Genomic screening: Who is Ready?

Mike Murray, MD

November 8, 2023 (9:35am)

NHGRI's Genomic Medicine XV: Genomics and Population Screening

Bethesda, MD

My Disclosure RE: Genomic Screening

I have published on where I think we are headed

- **Every Individual will have a comprehensive Genomic Dataset generated in the newborn period (created for their health and meant for use throughout their lives).**
- **This will be linked to their Electronic Health Record in a secure fashion.**
- **There will be two types of evidence-based indications to access it:**

  [1] Reiterative "population screening" (based on age or other triggers)

 **[2] Clinically indicated "diagnostic assessment"**

"Genomic Screening: Who is Ready?"

How long till we get there?

ACMG Population Screening Workgroup

▶ **<u>Primary Findings (PF)</u>** - are screening results generated from *data sets created for genomic screening.*

▶ **<u>Secondary Findings (SF)</u>** - are screening results generated by analyzing *data sets created for a primary purpose other than screening.*

- ➤ **<u>SF from Clinical Datasets</u>** - screening of newly generated clinical datasets at the time of diagnostic testing (WES & WGS) was initially proposed by ACMG 2013.

- ➤ **<u>SF from Research Datasets</u>** - screening of existing research datasets in appropriately consented research volunteers, followed by delivery of findings in a healthcare setting. Initiated at Geisinger 2015.

PROGRAMMATIC SCREENING FOR DISEASE
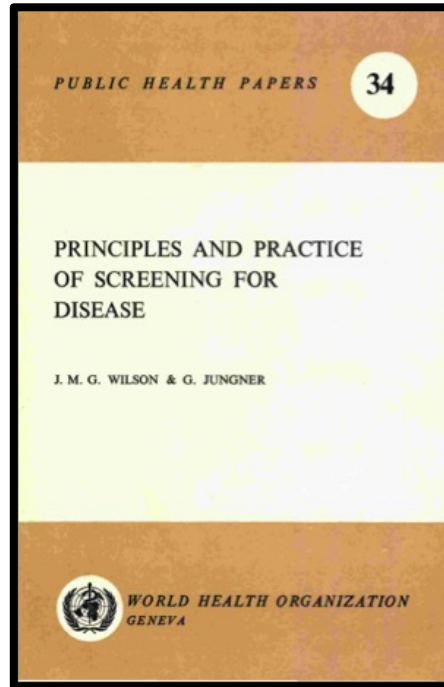
Wilson JMG, Jungner G.
Principles and practice of
screening for disease.
Geneva: WHO; 1968.

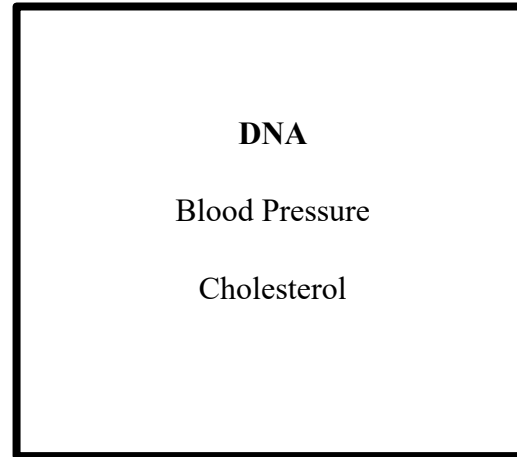# Screening for Disease v. Screening for Disease Risk

Detecting Disease → **Treatment**

California 1950s - Public Health Service mobile chest radiography

Cecily Miller et al. Eur Respir J 2017;49:1700364

**Detecting Disease Risk** → **Prevention & Early Diagnosis**

DNA

Blood Pressure

Cholesterol

Wilson and Jungner criteria in the context of DNA-based screening and population health

Table 2. Wilson and Jungner criteria in the context of DNA-based screening and population health.

|	Wilson and Jungner criteria	Criteria in DNA-based screening and population health context
1	The condition sought should be an important health problem.	Screening should focus on the identification of genomic risk(s) for important health problems.
2	There should be an accepted treatment for patients with recognized disease.	Options for evidence-based clinical actions should be communicated to patients in whom the genomic risk is identified.
3	Facilities for diagnosis and treatment should be available.	Clinical implementation strategies should be in place and available to anyone identified as having genomic risk.
4	There should be a recognizable latent or early symptomatic stage.	Screening should have the capability of identifying at-risk individuals during both presymptomatic and early symptomatic disease stages.
5	There should be a suitable test or examination.	The DNA-based strategy should constitute an improvement over existing strategies for risk identification and risk reduction.
6	The test should be acceptable to the population.	Proven screening applications should be available to all but individual participation should be optional.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.	Anticipated penetrance and expressivity (i.e., natural history) should be understood based on data from comparable populations.
8	There should be an agreed policy on whom to treat as patients.	Consensus should exist on clinical classification and management for those patients who screen positive for genomic risk but in whom the evidence of the associated health problems is absent (i.e., nonpenetrant risk).
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Appropriate health economic analyses should be in place to understand programmatic costs and benefits.
10	Case-finding should be a continuing process and not a "once and for all" project.	There should exist plans for both: - Periodic *reanalysis of DNA variants* using updated information. - Periodic *clinical re-evaluation* of individuals with nonpenetrant risk.

Diagnostic genetic test v. Screening genetic test
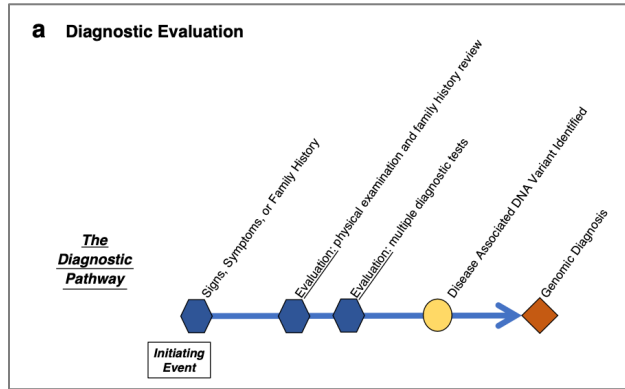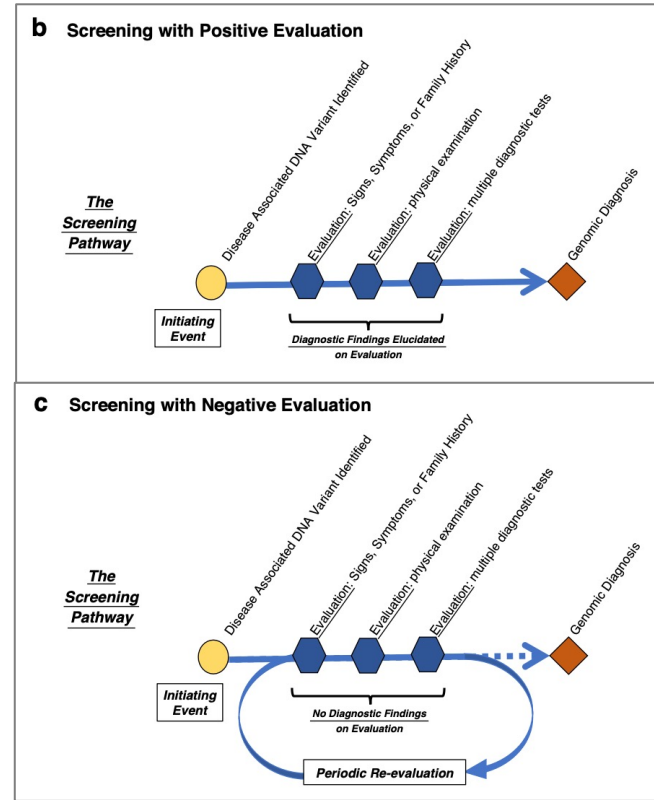
Imperfect Genotype-Phenotype Correlations are the Norm
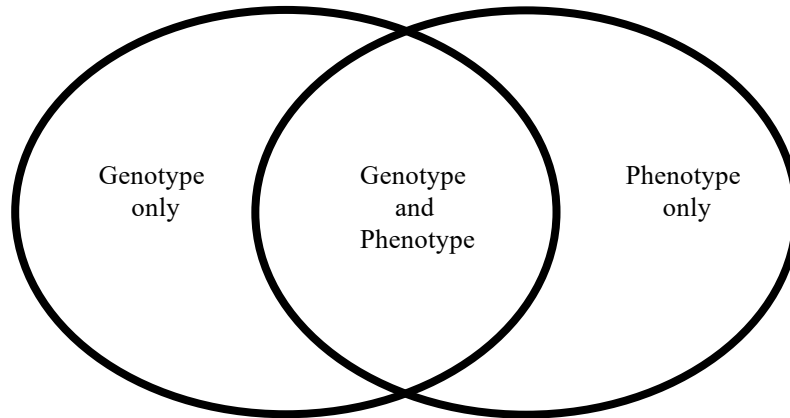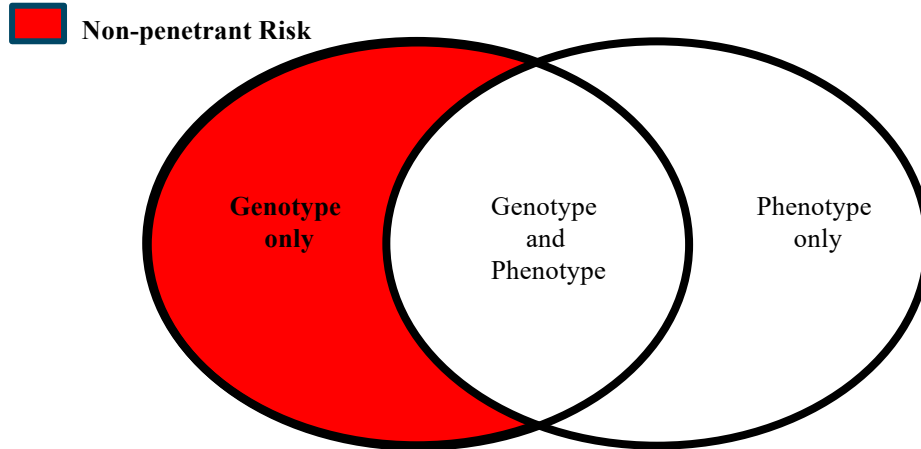
Genotype
only

Genotype
and
Phenotype

Phenotype
only

DEFINITION

- **Genotype-Phenotype Correlation -** how specific genetic variation(s) are correlated with certain observable traits in individuals.

Imperfect Genotype-Phenotype Correlations are the Norm

Non-penetrant Risk

Genotype only

Genotype and Phenotype

Phenotype only

DEFINITION

- **Genotype-Phenotype Correlation -** how specific genetic variation(s) are correlated with certain observable traits in individuals.

The details of the Venn diagram will almost certainly <u>vary with</u> the <u>DISEASE</u>, the <u>GENE</u>, (the <u>VARIANT</u>) and the <u>POPULATION</u>

Non-Penetrant Risk Prediction is Not Limited to DNA

Winnie Langley is pictured here lighting her cigarette using the candle on her own 100th birthday cake.

She lived another 2 years and died in 2010 at age 102 years old.

Non-penetrant risk does not necessarily run in families

Non-penetrant risk does not necessarily run in families

https://familyheart.org/family-screening-for-fh-and-the-use-of-genetic-testing
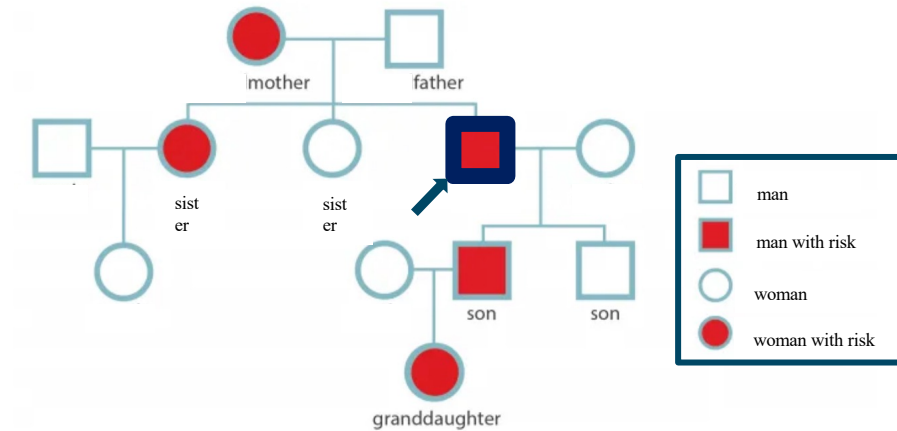
__Cascade testing__ is essential to evidence development in these early days of DNA-based Screening.

It is difficult but it is an important case identification multiplier that needs to be optimized

There is a recommended strategy in place for <u>screening women of BRCA 1/2</u>

USPSTF
2005
2014
2019

The DNA-based strategy should constitute an improvement over existing strategies for risk identification and risk reduction.

There is a recommended strategy in place for <u>screening women of BRCA 1/2</u>

Final Recommendation Statement

BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing

August 20, 2019

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade
Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with BRCA1/2 gene mutation	The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing.	B
Women whose personal or family history or ancestry is not associated with potential harmful BRCA1/2 gene mutations	The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations.	D

Divide all women into two groups

Just because Family History acquisition is not compensated doesn't mean its free

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

BRCA 1/2 Cases in ~50K Patients

- 20% ■ Prior Clinical Testing
- 80% □ No Prior Clinical Testing

Original Investigation | Genetics and Genomics

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

BRCA 1/2 Cases in ~50K Patients

- Prior Clinical Testing
- No Prior Clinical Testing, Meets Criteria for Testing — *Screening Failures*
- No Prior Clinical Testing, Does Not Meet Criteria for Testing — *Strategy Failures*

**How many people with P/LP variants in *BRCA1* or *BRCA2*
were unaware of their status prior to Genomic Screening?**

> 8 of 10 Adults

Healthy Nevada Project (HNP)

"CDC Tier 1" conditions
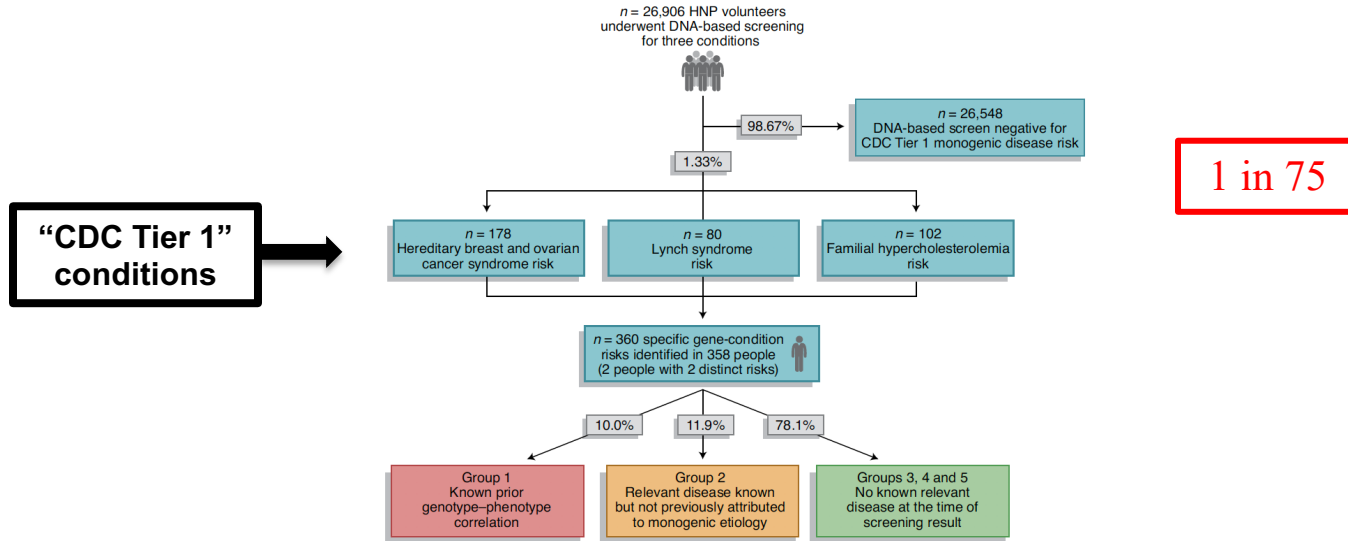
1 in 75

In 2023: Screening 9 Genes for Three Genetic Syndromes

would identify risk in
~ 4.3M people in the United States

1 in 75

SCREENING FOR ELEVATED RISK OF		
Heart Attack and Stroke	**Breast, Ovarian, Prostate, Pancreatic Cancer**	**Colon and Uterine Cancer**
Familial Hypercholesterolemia (FH)	Hereditary Breast and Ovarian Cancer (HBOC)	Lynch Syndrome (LS)

A screening strategy that includes this list is the likely starting point for population screens.

Which (if any) additional genes/conditions should be included is currently unclear.

Clinical implementation strategies should be in place and available to anyone identified as having genomic risk.

Annals of Internal Medicine ®

Population Genomic Screening for Three Common Hereditary Conditions

A Cost-Effectiveness Analysis

Conclusion:

Population genomic screening with a restricted panel of high-evidence genes associated with 3 CDC Tier 1 conditions is likely to be cost-effective in U.S. adults younger than 40 years if the testing cost is relatively low and probands 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 May;176(5):585-595. PMID: 37155986.

Appropriate health economic analyses should be in place to understand programmatic costs and benefits.

What does it come down to for <u>what's on the list?</u>

▶ **<u>Clinical Utility</u>** - the likelihood that a test will, by prompting an intervention, result in an improved health outcome.

What does it come down to for <u>what's on the list?</u>

- ▶ **<u>Medical Actionability</u>** – the availability of clinical actions that are evidence-based that should occur as follow-up to a genomic screening result.

and

- ▶ **<u>Clinical Utility</u>** - the likelihood that a test will, by prompting an intervention, result in an improved health outcome.

<u>**To paraphrase Grosse and Khoury**</u>
A screening test alone does not have inherent utility; the clinical utility of the screening test depends on effective access to appropriate interventions.

We are in an Era of "Genomic Screening Pilots"

Research Genomic screening:

- Engaged Populations and Engaged Expertise should drive the what's considered for return.

- For example:
  - Pathogenic Founder Variants in *APOL1* and *TTR* are not on the list for some populations and are essential in others.
  - Monogenic risk for major psychiatric illness is something many sites would not be capable of taking on. But some sites can and should.

ACMG Population Screening Workgroup

▶ **Primary Findings (PF)** - are screening results generated from *data sets created for genomic screening.*

▶ **Secondary Findings (SF)** - are screening results generated by analyzing *data sets created for a primary purpose other than screening.*

➤ **SF from Clinical Datasets** - screening of newly generated clinical datasets at the time of diagnostic testing (WES & WGS) was initially proposed by ACMG 2013.

➤ **SF from Research Datasets** - screening of existing research datasets in appropriately consented research volunteers, followed by delivery of findings in a healthcare setting. Initiated at Geisinger 2015.

United States 2023 population is estimated at <u>339,996,563 people</u>
<u>https://www.worldometers.info</u>

▶ Genomic screening: Who is Ready?

  o <u>We</u> are not ready for routine implementation. Lots more research needed.
  o <u>We</u> are going to discuss today and tomorrow some of the critically important ways that we are not ready, and why we need to work methodically and equitably to "get there".

What else to do?

  o <u>I think</u> consideration should be given to creating a timeline with milestones to completion of implementation.

Thank you!

Questions/Comments

Mike Murray (michael.murray@mssm.edu)