Population Genomic Health

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Objectives

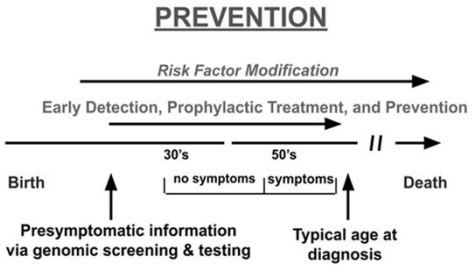
- Define population genomic screening
- Describe different types of population genomic screening programs
- Illustrate potential clinical utility and cost-effectiveness of population genomic screening programs
- Describe three case studies of population genomic screening initiatives

What is population genomic screening?

- **Definition:** the systematic genetic testing of the general population, or large subsets of it, to identify individuals with predispositions to specific, actionable hereditary conditions

- **Goal:** to proactively manage or prevent diseases by providing personalized risk information to individuals and their healthcare providers and integrate these findings into primary care to enable early, targeted treatments and interventions

The Goal of Precision Health Genomics



What is my experience in this area?

- The MyCode Community Health Initiative at Geisinger
  - Director and Principal Investigator
- The National Institutes of Health *All of Us* Research Program
  - Chair of the Advisory Board to the Genetic Counseling Resource
- Direct-to-consumer genetic testing company
  - Director of Population Health Genomics
  - Director of Genomic Health Programs and Medical Affairs
- Ohio State Genomic Health
  - Executive Director and Principal Investigator

Background

- >10 million Americans are predicted to have inherited risk for cancer, heart disease, and other serious conditions, but only 10% are aware of these risks
- Advances in clinical genomic screening capabilities, including reduced costs and knowledge gains, have bolstered the consideration of genomic screening in healthy adult populations
- Multiple genomic screening programs exist across the U.S., and internationally, today
- Current programs are diverse with respect to cost, clinical and research approaches, genes included in the screen, and implementation methods

Genomics and Population Health Action Collaborative

NATIONAL ACADEMIES Sciences Engineering Medicine

- Formed in 2015, GPHAC aimed to identify challenges and potential best practices for the widespread integration of evidence-based genomics applications in population health programs
- Applied the CDC Office of Genomics & Precision Public Health's groupings:
  - Tier 1 - "CDC Tier 1 conditions" - genomic applications with a strong clinical knowledge base and strong evidence for medical actionability
- GPHAC endorsed the 10 genes associated with the 3 "CDC Tier 1" conditions as a reasonable starting point for primary screening in the general population
  - *3 conditions:* Lynch syndrome (5), hereditary breast and ovarian cancer (2), and familial hypercholesterolemia (3)
  - *Rationale:* highly penetrant, well understood natural history, robust evidence-based clinical interventions to prevent or mitigate disease or risk in pre-symptomatic individuals, greatest likelihood to maximize benefit and minimize harm

https://www.nationalacademies.org/our-work/genomics-and-population-health-action-collaborative

Understanding CDC Tier 1 conditions and resulting interventions

FH

Genes: *LDLR, APOB, PCSK9* and *LDLRAP1*

- Hypercholesterolemia and increased risk for cardiovascular events

→ Interventions include cholesterol lowering medication, typically a statin

→ Early identification and treatment reduce the risk of cardiovascular events (MI, etc)

HBOC

Genes: *BRCA1* and *BRCA2*

- Significantly increased lifetime risk of breast, ovarian and other cancers

→ Intervention includes more frequent and enhanced screenings and in some cases prophylactic surgery

→ Earlier screenings and interventions result in earlier detection and potentially prevention of cancer

Lynch

Genes: *MLH1, MSH2, MSH6, PMS2* and *EPCAM*

- Significantly increased lifetime risk of colorectal, endometrial and other cancers

→ Intervention typically includes earlier and more frequent screenings, chemoprevention and in some cases prophylactic surgery

→ Earlier screening improves overall patient outcomes (i.e. colonoscopy reduces the incidence of CRC by ~60%)[1]

Helix

1 Järvinen HJ, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000 May;118(5):829-34. doi: 10.1016/s0016-5085(00)70168-5. PMID: 10784581.

Key Aspects of Population Genomic Screening

- Broad testing
- Focus on actionability
- Preventive healthcare
- Early detection
- Integration into primary care

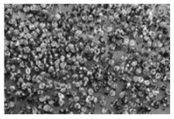
Traditional clinical genetic testing & population genomic screening

Clinical genetic testing

- Indication based: ordered based on personal and/or family history
- Sensitivity>specificity
- Diagnostic technology

Population genomic screening

- Not indication based: offered to all, or to all in a broad clinical category
- Specificity>sensitivity
- Screening technology



Types of population genomic screening programs

Genomic Screening Program Categories

Type of Program	Examples	Location
System-wide program	• Geisinger MyCode • University of Vermont The Genomic DNA Test • Sanford Health Imagenetics • Helix Research Network sites (i.e. Ohio State Genomic Health)	• Danville, PA • Burlington, VT • Sioux Falls, SD • 16 sites, 15 in U.S., 1 in Canada
Patients invited to health system pilot project	• Northshore DNA 10K • Oschner Health Population Genomic Screening Program • Stanford Humanwide	• Chicago, IL • New Orleans, LA • Palo Alto, CA
Statewide program	• Healthy Nevada Project • Alabama Genomic Health Initiative	• Nevada • Alabama
Nationwide program	• The NIH *All of Us* Research Program	• U.S.
Screening offered in a genetics clinic	• Brigham & Women's Preventive Genomics Clinic • St. Elizabeth Healthcare Precision Medicine & Genetics • UCSF Preventive Genomics Clinic	• Boston, MA • Edgewood, KY • San Francisco, CA

Multiple international programs, too!

Foss KS et al. The Rise of Population Genomic Screening: Characteristics of Current Programs and the Need for Evidence Regarding Optimal Implementation. *Journal of Personalized Medicine*. 2022; 12(5):692.

What is the potential clinical utility and cost-effectiveness?

Clinical utility and implementation: *What have we learned so far?*

Prevalence: Actionable genetic conditions are more common than previously thought	Improved identification: Genomic screening identifies individuals with P/LP variants more comprehensively than clinical ascertainment	Risk-benefit balance: Modest psychological impact of receiving P/LP variant result	Care: Majority of patients use genetic result to guide care (CDC Tier One)
Prevention: Genomic screening can facilitate primary and secondary prevention	Digital scaling tools: Chatbot is an acceptable tool for consent, patient follow-up, and facilitating family communication	Family Communication and Cascade Testing: Interventions needed to improve uptake	Cost effectiveness: Favorable economic modeling

Manickam K et al., 2018, JAMA Network Open; Abul-Husn NS et al., 2016, Science; Buchanan AH et al., 2020, Genet Med; Martin CL et al., 2020, JAMA Psych; Schmidlen T et al., 2019, J Genet Couns

ARTICLE | Genetics inMedicine

Open

Clinical outcomes of a genomic screening program for actionable genetic conditions

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Clinical Outcomes of Genomic Screening *The Geisinger MyCode Experience*

Study: Assessed genomic screening impact on risk management & early detection

Results:

- 87% (305/351) did not have a prior genetic diagnosis of their CDC Tier 1 result
- Of these, 65% had EHR evidence of relevant personal and/or family history of disease
- Of 255 individuals eligible to have risk management, 70% ($n = 179$) had a recommended risk management procedure after results disclosure
- 13% of participants (41/305) received a relevant clinical diagnosis after results disclosure

Conclusion: Genomic screening can identify previously unrecognized individuals at increased risk of cancer and heart disease and facilitate risk management and early detection

Buchanan AH et al. Clinical outcomes of a genomic screening program for actionable genetic conditions. *Genet Med.* 2020;22(11):1874-1882. doi:10.1038/s41436-020-0876-4

Is genomic screening cost-effective?

Study: Assessed cost-effectiveness of genomic screening for 3 CDC Tier 1 conditions

Results:

- Screening 30-, 40-, and 50-year-old cohorts was cost-effective in 99%, 88%, and 19% of probabilistic simulations, respectively, at a $100,000-per-QALY threshold.
- The test costs at which screening 30-, 40-, and 50-year-olds reached the $100 000-per-QALY threshold were $413, $290, and $166, respectively. Variant prevalence and adherence to preventive interventions were also highly influential parameters.

Conclusion: Population genomic screening for the 3 CDC Tier 1 conditions is likely to be cost-effective in U.S. adults <40y if the cost is relatively low and patients have access to preventive interventions

Guzauskas GF et al. Population Genomic Screening for Three Common Hereditary Conditions : A Cost-Effectiveness Analysis. *Ann Intern Med.* 2023;176(5):585-595. doi:10.7326/M22-0846

Key Lessons on Clinical Implementation

- Systems can manage scale by excluding variants of uncertain significance
- Sub-optimal uptake of recommended risk management underscores need for strategies to facilitate adherence for long-term population health management
- Promising strategies include
  - Fitting program into existing clinical workflows
  - Use of clinical decision support
  - Care coordination
  - Close collaboration with co-managing clinicians and primary care
- Achieving broad population health impact requires robust uptake of family testing
  - Early evidence points to need for family communication and testing tools

Buchanan, Rahm, Sturm. *Public Health Genomics.* 2024

American College of Medical Genetics and Genomics

Points to consider statement on DNA-based screening and population health

1. The ACMG secondary findings recommendations do not constitute a primary health screening recommendation or strategy.
2. DNA-based screening should not replace a standard-of-care evaluation for individuals with a clinical indication for diagnostic assessment.
3. Disease risks identified through screening should not include DNA variants of uncertain significance (VUS).
4. DNA-based screening should be linked to opportunities for evidence-based risk-reducing clinical care.
5. Risk-reducing clinical follow-up for DNA-based screening should be consistent with best practices outlined by professional societies with appropriate expertise.
6. Organizations involved in DNA-based screening are expected to participate in sharing of outcomes-related data.
7. DNA-based screening applications with proven beneficial clinical outcomes should be made available to entire populations to promote health-care equity and limit health disparities.

Murray et al. *Genetics in Medicine.* 2021

Three case studies of population genomic screening initiatives

All of Us, MyCode, and Ohio State Genomic Health

All of Us RESEARCH PROGRAM

NIH National Institutes of Health

Geisinger mycode

Ohio State Genomic Health
Better health is in your genes.

The Ohio State University Wexner Medical Center

Helix

The NIH *All of Us* Research Program

A Case Study

- **What is it?** National Institutes of Health (NIH) initiative to build a diverse national research platform for precision medicine
- **Participants:** ≥1 million people from all backgrounds across the United States to ensure the data is diverse
- **Data Collection:** surveys, electronic health records, physical measurements, and DNA samples
- **Goals:** aims to speed up medical research, develop individualized healthcare, and find better ways to prevent and treat diseases
- **Participation Benefits:** can learn about their health and DNA, including traits related to ancestry or potential disease risk, and help improve the health of future generations

https://allofus.nih.gov/

Returning DNA results to *All of Us* Participants

- By the end of 2024, *All of Us* delivered:
  - Research DNA results to >220,000 participants for genetic ancestry and traits
  - Health-related research DNA results to >128,000 participants who wanted them:
    - ~4,000 participants received information that they had a treatable or preventable hereditary condition
    - >108,000 participants learned about how their bodies process certain medications, like clopidogrel
- Some participants who said "yes" to genetic results are still waiting for their individual DNA results

https://allofus.nih.gov/article/announcement-a-new-chapter-in-dna-results-fulfilling-our-promise#:~:text=Research%20DNA%20results%20to%20over,faster%20than%20our%20initial%20approach.

Research Contributions Making a Difference

- Scientists are finding new subgroups of type 2 diabetes that could change how we treat the disease
- >414,000 whole genome sequences have been made available to over 17,000 researchers from all 50 states
- >275 million previously unreported genetic variants have been discovered
- DNA-based tests for certain chemotherapies are becoming more reliable
- Polygenic risk scores for common conditions are improving for all backgrounds
- Hundreds of peer-reviewed scientific articles have been published, with new research coming out every day

https://allofus.nih.gov/article/announcement-a-new-chapter-in-dna-results-fulfilling-our-promise#:~:text=Research%20DNA%20results%20to%20over,faster%20than%20our%20initial%20approach.

Population Genomic Screening at Geisinger, with the MyCode Community Health Initiative

A Case Study

What is the MyCode Community Health Initiative?

https://www.geisinger.org/precision-health/mycode/frequently-asked-questions

MyCode at Geisinger

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

MyCode Goals

Geisinger mycode

- Discover gene-disease connections
- Targeting new drug development
- Identify individuals with actionable variants, integrate results into care, and conduct related research
- Translating findings into clinical care

Ohio State Genomic Health

A case study

BECKER'S HOSPITAL REVIEW

OSU Wexner to launch Ohio's largest precision health initiative

Elizabeth Gregerson - Tuesday, July 23rd, 2024

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The Ohio State University Wexner Medical Center in Columbus has partnered with population genomics company Helix to launch the largest precision health initiative in the state.

Ohio State Genomic Health will launch later in 2024 and enroll 100,000 participants to participate in genetic screening for more than four years. The program will be optional and provided at no cost to participants, according to a July 23 news release from OSU Wexner Medical Center.

Helix's technology will be used to screen participants' genetic information for variants associated with breast and ovarian cancer, colorectal cancer and high cholesterol, the release said.

"This partnership will expand and accelerate research across Ohio State focused on understanding mechanisms underlying human disease as well as development of diagnostics and treatments for patients. This is a critical platform for prevention and treatment," Peter Mohler, PhD, executive vice president for research, innovation and knowledge at the university and chief scientific officer at OSU Wexner Medical Center, said in the release.

Evolution of genomics to be more effective and efficient

Current state….	Future state….
Focused on single services	Population-scale
Treated as one-off resource	Sequence Once, Query Often
Provided as short term value	Research backbone creates long-term impact

The Helix Research Network

Helix

The Helix Research Network (HRN)

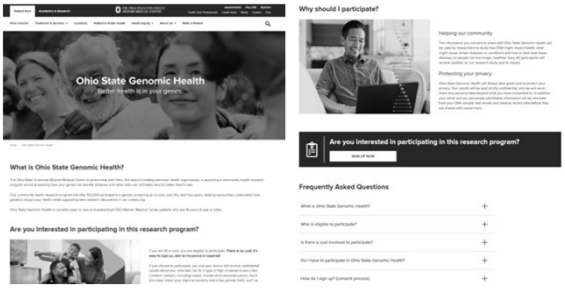
16 health systems with **1.6M diverse patients committed**

CLIA/CAP Exome+ on every participant w/ avg. of 12 years of longitudinal EMR for **applicable real-world evidence**

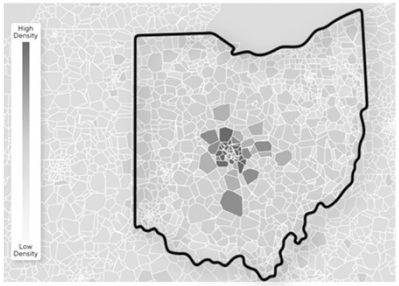
Proprietary Exome+® technology developed by ***the only FDA authorized clinical exome sequencing facility in the world***

Helix

Ohio State Genomic Health



Ohio State Genomic Health Heat Map
Consented Participant Location Density, by Zip Code



As of July 2025, OSGH has ≥1 patient consented from each of Ohio's 88 counties.

All Consented Participants in Ohio State Genomic Health Receive Genetic Screening for Three CDC Tier 1 Conditions

1-2% of patients will test positive for one of these conditions

- Hereditary Breast & Ovarian Cancer Syndrome (BRCA1/2)
- Lynch Syndrome
- Familial Hypercholesterolemia

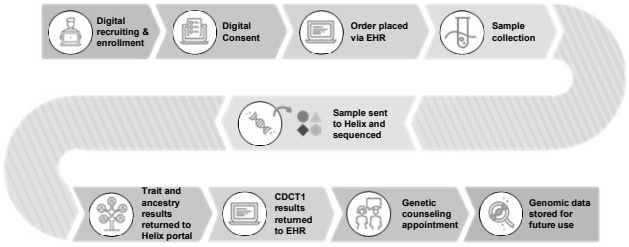
1 Poorly ascertained by healthcare systems

2 Public health burden of associated disease

3 Action can be taken to improve health and prevent disease

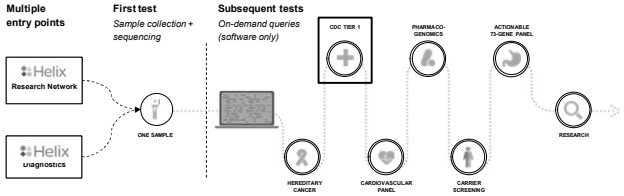
1 CDC Tier 1 Genomics Applications and their Importance to Public Health

Clinical workflow developed & integrated into current processes



Helix

Enabling Sequence Once, Query Often on Exome+



Tests can result in minutes because of our ability to automate interpretation process

Looking forward to the future of population genomic screening

Public Health Genomics

Perspectives

Public Health Genomics 2024;27:96–99
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A New Agenda for Implementing Population Genomic Screening

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There is much left to learn!

- **Effectiveness questions**
  - Prevalence/penetrance of variants in diverse individuals?
  - Other risk factors (e.g., polygenic risk, smoking history) that can refine risk?
  - Risk-benefit when screening for multiple conditions at once?
  - Factors that influence adherence?
- **Implementation questions**
  - Equitable access?
  - Payment?
  - Solutions needed to integrate results and longitudinal management?
  - Support needed for adherence and family testing?
  - Solutions needed for continuous improvement within local contexts?

Buchanan, Rahm, Sturm. *Public Health Genomics*. 2024

In Summary

- Nearly a decade into the proliferation of population genomic screening programs, such programs provide benefit, *in certain contexts*
- Population genomic screening for the CDC Tier 1 conditions has clinical utility and is cost-effective at younger ages
- Determining whether these programs provide net positive outcomes across diverse populations, will require additional research