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

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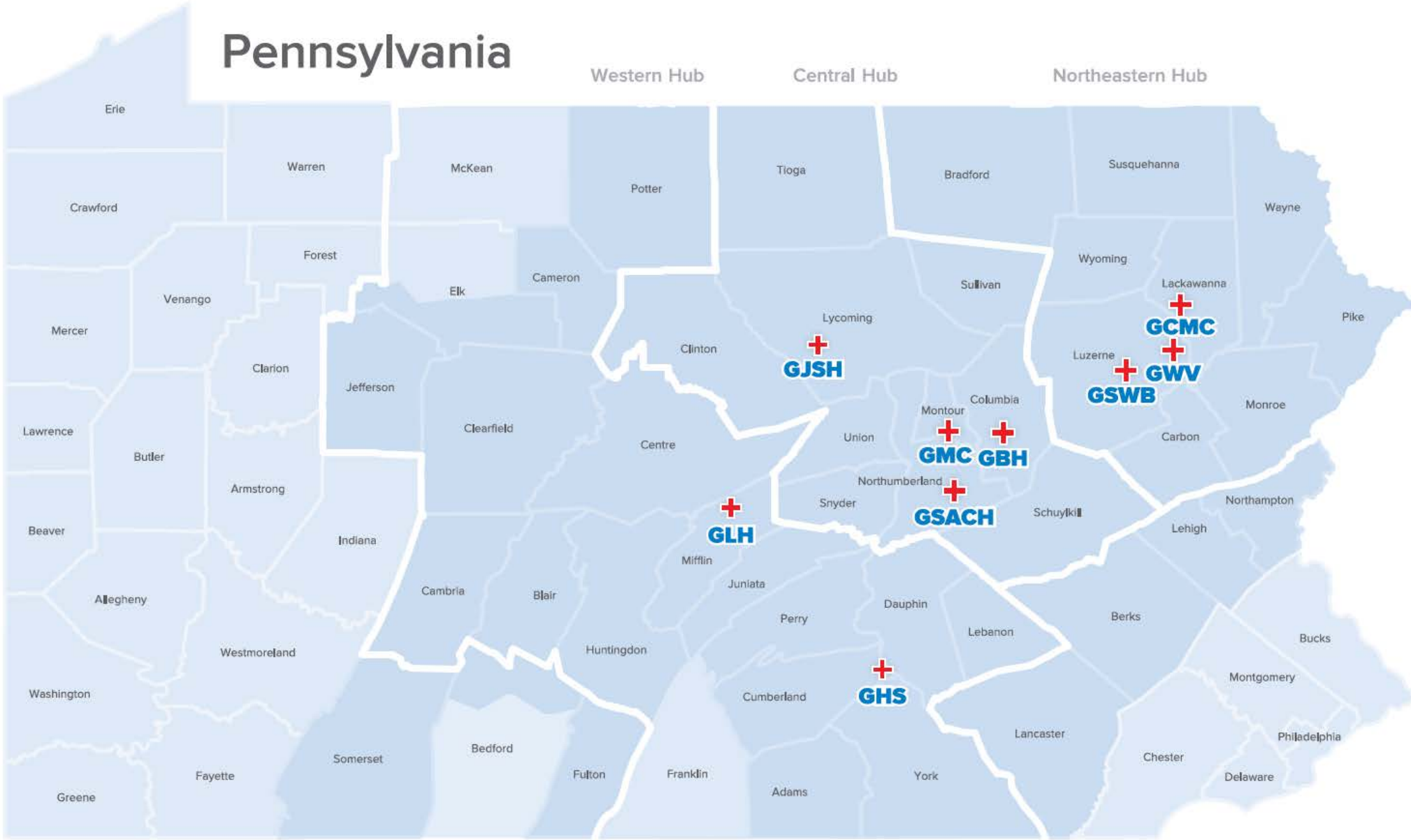
Geisinger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“Geisinger is as close to Iceland as you’ll find in the United States” - Glenn Steele, 2003

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

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

Condition	Genes	Diseases	Lifetime Risks	Interventions
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*	Early heart disease, stroke	Up to 50%	Lipid lowering therapy
Hereditary breast & ovarian cancer syndrome	*BRCA1, BRCA2*	Breast, ovarian, prostate & other cancers	Up to 70%	Surveillance, prophylactic surgery
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	Colon, uterine & other cancers	Up to 70%	Surveillance, prophylactic surgery

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, *JAMAs*

MyCode® scorecard

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

mycode

As of September 1, 2020

https://www.geisinger.org/-/media/OneGeisinger/pdfs/ghs/research/mycode/mycode-scorecard.pdf?la=en

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

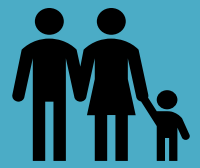
- Often unanticipated call
- May not be related to acute concerns

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

CDC ‘Tier 1’ Conditions Disclosed

MyCode® results reported

1612 patient-participants have received results*
from the Genomic Screening and Counseling Program

mycode | 250,000+ PARTICIPANTS

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

September 1, 2020

Risk Condition	Patients per risk condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)	413	*BRCA1*	141
		BRCA2	272
Familial hypercholesterolemia (early heart attacks and strokes)	157	*APOB*	36
		LDLR	121
Lynch syndrome (early colon, uterine and other cancers)	198	*PMS2*	84
		MSH6	86
		MSH2	15
		MLH1	13
Totals	1621		1621

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**

JAMA Network Open

Original Investigation | Genetics and Genomics

Exome Sequencing–Based Screening for *BRCA1/2* Expected Pathogenic Variants Among Adult Biobank Participants

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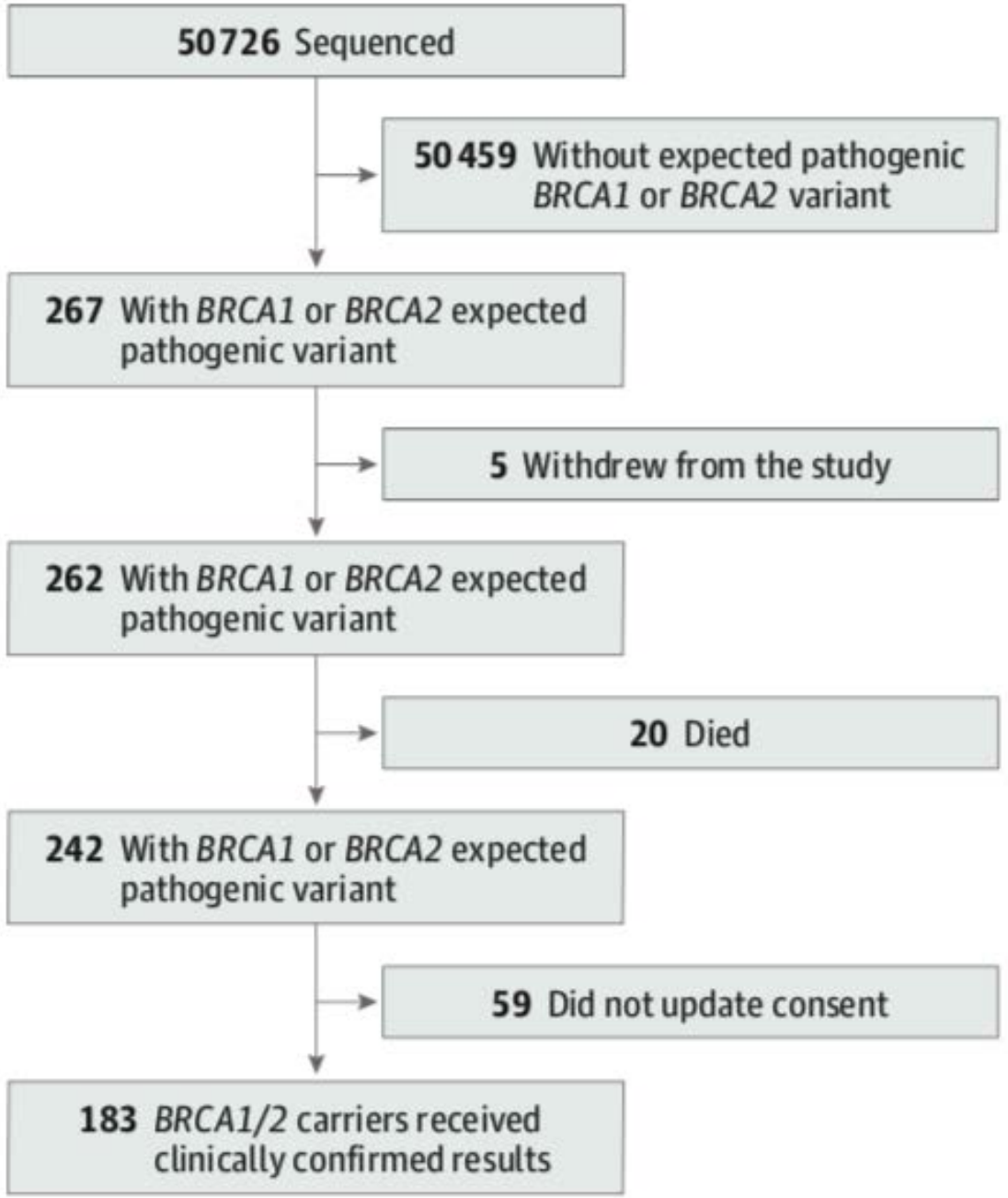
- Identify pathogenic & likely pathogenic (P/LP) *BRCA1/2* variants in unselected research cohort
- Characterize features associated with P/LP variants

Manickam K et al., 2018, *JAMA Network Open*

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*

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Clinical outcomes of a genomic screening program for actionable genetic conditions

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What is 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

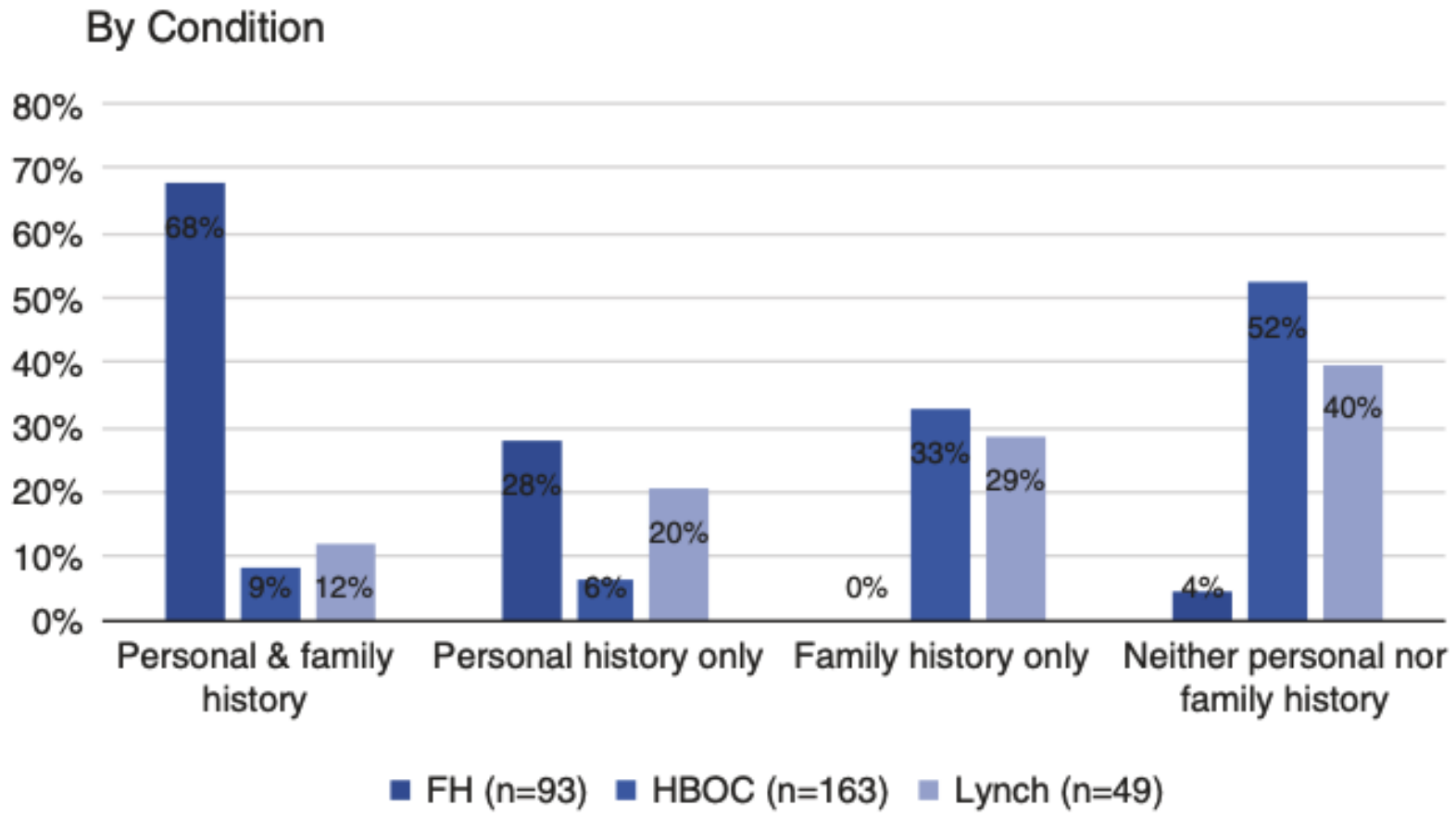
- Double-coded chart review performed by GCs, OB-GYN resident in June-Dec 2018
  - Median follow-up window: 21.8 months (inter-quartile range 15-31 months)

Buchanan AH et al., 2020, *Genet Med*

Characteristics	FH (*n*=93)	HBOC (*n*=202)	Lynch (*n*=56)	All study participants (*n*=351[a])
Female sex	56 (60.2%)	103 (51.0%)	32 (57.1%)	191 (54.4%)
Race: White	92 (98.9%)	291 (99.5%)	56 (100%)	349 (99.4%)
Race: African American	1 (1.1%)	1 (0.5%)	-	2 (0.6%)
Race: Other	-	-	-	-
Ethnicity: Non-Hispanic/ Non-Latino	92 (98.9%)	199 (98.5%)	56 (100%)	348 (99.2%)
Ethnicity: Other/ Hispanic/ Latino	1 (1.1%)	3 (1.5%)	-	3 (0.8%)
Current smoker	13 (14%)	43 (21.3%)	11 (19.6%)	67 (19,1%)
Alive at initial data pull	93 (100%)	194 (96.0%)	56 (100%)	343 (97.7%)
Median age in years (IQR)	62.7 (51.2, 72.0)	62.6 (50.6-72.1)	62.8 (53.8-73.8)	62.7 (51.0-72.2)
Median Charlson comobility Index (IQR)	5 (1-7)	4 (2-6)	4 (2-6.5)	4 (2-6)
Median follow-up in months (IQR, range)[b]	14.4 (12.8-30.5,7.4-43.3)	24,2 (21.1-32.8,0.6-43.3)	14.7 (12.6=28.9, 8.0-36.3)	21.8 (14.5-30.6, 0.6-43.3)
Prior genetic diagnosis	0/93 (0%)	39/202 (19.3%)	7/56 (12.5%)	46/351 (13.1%)

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

	FH (*n*=93)	HBOC (*n*=163)	Lynch (*n*=49)	All (*n*=305)
Risk management eligible [a]	93/93 (100%)	114/163 (69.9%)	48/49 (98.0%)	255/305 (83.6%)
Risk management predisclosure [b]	69/93 (74.2%)	43/114 (37.7%)	11/48 (22.9%)	123/255 (48.2%)
Risk management postdisclosure [c]	78/93 (83.9%)	82/114 (71.9%)	19/48 (39.5%)	179/255 (70.2%)
New diagnosis postdisclosure [d]	26/93 (28.0%)	10/163 (6.1%)	5/49 (10.2%)	41/305 (13.4%)

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

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

*All tumors stage IIA or earlier

STIC = serous tubal intraepithelial carcinoma

Priority Research Questions con.

- **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)

Manickam K et al., 2018, *JAMA Network Open*; Abul-Husn NS et al., 2016, *Science*; Buchanan AH et al., 2018, *Genet Med*; Buchanan AH et al., 2020, *Genet Med*

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 anually])?
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)?

Murray MF et al., 2019, *JAMA*

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