Patient-Centered Precision Health in a Learning Health Care System: Geisinger’s Genomic Medicine Experience

Marc S. Williams, MD, FAAP, FACMG, FACMI
Professor and Director Emeritus, Genomic Medicine Institute
@Marc_GeneDoc
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
A face of our project

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
Assertion

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
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.’

Geisinger
“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)
In a learning health system, research influences practice, and practice influences research.

**STUDY**
Collect data and analyze results to show what works and what doesn’t.

**ACT**
Use evidence to influence continual improvement.

**DO**
Apply plan.

**PLAN**
Design a change and its evaluation based on evidence generated here and elsewhere.

**DISSEMINATE**
Share results to improve care for everyone.

**INTERNAL AND EXTERNAL SCAN**
Identify problems and potentially innovative solutions.

Source: KP Washington Health Research Institute
Geneticists know how to do this
Genomics at scale
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.
MYCODE® Scorecard

2 million Geisinger patients

Total consented participants: 291,504
Samples provided: 203,384
DNA sequences available for research: 184,293
DNA sequences eligible and analyzed for clinical review: 61,870
Participants with clinical result reported: 2,733

As of September 1, 2021
High Level Process

1. Consent and sample collection
2. Sequence interpretation, confirmation and reporting
3. Reporting results to participants and family
4. 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
Challenges to Scale

- Standardization of Genetic Phenotypes
- Getting Discrete Data from the Lab to the EHR
- Address the Role of the LIS in the process
- Discordance between HL7 genomic report and FHIR molecular sequence resource
- Integration with existing maintenance guidelines
- Inability to represent variant level data for PGx (* system unique to PGx)
- Overall lack of standards and standard approaches for each step in the process
Reporting Results to Participants and Families
How are results disclosed and discussed?

- **Primary care provider notified of a patient’s result**
  - Electronic health record communication
  - Option for PCP to disclose

- **Genetic counselor discloses result by phone**
  - Often unanticipated call
  - May not be related to acute concerns

- **Brief description of risk and specific gene**
  - Gene causes risk for heart disease, early cancer...
  - Screening and prevention may include...

- **Recommend discussion with genetic counselor**
  - Service provided at no charge
  - Refer to other appropriate healthcare provider

- **Recommend discussing result with family members**
  - Program provides letters and resources to help with this communication

Geisinger
Challenges to Scale

• Lack of standard resources for patient/provider information
  o ACMG ACT sheets for secondary findings
• Creation and maintenance of clinical decision support
  o Need structured data to run CDS rules
  o Standard CDS format to enhance generalizability (e.g. CDSHooks)
  o Reuseable CDS rules (CDSKB)
    ▪ Currently only narrative and flow chart—no code
• Different perceptions of discrete genomic data versus scanned report
• Gaps in current proposed standards
  o Inability to handle recessive conditions with compound heterozygotes
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

NO DIAGNOSIS OF GENOMIC SYNDROME WHEN TESTED
Genotype without Phenotype

GENOMIC SYNDROME DIAGNOSED
Both Genotype and 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 <em>(LDLR, APOB, PCSK9)</em></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 <em>(BRCA1, BRCA2)</em></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 <em>(MLH1, MSH2, MSH6, PMS2)</em></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><strong>TOTAL</strong></td>
<td><strong>~ 1 in 100</strong></td>
<td><strong>Multiple Cancers and Cardiovascular Diseases</strong></td>
<td><strong>Life-saving screening and intervention before development of disease</strong></td>
</tr>
</tbody>
</table>
### Progress to date

**MYCODE®**

**Results reported**

2736 patient-participants have received results* from the Genomic Screening and Counseling Program.

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

**285,000+ participants have made the success of MyCode possible**

<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 (early breast, ovarian, prostate and other cancers)</td>
<td>634</td>
<td>BRCA1</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2</td>
<td>425</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (early heart attacks and strokes)</td>
<td>280</td>
<td>APOB</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDLR</td>
<td>179</td>
</tr>
<tr>
<td>Lynch syndrome (early colon, uterine and other cancers)</td>
<td>342</td>
<td>PMS2</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>25</td>
</tr>
<tr>
<td>Hereditary hemochromatosis (too much iron in blood, can lead to liver and heart problems)</td>
<td>356</td>
<td>HFE</td>
<td>356</td>
</tr>
<tr>
<td>Outcome Type</td>
<td>Description</td>
<td>Examples</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td></td>
</tr>
<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>
<td></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>
<td></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>
<td></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
Measuring Outcomes Attributable to Reporting

• Define outcomes to be collected
• Implement systems to capture outcomes

• Determination of attribution not standardized
• Reliance on manual collection
• Patient self-reported data necessary (and desirable in some cases)
• Outcomes not harmonized across different projects
• Standardized outcomes not available for the most part
  ○ PROMIS for patient reported outcomes
What is Value?

• Crudely can be thought of as a relationship between outcomes and cost of care

• Patient centered outcomes would include
  o Medical outcomes (treatment, prevention, safety)
  o Service outcomes (number of visits, disruption of life routine)
  o 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>
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<tr>
<td>Improved</td>
<td>Green</td>
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<td>Yellow</td>
</tr>
<tr>
<td>Unchanged</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Worsened</td>
<td>Yellow</td>
<td>Red</td>
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</tbody>
</table>
Genomic LHS in action

I have a big heart because I have hypertrophic cardiomyopathy.
Exome Sequencing-Based Screening for BRCA1/2 Expected Pathogenic Variants Among Adult Biobank Participants

Kandamurugu Manickam, MD, MPH; Adam H. Buchanan, MS, MPH; Marc L. B. Schwartz, ScM; Miranda L. G. Hallquist, MSc; Janet L. Williams, MS; Alanna Kulkach Rahm, PhD, MS; Heather Rocha, MS; Juliann M. Savatt, MS; Alyson E. Evans, BS; Loren M. Butry, MS; Amanda L. Lazzeri, BS; D'Andra M. Lindbuchler, MSN; Carroll N. Flansburg, MPH; Rosemary Leeming, MD, MHCM; Victor G. Vogel, MD, MHS; Matthew S. Lebo, PhD; Heather M. Mason-Suarez, PhD; Derick C. Hoskinson, PhD; Nosra S. Abul-Husn, MD, PhD; Frederick E. Dewey, MD; John D. Overton, PhD; Jeffrey G. Reid, PhD; Aris Baras, MD; Huntington F. Willard, PhD; Cara Z. McCormick, MPH; Sarah B. Krishnamurthy, PhD; Dustin N. Hartzel, BS; Korey A. Kost, BS; Daniel R. Lavege, BS; Amy C. Sturm, MS; Lauren R. Frisbie, BS; T. Nate Person, MS; Raghu P. Mettally, PhD; Monica A. Giovanni, MS; Lucy E. Lowry, MD; Joseph B. Leader, BA; Marylyn D. Ritchie, PhD; David J. Carey, PhD; Anne E. Justice, PhD; H. Lester Kirchner, PhD; W. Andrew Faucett, MS; Marc S. Williams, MD; David H. Ledbetter, PhD; Michael F. Murray, MD

- Identify pathogenic & likely pathogenic (P/LP) BRCA1/2 variants in unselected research cohort
- Characterize features associated with P/LP variants

Manickam K et al. JAMA Network Open 1.5 (2018): e182140-e182140

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2703131
Results – prevalence & genetic testing history

- 36% BRCA1 (n=95), 64% BRCA2 (n=172)
- Prevalence: 1:180 (corrected for relatedness)
- Only 18% had prior clinical BRCA1/2 testing
- ~50% of those without prior testing did not meet NCCN genetic testing criteria
- BRCA-associated cancers more common in cases vs. controls

Manickam K et al. JAMA Network Open 1.5 (2018): e182140-e182140

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2703131
What is clinical utility of genomic screening program among MyCode patients with a ‘CDC Tier 1’ genomic condition?

- 350 patients with HBOC, Lynch, or FH result (May 2015-February 2018)
- Double-coded chart review performed by clinicians in June-Dec 2018
- Median follow-up window: 21.8 months (inter-quartile range 15-31 months)

### Results, Conclusions

**Majority of patients in genomic screening program:**

<table>
<thead>
<tr>
<th>Previously unaware of their Tier 1 variant (87%)</th>
<th>Eligible to perform risk management (86%)</th>
<th>Performed some management post-disclosure (68%)</th>
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Ascertainment of genomic risk led to relevant disease diagnoses during follow-up period (13%)

Supports effectiveness of genomic screening programs in identifying previously undetected individuals at risk for preventable cancers and heart disease
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Selected Active and Future Studies

**Additional clinical utility questions**
- Clinical outcomes for Tier 1 & non-Tier 1 genes/conditions
- Risk management performance & post-disclosure disease diagnosis in *HFE C282Y* homozygote

**Assessment of intermediate health outcomes**
- Lipid levels at goal, high-intensity statin initiated

**Penetrance**
- Understanding phenotypic burden, link with exercise and penetrance and subtle cardiac phenotypes in ARVC

**Family Member Testing**
- Uptake of cascade testing among first-degree relatives

Geisinger
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

\textbf{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-oopherectomy 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
Acknowledgements

Thank you to:
Our MyCode patient-participants, Geisinger Providers and Staff, and the MyCode Research Team

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Further Reading

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