Population-Based Genomic Screening: Recent Results & the Road Ahead

Adam Buchanan, MS, MPH, CGC
Co-Director, MyCode Genomic Screening & Counseling program
Director, Genomic Medicine Institute
Attractive features for longitudinal, genomic medicine research and implementation:

- Large, stable population: >3 M people (>1 M active patients) with many 3+ generation families
- Strong and trusting relationship between patients and Geisinger
- Integrated healthcare delivery system
- Longstanding EHR and comprehensive clinical data
- Epic implementation from 1996 (2nd or 3rd customer)
- Innovative and supportive leadership
- MyCode® BioBank began in 2007
  Now MyCode® Community Health Initiative

“Geisinger is as close to Iceland as you’ll find in the United States”
- Glenn Steele, 2003
DiscovEHR - Collaboration

• Since 2014, Regeneron Genetics Center has been our main scientific partner under MyCode Community Health Initiative
• RGC is subsidiary of Regeneron, a leading, science-focused biotechnology company
• Goals of “DiscovEHR” collaboration:
  • Map genetic variation across human genome
  • Advance understanding of human biology, discovering gene-disease connections, and identifying potential targets for new medicines
• Through DiscovEHR, Geisinger and RGC are creating one of world’s most comprehensive genetics databases, matching genetic data to de-identified electronic health records of nearly 145,000 people so far
Genomic screening opportunity

• Reviewing exome data for actionable findings could improve identification of genetic risk
  • Clinically actionable genetic conditions are common (2-6%)
  • At least 1% of U.S. has ‘CDC Tier 1’ condition, but few are aware
  • Opportunity to mitigate risks for cancer and heart disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genes</th>
<th>Diseases</th>
<th>Lifetime Risks</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDLR, APOB, PCSK9</td>
<td>Early heart disease, stroke</td>
<td>Up to 50%</td>
<td>Lipid lowering therapy</td>
</tr>
<tr>
<td>Hereditary breast &amp; ovarian cancer syndrome</td>
<td>BRCA1, BRCA2</td>
<td>Breast, ovarian, prostate &amp; other cancers</td>
<td>Up to 70%</td>
<td>Surveillance, prophylactic surgery</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Colon, uterine &amp; other cancers</td>
<td>Up to 70%</td>
<td>Surveillance, prophylactic surgery</td>
</tr>
</tbody>
</table>

Green RC et al., 2013, Genet Med; Dorschner MO et al., 2013, AJHG; Retterer K et al., 2015; Genet Med; https://www.ncbi.nlm.nih.gov/books/NBK1116; Kuchenbaecker KB et al., 2017, JAMA; Manickam K et al., 2018, JAMA Netw Open; Abul-Husn NS et al., 2016, Science; Win AK et al., 2017, CEBP; Austin MA et al., 2004, Am J Epidemiol; Hampel H et al., 2011, Cancer Prev Res; Nordestgaard BG et al., 2013, Eur Heart J; King MC, 2014, JAMA
MyCode®
scorecard

2 million Geisinger patients

Total consented participants: 266,155
Samples provided: 191,022
DNA sequences available for research: 144,204
DNA sequences eligible and analyzed for clinical review: 62,892
Participants with clinical result reported: 1,612

As of September 1, 2020

# MyCode Genomic Screening and Counseling (GSC) Program

**Vision:**
- MyCode patient-participants and their families are empowered to act on genomic information and prevent disease

**Mission:**
- Implement an innovative, scalable clinical program that supports patients, their families and healthcare professionals in the routine integration of genomic results into care
MyCode GSC Program Principles: SCREENING

- Reach broad expert consensus on which genes to evaluate & return
  - Determined by multiple stakeholders & reviewed regularly

- Return only pathogenic/likely pathogenic variants in clinically actionable genes

- Minimize false positives (specificity > sensitivity)
  - Only want to call “slam-dunk” positives

- Supportive infrastructure for patients & clinicians
Results disclosure

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, e.g., heart disease, early cancer
- Screening and prevention may include...

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

Recommend discussing result with family members
- Program provides letters and resources to help with this communication
<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>413</td>
<td>BRCA1</td>
<td>141</td>
</tr>
<tr>
<td>(early breast, ovarian, prostate and other cancers)</td>
<td></td>
<td>BRCA2</td>
<td>272</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>157</td>
<td>APOB</td>
<td>36</td>
</tr>
<tr>
<td>(early heart attacks and strokes)</td>
<td></td>
<td>LDLR</td>
<td>121</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>198</td>
<td>PMS2</td>
<td>84</td>
</tr>
<tr>
<td>(early colon, uterine and other cancers)</td>
<td></td>
<td>MSH6</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>13</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>1621</strong></td>
<td></td>
<td><strong>1621</strong></td>
</tr>
</tbody>
</table>

CDC ‘Tier 1’ Conditions Disclosed
Priority Research Questions

• Overall goal – Measure population health impact of our program by evaluating:
  • Penetrance of actionable variants in unselected population
  • Family communication and cascade testing interventions
  • Adherence to risk management recommendations
  • Digital scaling tools (e.g., chatbots)
  • Novel genomic counseling models
  • Risk-benefit balance of genomic screening

• Multi-disciplinary, mixed methods approaches to addressing questions
• Identify pathogenic & likely pathogenic (P/LP) \textit{BRCA1}/2 variants in unselected research cohort

• Characterize features associated with P/LP variants
Key points

• 36% BRCA1 (n=95) 64% BRCA2 (n=172)
• Prevalence: 1:180 (corrected for relatedness)
• Only 18% had prior clinical BRCA 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., 2018, JAMA Network Open
Clinical outcomes of a genomic screening program for actionable genetic conditions

Adam H. Buchanan, MS, MPH¹, H. Lester Kirchner, PhD², Marci L. B. Schwartz, ScM¹, Melissa A. Kelly, MS¹, Tara Schmidlen, MS¹, Laney K. Jones, PharmD, MPH¹, Miranda L. G. Hallquist, MSc¹, Heather Rocha, MS¹, Megan Betts, MS¹, Rachel Schwiter, MS¹, Loren Butry, MS¹, Amanda L. Lazzeri, BS¹, Lauren R. Frisbie, BS¹, Alanna Kulchak Rahm, PhD, MS¹, Jing Hao, PhD, MD¹,², Huntington F. Willard, PhD¹,³, Christa L. Martin, PhD¹,⁴, David H. Ledbetter, PhD¹,⁴, Marc S. Williams, MD¹ and Amy C. Sturm, MS¹
What is \textit{clinical utility} of genomic screening program among MyCode patients with a ‘CDC Tier 1’ genomic condition?

- Focus on patients for whom result is new information
  - Personal/family history of relevant disease prior to disclosure
  - Risk management procedure(s) post-disclosure
  - Relevant diagnosis post-disclosure

- Double-coded chart review performed by GCs, OB-GYN resident in June-Dec 2018
  - Median follow-up window: 21.8 months (inter-quartile range 15-31 months)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FH (n=93)</th>
<th>HBOC (n=202)</th>
<th>Lynch (n=56)</th>
<th>All study participants (n=351a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>56 (60.2%)</td>
<td>103 (51.0%)</td>
<td>32 (57.1%)</td>
<td>191 (54.4%)</td>
</tr>
<tr>
<td>Race: White</td>
<td>92 (98.9%)</td>
<td>291 (99.5%)</td>
<td>56 (100%)</td>
<td>349 (99.4%)</td>
</tr>
<tr>
<td>Race: African American</td>
<td>1 (1.1%)</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Race: Other</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ethnicity: Non-Hispanic/Non-Latino</td>
<td>92 (98.9%)</td>
<td>199 (98.5%)</td>
<td>56 (100%)</td>
<td>348 (99.2%)</td>
</tr>
<tr>
<td>Ethnicity: Other/Hispanic/Latino</td>
<td>1 (1.1%)</td>
<td>3 (1.5%)</td>
<td>-</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (14%)</td>
<td>43 (21.3%)</td>
<td>11 (19.6%)</td>
<td>67 (19.1%)</td>
</tr>
<tr>
<td>Alive at initial data pull</td>
<td>93 (100%)</td>
<td>194 (96.0%)</td>
<td>56 (100%)</td>
<td>343 (97.7%)</td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>62.7 (51.2, 72.0)</td>
<td>62.6 (50.6-72.1)</td>
<td>62.8 (53.8-73.8)</td>
<td>62.7 (51.0-72.2)</td>
</tr>
<tr>
<td>Median Charlson comobility Index (IQR)</td>
<td>5 (1-7)</td>
<td>4 (2-6)</td>
<td>4 (2-6.5)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Median follow-up in months (IQR, range)</td>
<td>14.4 (12.8-30.5, 7.4-43.3)</td>
<td>24.2 (21.1-32.8, 0.6-43.3)</td>
<td>14.7 (12.6=28.9, 8.0-36.3)</td>
<td>21.8 (14.5-30.6, 0.6-43.3)</td>
</tr>
<tr>
<td>Prior genetic diagnosis</td>
<td>0/93 (0%)</td>
<td>39/202 (19.3%)</td>
<td>7/56 (12.5%)</td>
<td>46/351 (13.1%)</td>
</tr>
</tbody>
</table>
Relevant personal & family history

• Among 305 w/o prior molecular diagnosis

• 65% had relevant personal and/or family history

• Significant differences by genetic condition

Buchanan AH et al., 2020, Genet Med; Katz AE et al., 2020; AJHG
Risk management

- 70% of eligible patients had post-disclosure risk management
- Factors associated with risk management:
  - Post-disclosure genetic counseling
  - Genetic condition
  - Prior risk management

<table>
<thead>
<tr>
<th></th>
<th>FH (n=93)</th>
<th>HBOC (n=163)</th>
<th>Lynch (n=49)</th>
<th>All (n=305)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk management eligible a</td>
<td>93/93 (100%)</td>
<td>114/163 (69.9%)</td>
<td>48/49 (98.0%)</td>
<td>255/305 (83.6%)</td>
</tr>
<tr>
<td>Risk management predislosure b</td>
<td>69/93 (74.2%)</td>
<td>43/114 (37.7%)</td>
<td>11/48 (22.9%)</td>
<td>123/255 (48.2%)</td>
</tr>
<tr>
<td>Risk management postdisclosure c</td>
<td>78/93 (83.9%)</td>
<td>82/114 (71.9%)</td>
<td>19/48 (39.5%)</td>
<td><strong>179/255 (70.2%)</strong></td>
</tr>
<tr>
<td>New diagnosis postdisclosure d</td>
<td>26/93 (28.0%)</td>
<td>10/163 (6.1%)</td>
<td>5/49 (10.2%)</td>
<td>41/305 (13.4%)</td>
</tr>
</tbody>
</table>

Buchanan AH et al., 2020, Genet Med
## Post-disclosure diagnoses

- 13% (41/305) had post-disclosure diagnosis
- 25 of these (61%) had EHR documentation of diagnosis being precipitated by genomic results disclosure

<table>
<thead>
<tr>
<th>FH (n=26)</th>
<th>HBOC (n=10)*</th>
<th>Lynch (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &gt;190 mg/dL (20)</td>
<td>Breast cancer (4)</td>
<td>Colon adenoma (4)</td>
</tr>
<tr>
<td>Atherosclerosis (5)</td>
<td>Prostate cancer (3)</td>
<td>Sebaceous adenoma (1)</td>
</tr>
<tr>
<td>Claudication/peripheral vascular disease (4)</td>
<td>Fallopian tube cancer (1)</td>
<td></td>
</tr>
<tr>
<td>Corneal arcus (4)</td>
<td>STIC lesion (1)</td>
<td></td>
</tr>
<tr>
<td>Xanthoma or xanthelasma (3)</td>
<td>Ampulla of Vater cancer (1)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All tumors stage IIA or earlier

STIC = serous tubal intraepithelial carcinoma
What have we learned so far?
- Actionable genetic conditions are more common than previously thought
- Genomic screening identifies at-risk individuals more comprehensively than clinical ascertainment
- Majority of patients use genetic result to guide care
- Genomic screening can lead to early cancer diagnoses

What’s left?
- Penetrance in diverse unselected populations
- Longer-term health outcomes
- Cost (financial, psychological, healthcare system)
eBox. Twelve Questions to Be Addressed in Pilot Studies of Large-Scale DNA-Based Screening

1. How should screening be designed to offer inclusive benefits for the whole population (with specific attention to the poor, as well as underrepresented racial and ethnic groups)?

2. What are the appropriate population characteristics for screening (eg, age, sex)?

3. What is the optimal testing strategy/technology (eg, exome sequencing, multigene panel, single-nucleotide polymorphism array)?

4. What are the ideal lead institutions for carrying out DNA-based screening (eg, health care provider organizations, departments of public health, for-profit companies)?

5. How should DNA-based screening (primary screen) be paid for (eg, government funding, private insurance, self-pay)?

6. How should clinical follow-up (secondary screen) be paid for (eg, government funding, private insurance, self-pay)?

7. How often should data be reanalyzed (eg, compared with evolving databases like ClinVar [updated annually])?

8. What strategy should be pursued for cascade testing (eg, should at-risk family members be automatically contacted by health system)?

9. What are the short-term clinical outcomes (eg, correcting diagnostic misattribution, presymptomatic diagnosis of cancer or heart disease)?

10. What are the long-term clinical outcomes (eg, nonpenetrance, overdiagnosis)?

11. What are the best practices regarding negative screening result reporting (critically important to avoid false reassurance)?

12. What are the clinical workforce needs related to delivering DNA-based results and clinical follow-up at population scale (ie, how many medical geneticists, genetic counselors, specialists, others)?
Acknowledgements

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

Geisinger MyCode Executive Committee
David H. Ledbetter, PhD
Christa Lese Martin, PhD
Amy Sturm, MS
Adam Buchanan, MS, MPH
Daniel Davis, PhD
David Rolston, MD

Regeneron Genetics Center
Aris Baras, MD, PhD
Jeff Reid, PhD
John Overton, PhD

Funding from:
Geisinger
Regeneron Pharmaceuticals

Genomic Screening & Counseling program:
Amy Sturm, MS
Adam Buchanan, MS, MPH
Marc Williams, MD
Cara McCormick, MPH
Amanda Lazzeri, BS
Gary Bellus, MD
Laney Jones, MPH, PharmD
Alanna Kulchak Rahm, PhD, MS
Marci Schwartz, ScM
Heather Rocha, MS
Tara Schmidlen, MS
Miranda Hallquist, MSc
Megan Betts, MS
Rachel Schwiter, MGC
Nicole Deckard, MS
Gretchen Thone, MS
Kerrianne Fry, MS
Missie Kelly, MS
Tasha Strande, PhD
Alyson Evans, MS
Eric Tricou, MS
Krista Zimmerman, BS
Amie Decker, BS