>1 in 440</td>
<td>Early-onset Colon and Uterine Cancers</td>
<td>Targeted screening and management of pre-cancerous changes</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>

**Opportunities**

- Familial Hypercholesterolemia: Early-onset Coronary Artery Disease and Stroke
  - Targeted screening and aggressive medical management

- Hereditary Breast and Ovarian Cancer Syndrome: Early-onset Breast, Ovarian, and Prostate Cancers
  - Targeted screening with prophylactic medical and surgical intervention

- Lynch Syndrome: Early-onset Colon and Uterine Cancers
  - Targeted screening and management of pre-cancerous changes

- **TOTAL**: Life-saving screening and intervention before development of disease
Progress to date

MyCode® results reported
1044 patient-participants have received results* from the Genomic Screening and Counseling Program

For the latest results, see geisinger.org/MyCode-results.

<table>
<thead>
<tr>
<th>Risk Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>284</td>
<td>BRCA1</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2</td>
<td>185</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>118</td>
<td>APOB</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDLR</td>
<td>83</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>98</td>
<td>PMS2</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>6</td>
</tr>
</tbody>
</table>

* CDC tier 1 conditions (click link)
## Outcomes

<table>
<thead>
<tr>
<th>Outcome Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process</strong></td>
<td>These measures are the specific steps in a process that lead — either positively or negatively — to a particular health outcome</td>
<td>Lipid profile performed after return of a pathogenic variant in LDLR a gene associated with familial hypercholesterolemia</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>A biomarker associated — either positively or negatively — to a particular health outcome</td>
<td>An LDL cholesterol level at or below the target level of 100 mg/dl in response to interventions recommended based on presences of a pathogenic variant in LDLR</td>
</tr>
<tr>
<td><strong>Health</strong></td>
<td>Change in the health of an individual, group of people or population which is attributable to an intervention or series of interventions</td>
<td>Decrease in myocardial infarction, or cardiac revascularization procedures in response to interventions recommended based on presences of a pathogenic variant in LDLR</td>
</tr>
</tbody>
</table>
| **Cost**        | Standard costs associated with the interventions and health states experienced by the patient. Can also include costs associated with patient report outcomes from self-reported health state and life disruption. | Cost of sequencing  
Cost of genomics results delivery infrastructure  
Direct costs of care related to return of genomic information  
Utilization  |
| **Behavioral**  | Change in patient or provider behavior attributable to genomic information    | Improved adherence to medication  
Modification of care based on condition-specific recommendations |
| **Patient-reported** | Report of the status of a patient's health condition, knowledge, or service outcomes that comes directly from the patient, without interpretation of the patient's response | Satisfaction with service  
Engagement with self-care  
Knowledge about gene and disease  
Access to recommended care  
Self-assessed well being  
Family communication of genomic risk result and uptake of cascade testing |
System Outcomes

- Costs incurred/avoided
- Utilization
- Visibility/reputation
- Patient experience
What is Value?

- Crudely can be thought of as a relationship between outcomes and cost of care
- Patient centered outcomes would include
  - Medical outcomes (treatment, prevention, safety)
  - Service outcomes (number of visits, disruption of life routine)
  - Information?
    - Highly valued in genetics
    - Difficult to value economically
    - Personal utility vs. control of health care costs
- In general we do a poor job measuring cost of services
## Value Plot

<table>
<thead>
<tr>
<th>Medical and/or Service Outcomes</th>
<th>Cost of care decreased</th>
<th>Cost of care unchanged</th>
<th>Cost of care increased</th>
</tr>
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<tr>
<td>Improved</td>
<td></td>
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</tr>
<tr>
<td>Unchanged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Genomic LHS in action

I have a big heart because I have hypertrophic cardiomyopathy.
Clinical Underascertainment of BRCA1/2 Cancer Risk in 50,726 Unselected Adult Biobank Participants

Manickam K, et al. JAMA Open [In Press]

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2703131
Methods

• Identify MyCode participants with BRCA1/2 pathogenic/likely pathogenic variants identified
  o Ascertain
    ▪ Prior clinical testing for BRCA1/2
    ▪ Personal history of cancer
    ▪ Family history of cancer
  o Apply clinical screening criteria to identify participants that met current threshold for clinical testing of BRCA1/2
  o Assess differences in disease penetrance between BRCA1 and BRCA2 variant carriers
  o Identify potential care gaps in clinical testing
Risk for BRCA1/2 variant carrier compared to sequenced population

- **History of breast cancer (women)**
  - Carrier 20.95%
  - Non-carrier 5.27%
  - Odds ratio 5.95 (95% CI: 3.88, 9.13); P<0.0001

- **History of ovarian cancer**
  - Carrier 10.14%
  - Non-carrier 0.65%
  - Odds ratio 18.30 (95% CI: 10.48, 31.4); P<0.0001
### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Participants with BRCA Variants (Cases)</th>
<th>Participant Sex</th>
<th>Vital Status</th>
<th>Prior Testing Status</th>
<th>BRCA1 vs. BRCA2 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Women with BRCA Variants</td>
<td>Men with BRCA Variants</td>
<td>Deceased Participants with BRCA Variants</td>
<td>Living Participants with BRCA Variants</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>267</td>
<td>148</td>
<td>119</td>
<td>23</td>
<td>244</td>
</tr>
<tr>
<td>Group 1/2/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.5% (52/267)</td>
<td>26.4% (39/148)</td>
<td>10.9% (13/119)</td>
<td>47.8% (11/23)</td>
<td>16.8% (41/244)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>OR 2.92 (1.47, 5.77)</strong></td>
<td><strong>p=0.0016</strong></td>
<td></td>
<td><strong>OR 4.54 (1.87, 10.99)</strong></td>
</tr>
<tr>
<td><strong>HBOC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>5.2% (14/267)</td>
<td>8.8% (13/148)</td>
<td>0.8% (1/119)</td>
<td>17.3% (4/23)</td>
<td>4.1% (10/244)</td>
</tr>
<tr>
<td>Group 2</td>
<td>12.7% (34/267)</td>
<td>15.5% (23/148)</td>
<td>9.2% (11/119)</td>
<td>30.4% (7/23)</td>
<td>11.1% (27/244)</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.5% (4/267)</td>
<td>2% (3/148)</td>
<td>0.8% (1/119)</td>
<td>0%</td>
<td>1.6% (4/244)</td>
</tr>
<tr>
<td><strong>HBOC Not</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4/5</td>
<td>80.5% (215/267)</td>
<td>73.6% (196/148)</td>
<td>89.1% (108/119)</td>
<td>52.2% (12/23)</td>
<td>83.2% (203/244)</td>
</tr>
</tbody>
</table>
Analysis of Referral and Testing Criteria in 122 BRCA Cases

For those without prior testing, 51% met NCCN testing criteria (61% of women and 40% of men)

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Subgroups of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with P/LP Variants and Completed Pedigrees (N=122)</td>
<td>Prior Testing Status</td>
</tr>
<tr>
<td>Median Age</td>
<td>58.6</td>
</tr>
<tr>
<td>Percent Meeting NCCN Testing Guidelines</td>
<td>63% (77/122)</td>
</tr>
<tr>
<td>Percent Meeting NCCN Referral Guidelines</td>
<td>66% (50/122)</td>
</tr>
<tr>
<td>Percent Meeting ACMG-NSGC Referral Guidelines</td>
<td>57% (70/122)</td>
</tr>
<tr>
<td>Percent Meeting USPSTF Referral Criteria</td>
<td>NA</td>
</tr>
</tbody>
</table>
Conclusions

- Analysis in an unselected population confirms increased risk for breast and ovarian cancer in \textit{BRCA1/2} carriers
- Two significant care gaps identified
  - Significant number of patients who meet criteria for clinical \textit{BRCA1/2} testing are not being tested
  - Criteria to define eligibility for clinical testing are insensitive
- Take away: about 75\% of patients at risk for HBOC in our system are currently unidentified representing lost opportunities for prevention
# Value Plot

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<td>![Green]</td>
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</tr>
<tr>
<td>Unchanged</td>
<td>![Green]</td>
<td>![Green]</td>
<td>![Red]</td>
</tr>
<tr>
<td>Worsened</td>
<td>![Yellow]</td>
<td>![Red]</td>
<td>![Red]</td>
</tr>
</tbody>
</table>
A face of our project

Found to have a pathogenic variant in \textit{BRCA1}.
Result returned and she proceeded to have a mammogram which was normal.
Counseled per guidelines.

**NCCN Guidelines: Medical Management**

- Annual mammogram and breast MRI (alternate 6 months)
- Consider RRM and RRSO
- Clinical Breast Exam every 6-12 months
- Encourage Breast awareness
- Consider risk reduction agents and investigational imaging trials
A face of our project

After several months elected to pursue BSO
“I need to be around for my grandchildren”
A face of our program

Had bilateral salpingo-oophorectomy in August 2016

No complications from surgery

Follow up pathology by serial sectioning showed: right fallopian tube high grade serous carcinoma 1.4 cm with stromal invasion

Pre-surgical ovarian ultrasound did not detect and CA-125 was normal
A face of our program

Pelvic washing also positive- Stage 1C (though could easily be up-staged to 2C because of nature of this tumor)

Started chemotherapy less than month later: Carboplatin and Taxol

Stopped Crohn’s disease treatment because of immunosuppression and risk with biological agents (2 years post treatment can be restarted)
8 faces of our program

• As a result of surveillance recommended by return of *BRCA1/2* pathogenic variants we identified:
  o 3 Breast cancers (1 bilateral DCIS)
  o 3 Prostate cancers
  o 1 Fallopian tube carcinoma (discussed)
  o 1 carcinoma Ampulla of Vater

• All were stage 2 or earlier
Takeaways

• Implementation of genomic medicine using LHS model can be used to develop evidence-based best practices
• Significant care gaps exist for patients with genetic conditions
• Successful delivery models must be studied to allow replication and rapid dissemination
• Understanding the value proposition from the organizational perspective is essential for success
• We can’t forget that at the end of the day this is impacting the lives of our patients
Acknowledgments

• MyCode Participants: over 200,000 Geisinger Patients
• Genomic Screening and Counseling Program
• DiscovEHR Collaborators: At Regeneron and Geisinger
Further Reading

Patient-Centered Precision Health In A Learning Health Care System: Geisinger’s Genomic Medicine Experience