Population Based Genomic Screening – Are We Ready?

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CDC

OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION

Population Based Genomic Screening – Are We Ready?

Learning Objectives

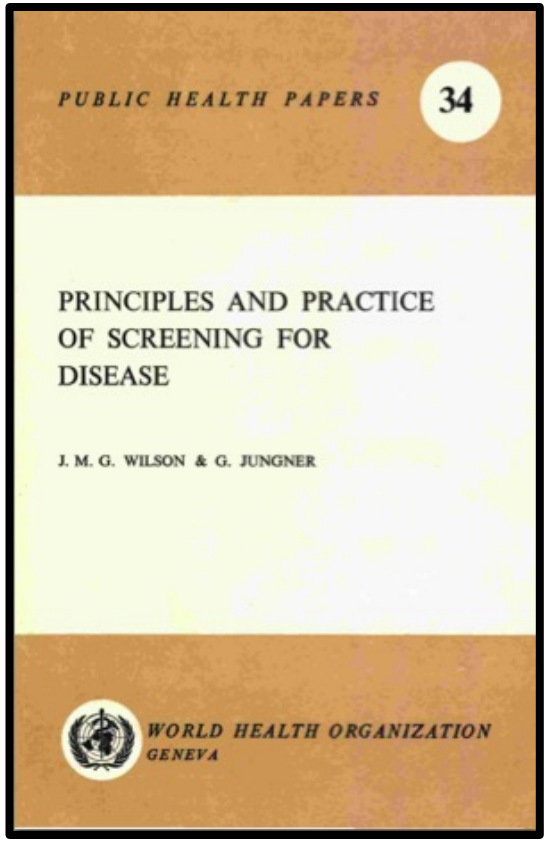
1. Review key concepts underlying genomic screening.
2. Describe progress toward building an evidence-base for genomic screening.
3. Examine some obstacles & opportunities that lie ahead for population based genomic screening.

TWO QUESTIONS TO PONDER

1. **Why do >80% of individuals with *BRCA1/2* cancer risk remain unidentified, despite USPSTF recommendations (in 2005, 2014, 2019) that primary care providers screen women in order to identify this cancer risk?**
    - **A. Failure to apply the endorsed "risk identification strategy" *(i.e., medical history based screening)***
    - **B. Lack of sensitivity of the endorsed "risk identification strategy" *(i.e., medical history based screening)***
    - **C. Both (a) and (b)**
    - **D. Neither (a) nor (b)**
    - **E. The condition sought is not an important health problem.**

2. **The aggregate frequency of genetic risk for the "CDC Tier 1 Genomic Health Priority Conditions" (i.e., hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia) is "1 in ___ people in the population":**
    - **A. 1 in 750,000**
    - **B. 1 in 75,000**
    - **C. 1 in 7,500**
    - **D. 1 in 750**
    - **E. 1 in 75**

Programmatic Screening for Disease



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

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.

DNA-based screening and population health: a points to consider statement from the ACMG. Genet Med. 2021 Jun;23(6):989-995.

Population Based Genomic Screening – Are We Ready?

NO

Population Based Genomic Screening – Are We Ready?

NO… but before describing our state of readiness further, I want to paint a picture of where I think we are headed.

Population Based Genomic Screening – Are We Ready?

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”

Murray MF. J Pers Med. 2022 Jan 26;12(2):158

Population Based Genomic Screening – Are We Ready?

What if we use the *historical perspective* of NBS to gauge where we're at?

Newborn Screening Milestones

- 1930s - George Jervis identifies 185 individuals among 15,000 institutionalized individuals whose mental retardation was attributed to Phenylketonuria (PKU).
- 1953 - Horst Bickel demonstrates clinical utility of restricted diet in PKU and suggests that early therapeutic diet could prevent development of the mental retardation. And maximally effective therapy will require PKU diagnosis prior to the onset of symptoms.
- 1958 - Robert Guthrie devises a simple and inexpensive blood test which allows screening for PKU shortly after birth.
- 1960 - Robert Guthrie coordinates a 29-state pilot study of 400,000 newborns to identify those affected with PKU.
- 1963 - The first mandated newborn screening program begins in Massachusetts.
- 1966 - PKU testing becomes mandatory in most states.
- 1968 - New York starts pilot testing for galactosemia and maple syrup urine disease (MSUD) in Albany and Buffalo.
- 1975 - New York begins universal testing for sickle cell disease. Testing also begins for homocystinuria, adenosine deaminase deficiency, histidinemia, MSUD and galactosemia.
- 1990s - Tandem Mass Spec allows for one test to screen for ~ 50 conditions

Then we are currently in or around 1960

In US ~4M newborns/yr
(≥29 conditions)
1 in 15,000 has PKU
1 in 320 screens pos

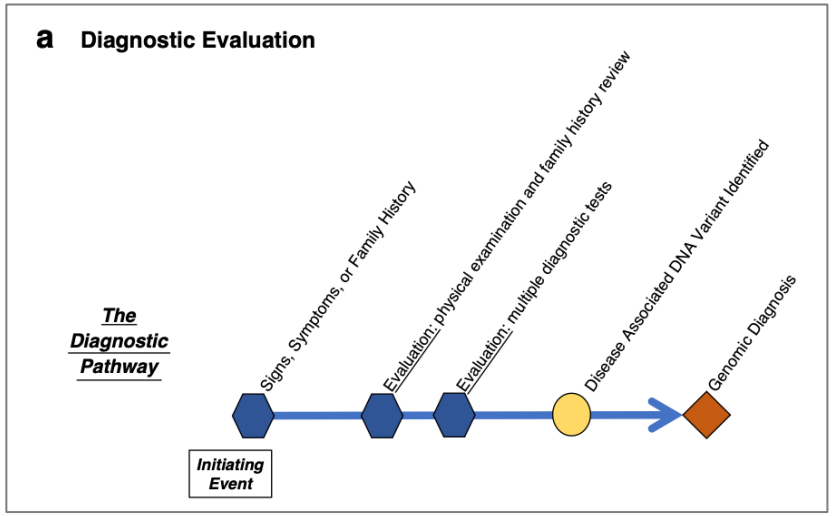
Adapted from Wadsworth Center

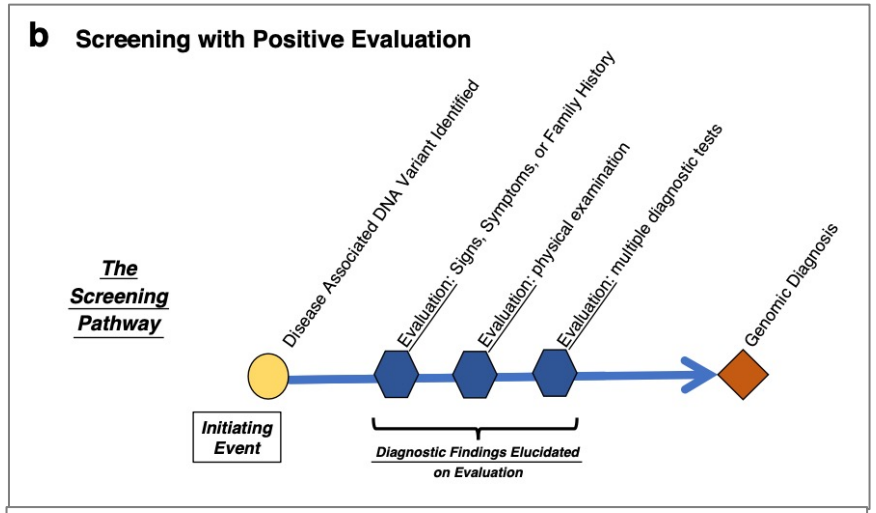
DNA as a screening tool

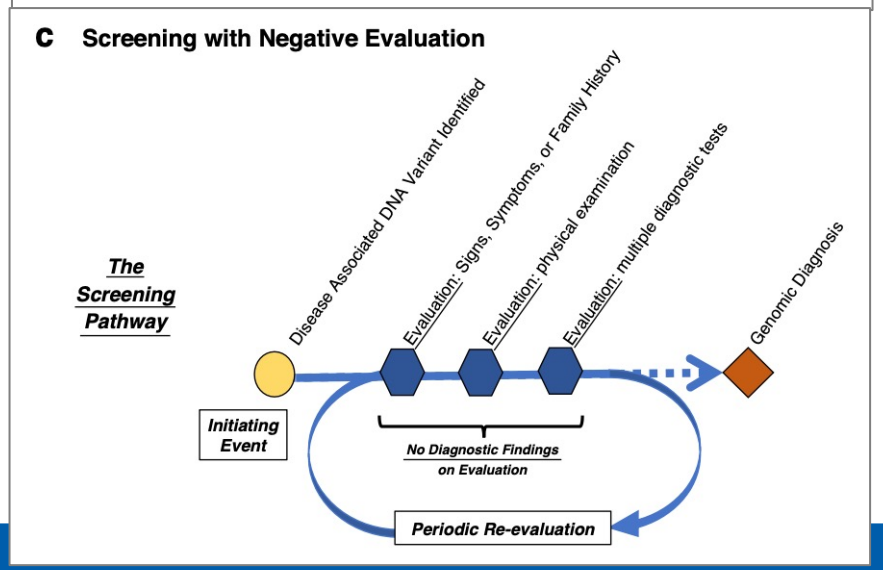
- DNA can be used in many forms and for numerous applications as a screening tool.

- **Note**: This talk will focus mostly on the use of germline DNA in the screening of adults for monogenic disease risk.

Diagnostic genetic test v. Screening genetic test







Genetic Test Result

DNA-based screening and population health: a points to consider statement from the ACMG. Genet Med. 2021 Jun;23(6):989-995.

DNA Variant classification

1. Pathogenic (P)
2. Likely Pathogenic (LP)
3. Variant of Uncertain Significance (VUS)
4. Likely Benign
5. Benign

Richards S, et al; Standards and guidelines for the interpretation of sequence variants. Genet Med. 2015 May;17(5):405-24. PMID: 25741868

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Suitable as Screening Results

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P/LP = Pathogenic and Likely Pathogenic

DNA Variant classification

1. **Pathogenic (P)**
2. **Likely Pathogenic (LP)**

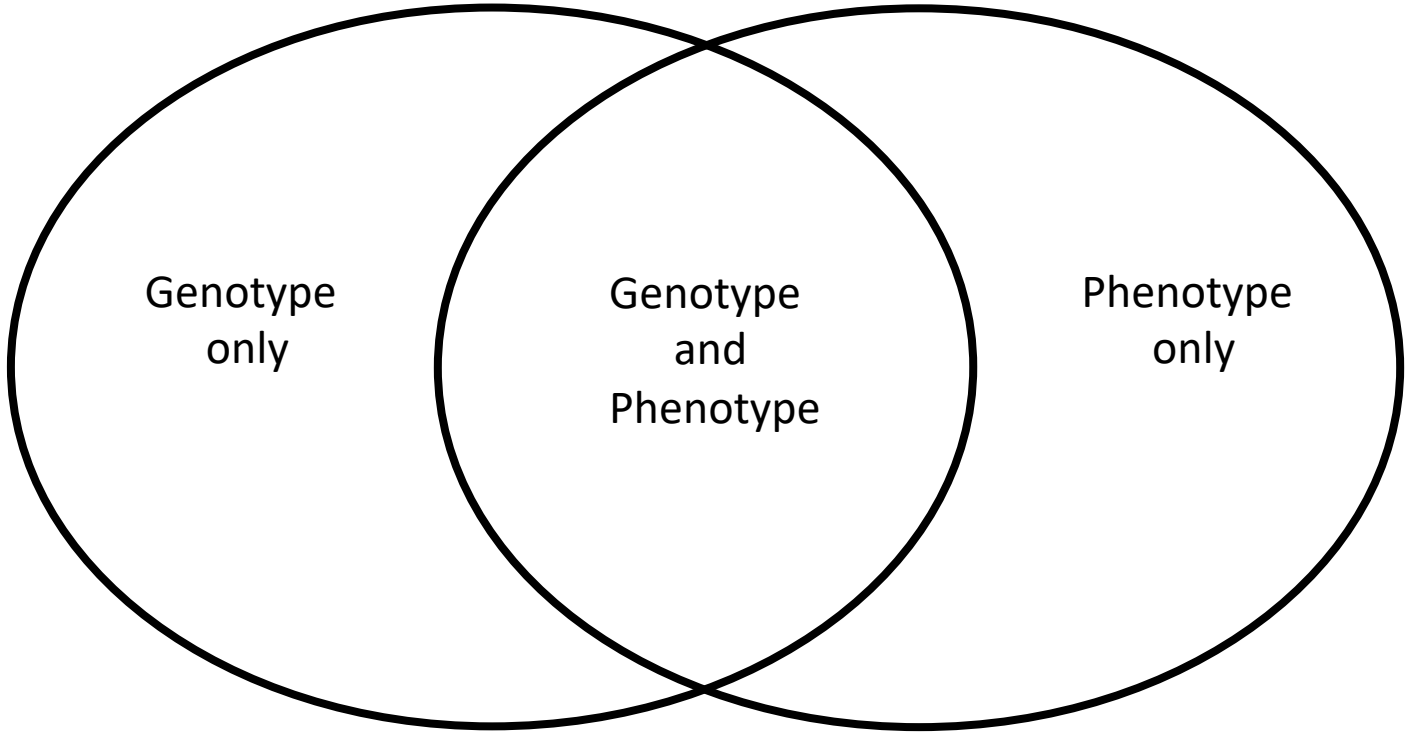
Suitable as Screening Results

~~3. Variant of Uncertain Significance (VUS)~~ **Not Suitable as Screening Results**

4. Likely Benign
5. Benign

P/LP = Pathogenic and Likely Pathogenic

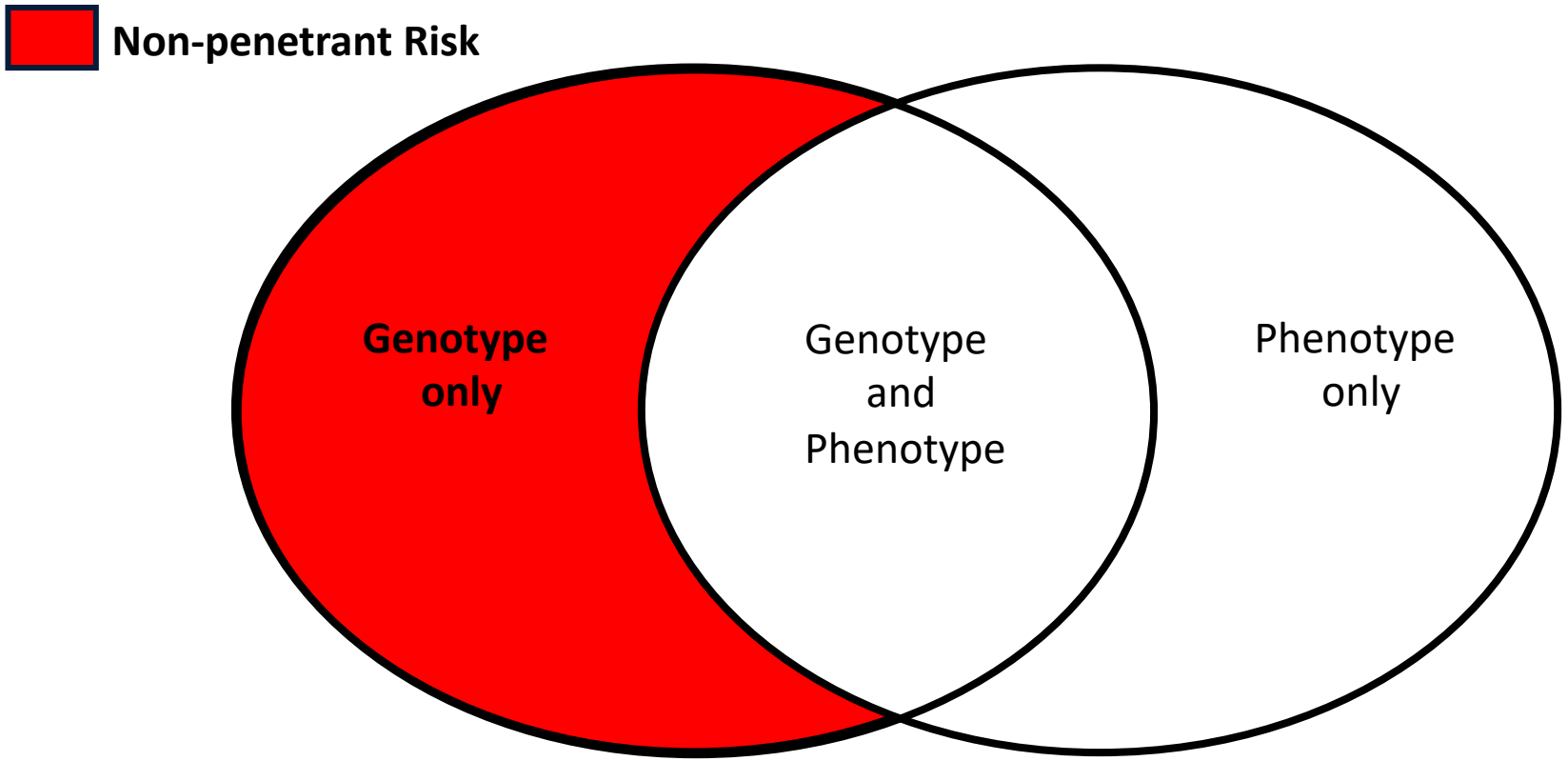
Imperfect Genotype-Phenotype Correlations are the Norm



DEFINITION

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

Imperfect Genotype-Phenotype Correlations are the Norm



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Non-Penetrant Risk Prediction is Not Limited to DNA

Non-Penetrant Risk Prediction is Not Limited to DNA

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

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

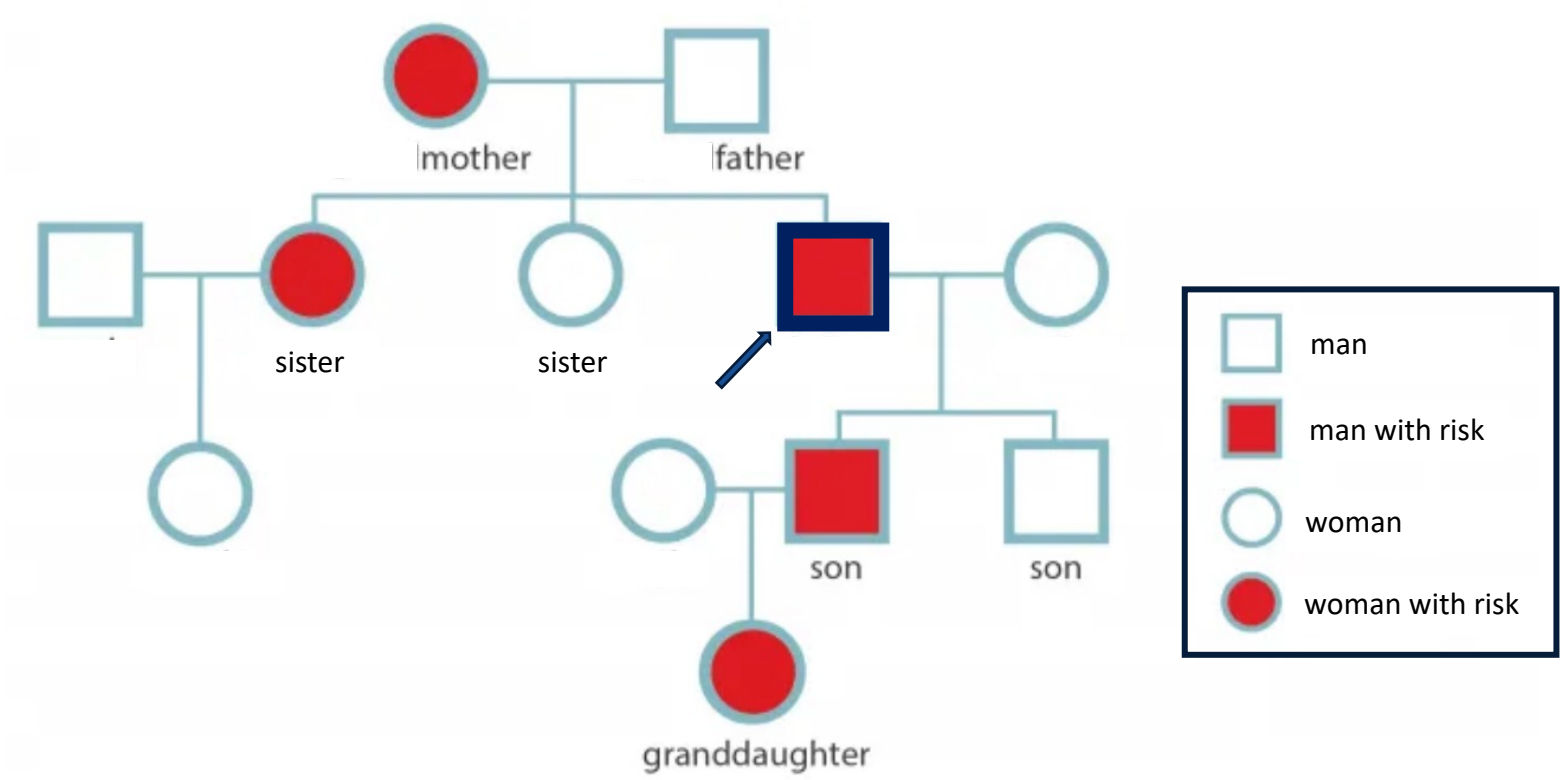
Cascade Testing following Genomic Screening

Cascade testing is an important case identification multiplier that needs to be optimized

When autosomal dominant monogenic risk is identified through screening, then that individual's

- Parents
- Siblings
- Children

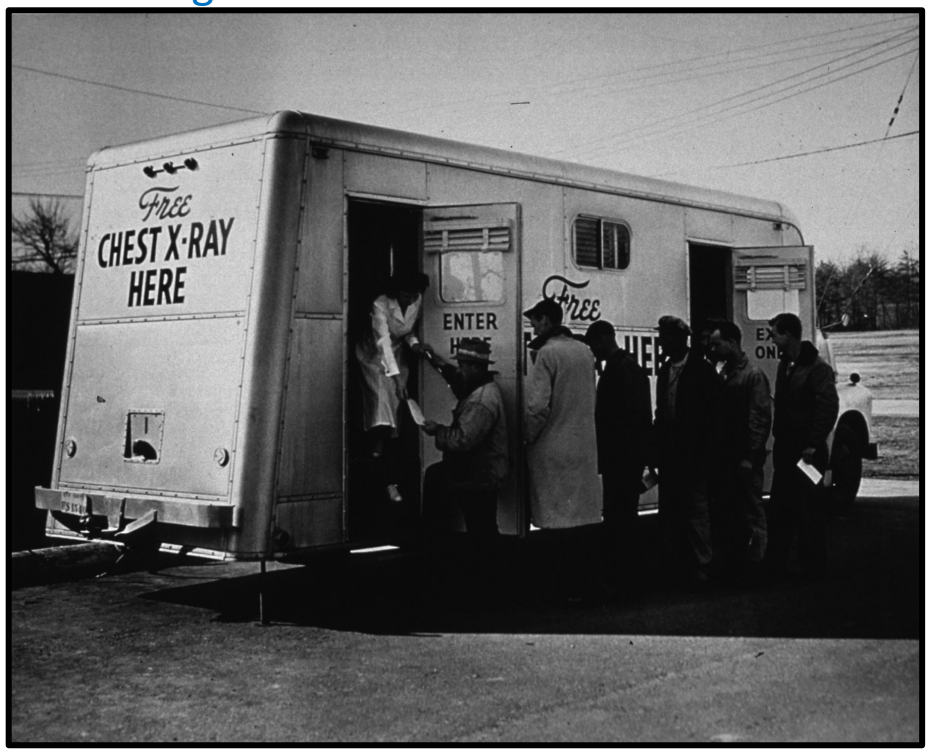
each have a 50% chance of the same genetic risk



https://familyheart.org/family-screening-for-fh-and-the-use-of-genetic-testing

Screening for Disease v. Screening for Disease Risk

Detecting Disease → Treatment



California 1950s - Public Health Service mobile chest radiography

Detecting Disease Risk → Prevention/Early Diagnosis

DNA

Blood Pressure

Cholesterol

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

Genomic Screening – Terminology

Genomic screening results that drive medical care can be divided into:

SECONDARY FINDINGS & PRIMARY FINDINGS

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

Genomic Screening – Terminology

MEDICAL ACTIONABILITY & CLINICAL UTILITY

- **Medical Actionability** – the availability of clinical actions that are evidence-based that should occur as follow-up to a genomic screening result.
- **Clinical Utility** - the likelihood that a test will, by prompting an intervention, result in an improved health outcome.

To paraphrase Grosse and Khoury

A screening test alone does not have inherent utility; the clinical utility of the screening test depends on effective access to appropriate interventions.

Genomic Screening – Terminology

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> ***"there is no health benefit to learning about a mutation if a carrier doesn't do anything"***
>
> **Glenn Palomaki 2017**

Some historical perspective, specific to Genomic Screening

New York Times (April 1st 1996)

The New York Times

"All the News That's Fit to Print"

Late Edition

VOL. CXLV ... No. 50,384 NEW YORK, MONDAY, APRIL 1, 1996 60 CENTS

DELAYS BY I.M.O. LEAVING PATIENTS HAUNTED BY BILLS

MANAGED-CARE QUAGMIRE

H.I.P., Biggest NewYork Plan, Has Scene Members Facing Lawsuits From Doctors

The Speaker's Gruff No. 2 Takes Charge in the House

FACING ELECTION, YELTSIN IS HALTING WAR ON CHECHENS

OFFERS MORE AUTONOMY

He Also Approves Talks With Rebel Chief in Pushing for Peace Before June Vote

Breaking Ranks, Lab Offers Test To Assess Risk of Breast Cancer

An Accountability Issue

As States Gain Political Power, a Ruling Seems to Free Them of Some Legal Reins

Leadership Debate At Investors' Group

As China Undercuts Democracy, Hong Kong Scuffles for Passports

Program Creates Community for Foster Care

INSIDE

“Breaking Ranks, Lab Offers Test to Assess Risk of Breast Cancer”

New York Times (April 1st 1996)

“That decision…to offer the test…has outraged some leading geneticists, raising the question of <u>how, and by whom, the dissemination of new genetic tests should be controlled</u>.” *Gina Kolata NYT 04-01-96*

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"Breaking Ranks, Lab Offers Test to Assess Risk of Breast Cancer"

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OUTRAGED GENETICISTS !

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Article Raises Questions

- Is there clinical utility?
- Do benefits outweigh harms?

Note that the test was

- Expensive
- Difficult to interpret
- Limited pool of experts

“Breaking Ranks, Lab Offers Test to Assess Risk of Breast Cancer”

New York Times (April 1st 1996)

- 1994 - The role of *BRCA1* in risk for breast cancer identified
- 1995 - The role of *BRCA2* in risk for breast cancer identified
- 1996 - First clinical testing for *BRCA1* offered (reported in NYT)

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- Late 1990s - Rational barriers to implementation were set in place.
  - Including testing only those with “high pre-test probability”
- In the 27 years since 1996:
  - Clinical utility proven & Benefit:Risk ratio understood.
  - Cost has decreased & Interpretability increasing daily.
  - However, implementation barriers created in the 1990s persist and they are applied for both diagnostic use and screening use

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Consider this with regard to diagnostic approach to *BRCA* testing

~ 13% of women with both

breast cancer and an underlying P/LP *BRCA* variant

don't meet clinical criteria for *BRCA* testing.

Yadav S, et al. J Clin Oncol. 2020 May 1;38(13):1409-1418

Consider this with regard to diagnostic approach to *BRCA* testing

~ 13% of women with both

breast cancer and an underlying P/LP *BRCA* variant

don't meet clinical criteria for *BRCA* testing.

This despite the fact that

***"BRCA* positive Breast Cancer" has**
distinct surgical options and therapeutic options with proven clinical utility
compared to clinical management options for *"BRCA* negative breast cancer"

Consider this with regard to screening approach to *BRCA* testing

Annals of Internal Medicine | CLINICAL GUIDELINES

Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility, along with the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is included in the evidence synthesis available through the USPSTF Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse (www.guideline.gov).

USPSTF
2005
2014
2019

Annals of Internal Medicine | CLI

Risk Assessment, Genetic Counseling, and Genetic
BRCA-Related Cancer in Women: U.S. Preventive S
Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2005 U.S. Preventive Services Task Force (USPSTF) recommendation on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility.

Methods: The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful BRCA mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in the family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening, medications, and risk-reducing surgery.

Population: This recommendation applies to asymptomatic women who have not been diagnosed with BRCA-related cancer.

Recommendation: The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritone
designed to identify a fam
increased risk for potent
susceptibility genes (*BRC*
screening results should r
after counseling, BRCA te
The USPSTF recommer
BRCA testing for wome
with an increased risk f
BRCA1 or *BRCA2* genes.

Ann Intern Med. 2014;160:271
For author affiliation, see end
* For a list of the members o
www.annals.org).
This article was published onli
2013.

Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Potentially harmful mutations of the breast cancer susceptibility 1 and 2 genes (*BRCA1/2*) are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer. For women in the United States, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death. In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.

OBJECTIVE To update the 2013 US Preventive Services Task Force (USPSTF) recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.

EVIDENCE REVIEW The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1/2* mutations in asymptomatic women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous diagnosis of breast, ovarian, tubal, or peritoneal cancer who have completed treatment and are considered cancer free. In addition, the USPSTF reviewed interventions to reduce the risk for breast, ovarian, tubal, or peritoneal cancer in women with potentially harmful *BRCA1/2* mutations, including intensive cancer screening, medications, and risk-reducing surgery.

FINDINGS For women whose family or personal history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, or who have an ancestry associated with *BRCA1/2* gene mutations, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate. For women whose personal or family history or ancestry is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are small to none. Regardless of family or personal history, the USPSTF found adequate evidence that the overall harms of risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

CONCLUSIONS AND RECOMMENDATION 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 *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 recommendation) 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 recommendation)

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Author Audio Interview
Related article page 666 and JAMA Patient Page page 702
CME Quiz at jamanetwork.com/learning
Related articles at jamaoncology.com jamasurgery.com jamanetworkopen.com

Corresponding Author: Douglas K. Owens, MD, MS, Stanford University, 616 Serra St, Encina Hall, Room C336, Stanford, CA 94305-6019 (chair@uspstf.net).

JAMA. 2019;322(7):652-665. doi:10.1001/jama.2019.10987
Last corrected on November 12, 2019.

CDC

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Consider this with regard to screening approach to *BRCA* testing

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

Divides all women into two groups

18 years later: how's this working out?

JAMA Network Open™

Original Investigation | Genetics and Genomics

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

Genomic Screening was carried out in 50,726 adults and 267 were found to have a pathogenic or likely pathogenic (P/LP) *BRCA1* or *BRCA2* variant

1:190

Manickam K et al. *JAMA Network Open* 2018

JAMA Network | Open

Original Investigation | Genetics and Genomics

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

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

> 8 of 10 Adults

Manickam K et al. *JAMA Network Open* 2018

JAMA Network | Open

Original Investigation | Genetics and Genomics

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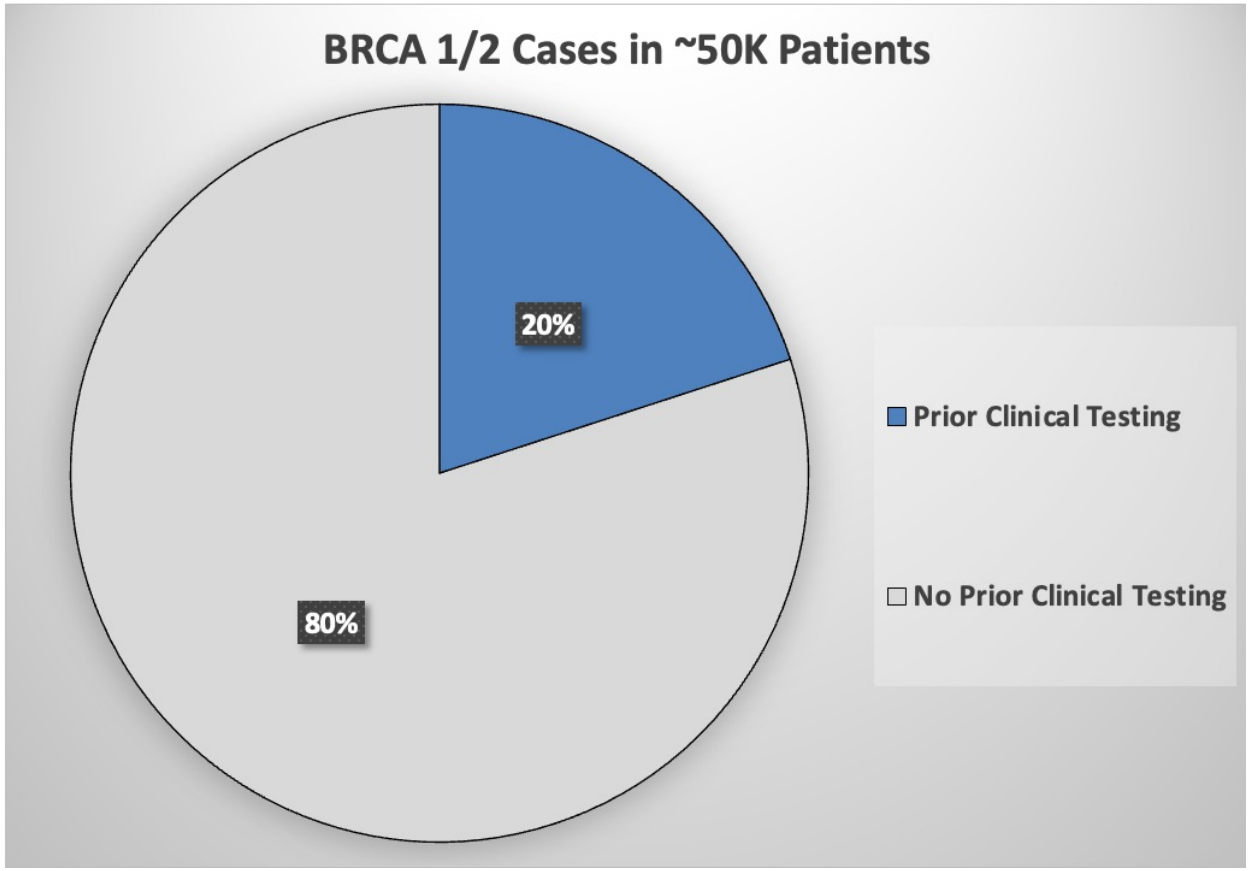

JAMA Network | Open

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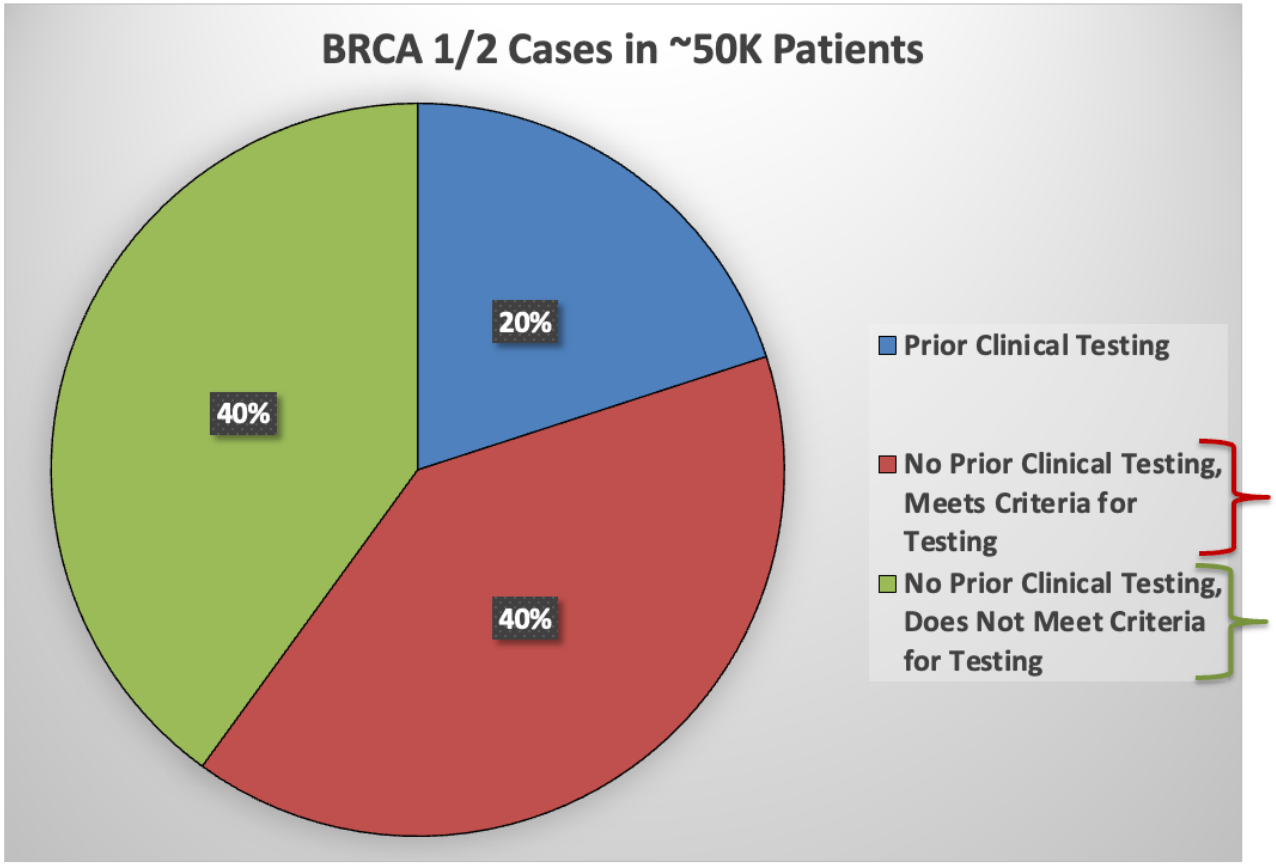

Healthy Nevada Project (HNP)

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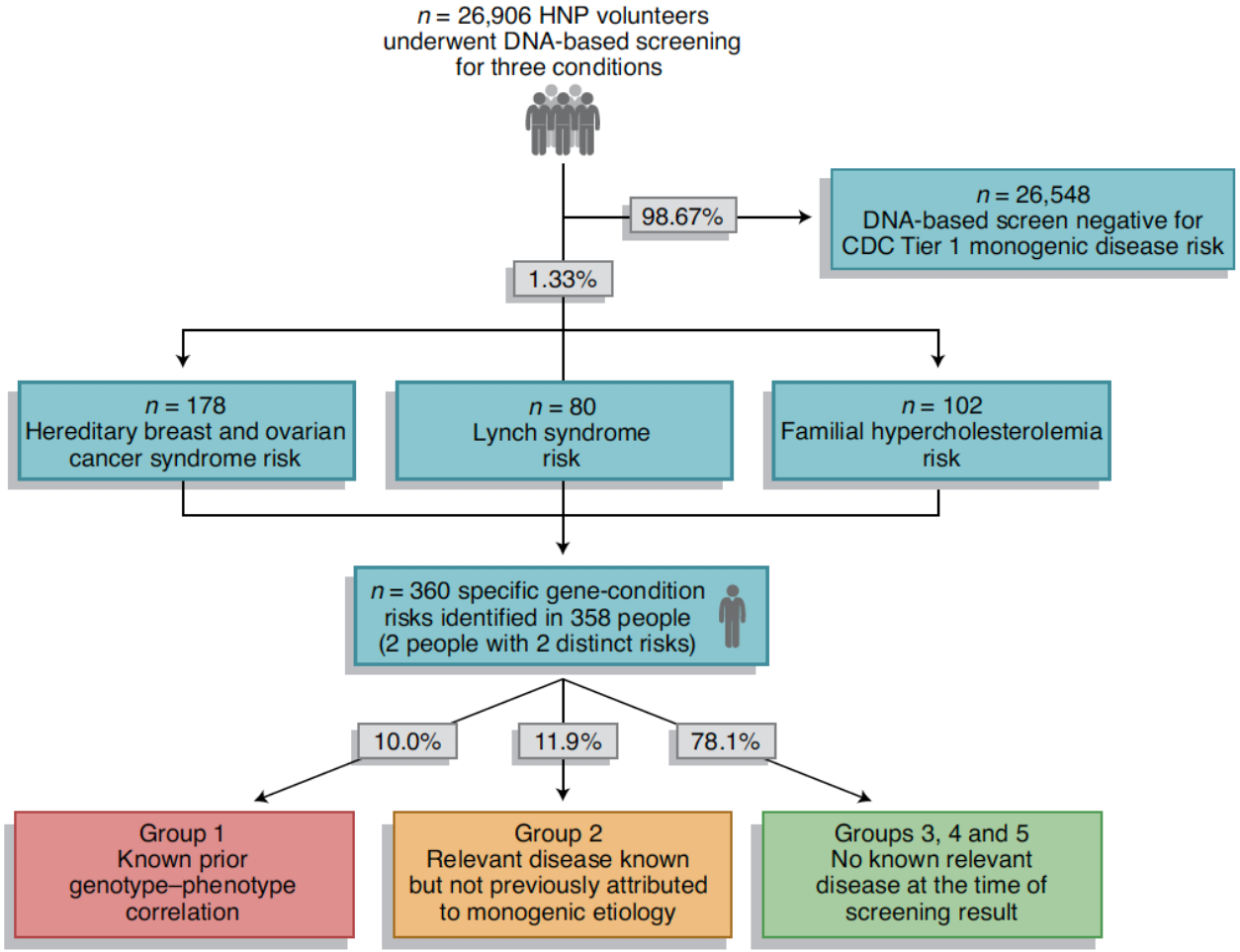


1 in 75

Nat Med. 2020 Aug

In 2023: Screening 9 Genes for Three Genetic Syndromes

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)

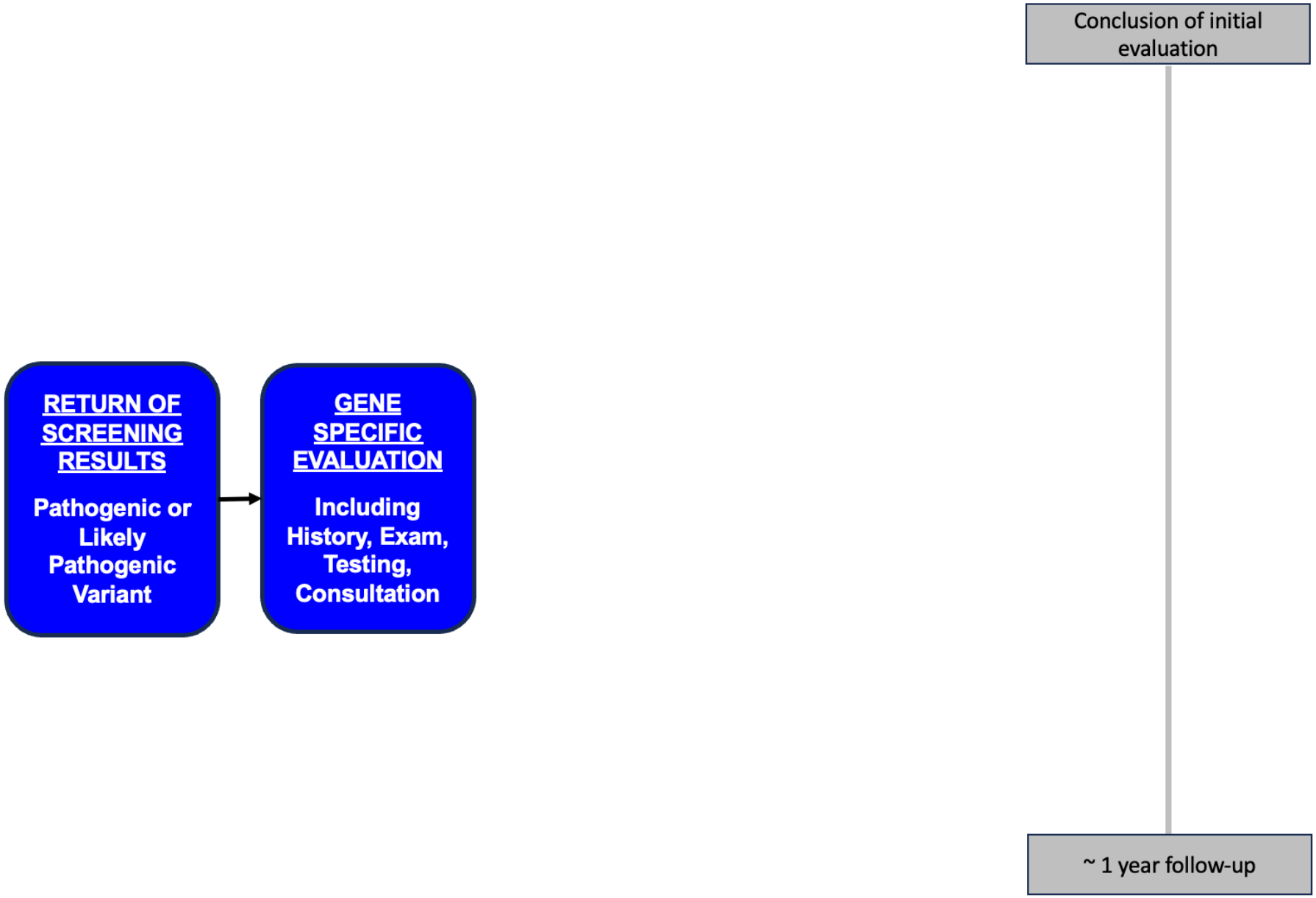
would identify risk in ~4.3M people in the United States

1 in 75

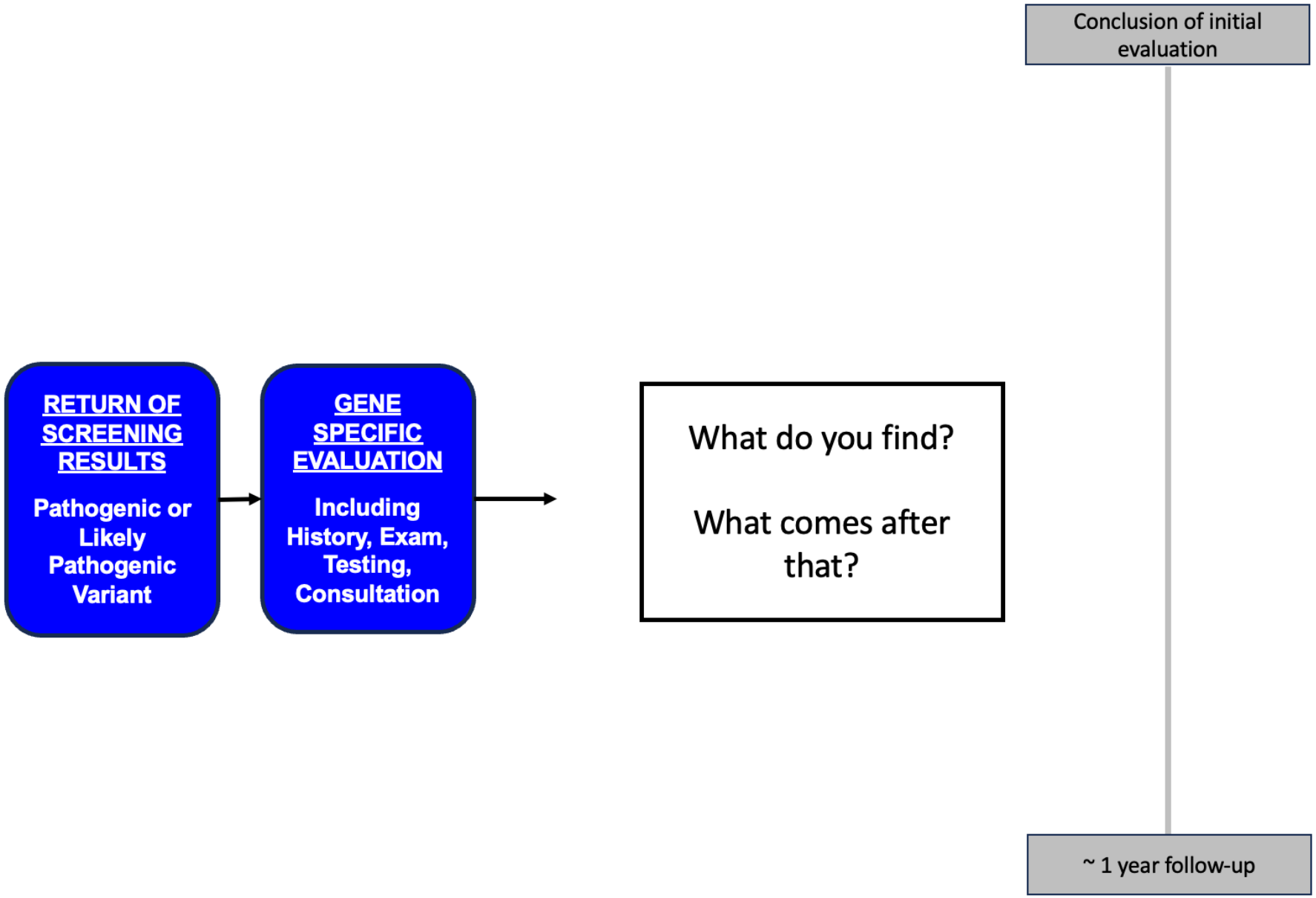
A screening strategy that includes this list is the likely starting point for population screens.

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

FIVE DIAGNOSTIC GROUPS
FOLLOWING GENOMIC SCREENING AND CLINICAL FOLLOW-UP



FIVE DIAGNOSTIC GROUPS
FOLLOWING GENOMIC SCREENING AND CLINICAL FOLLOW-UP



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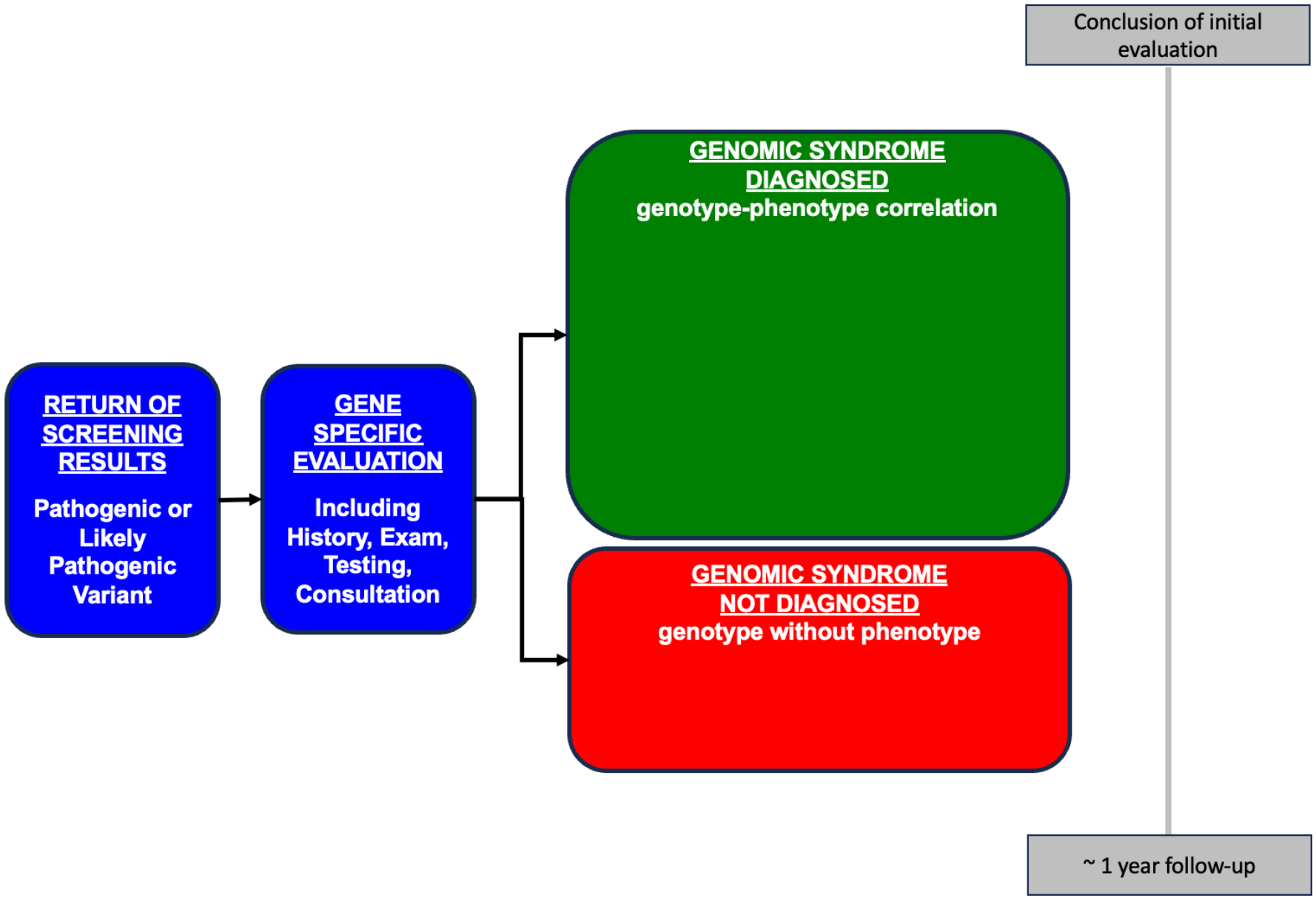

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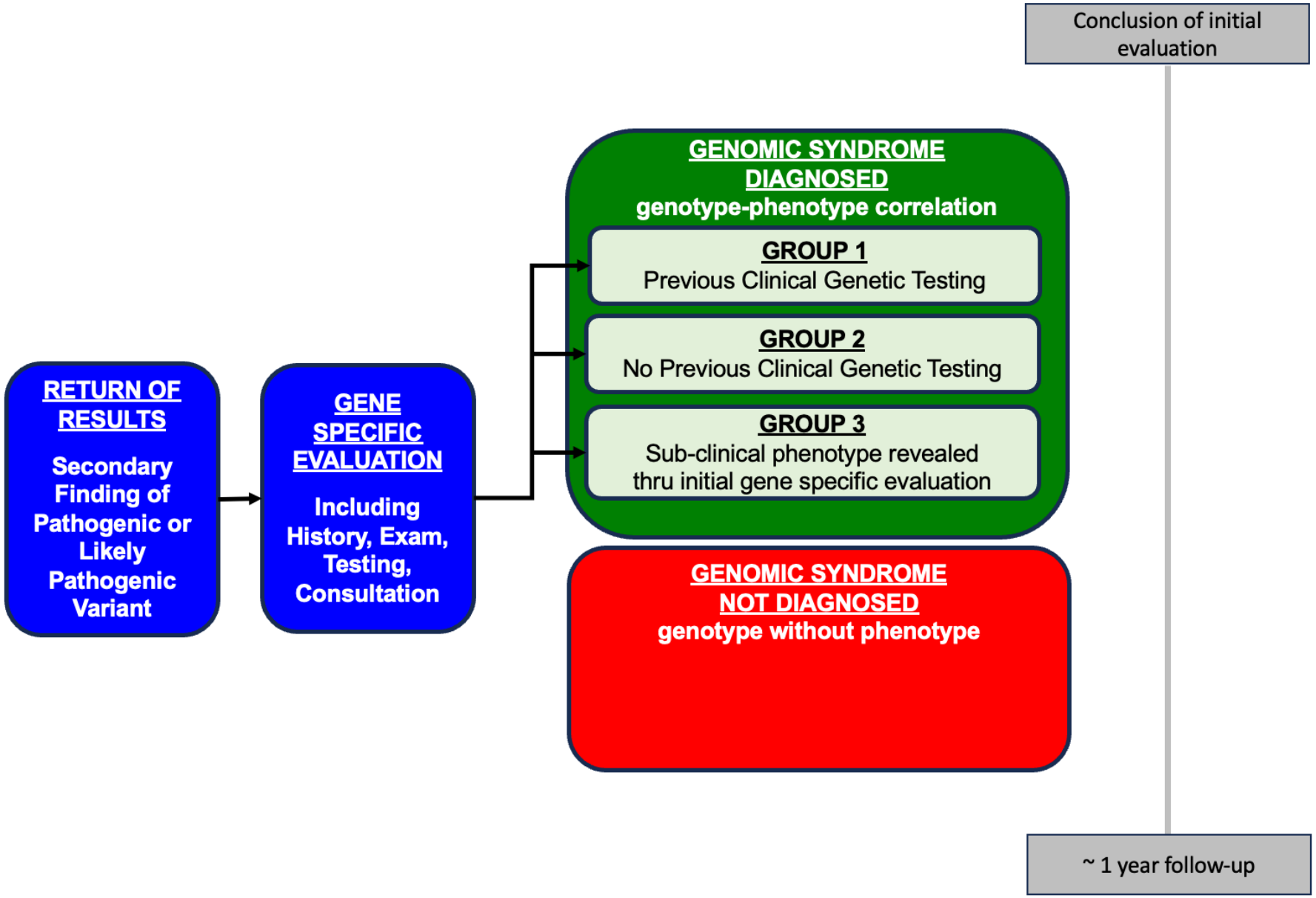

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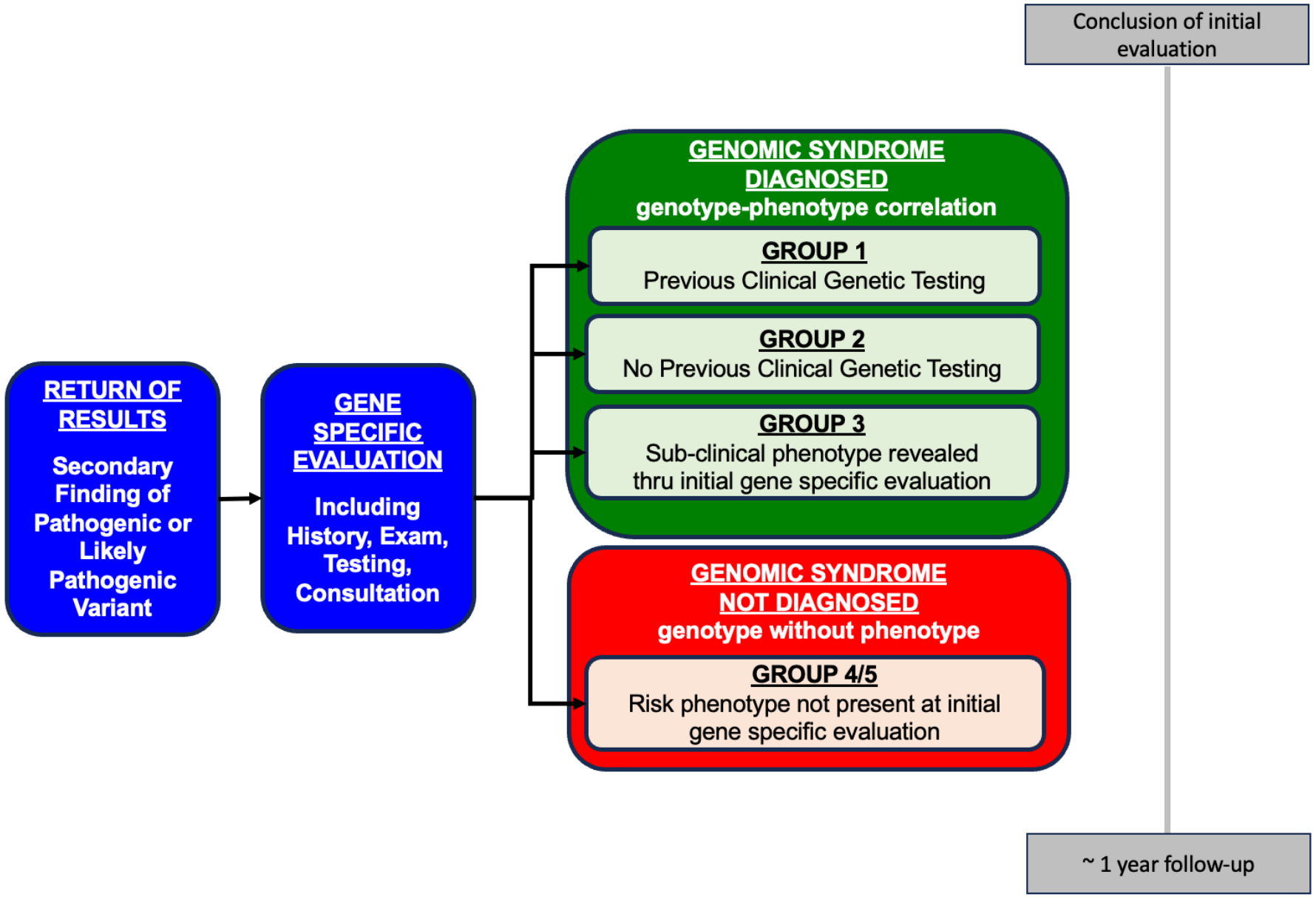

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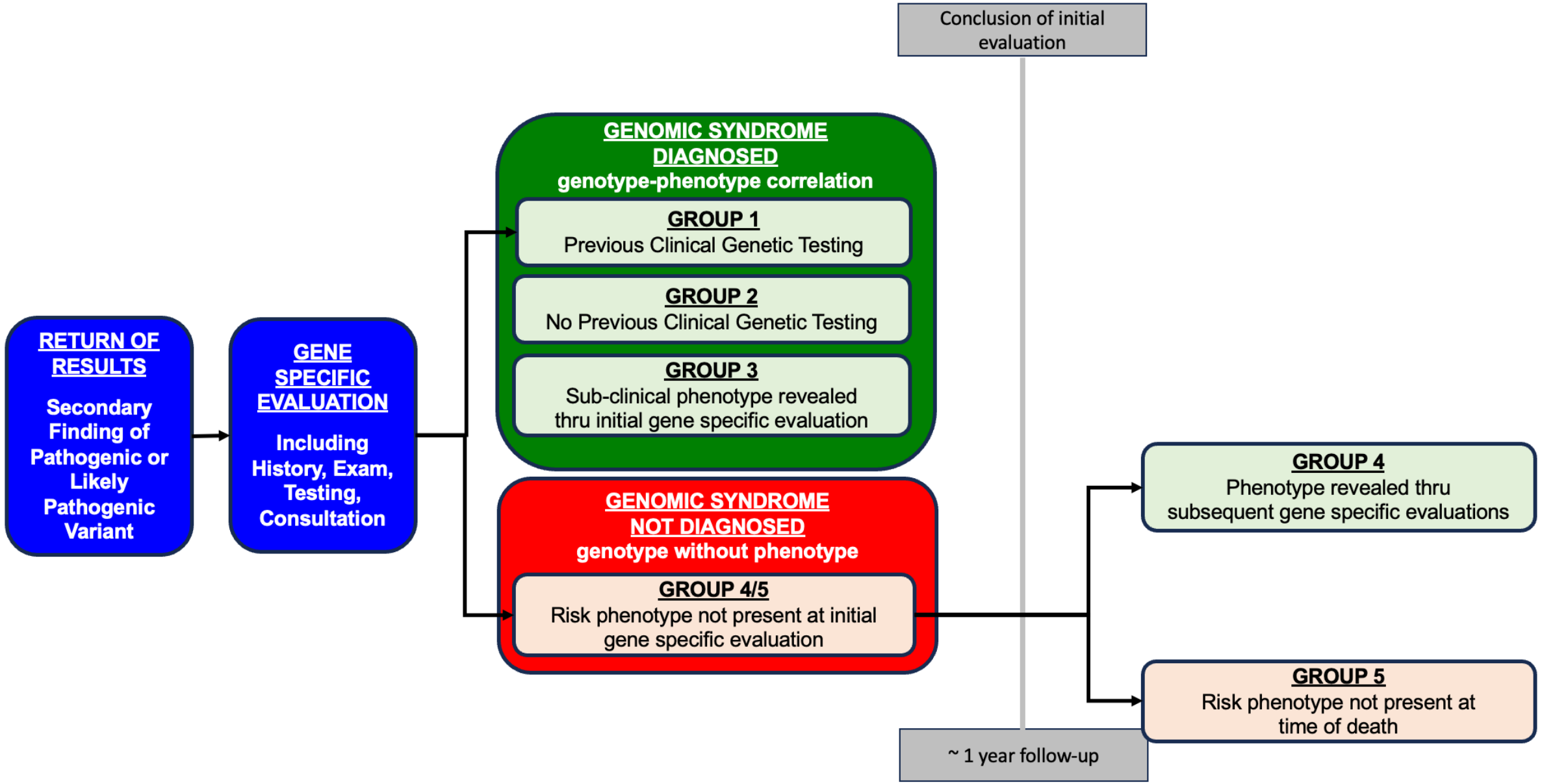
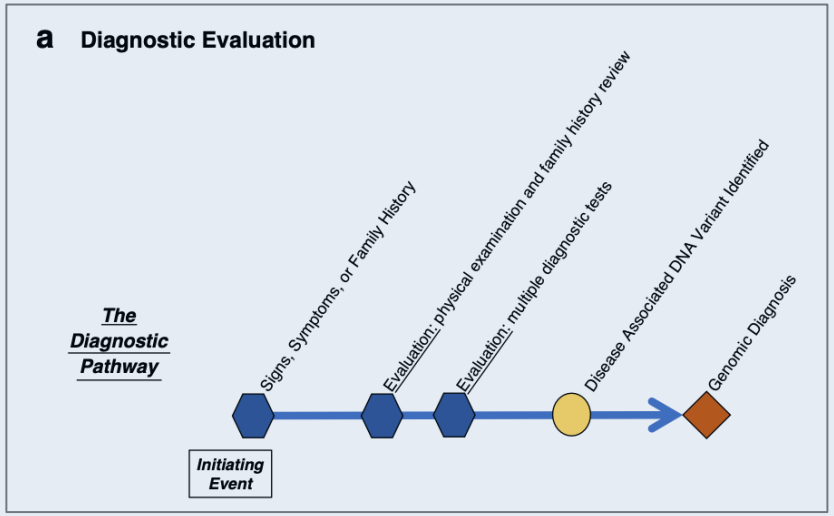
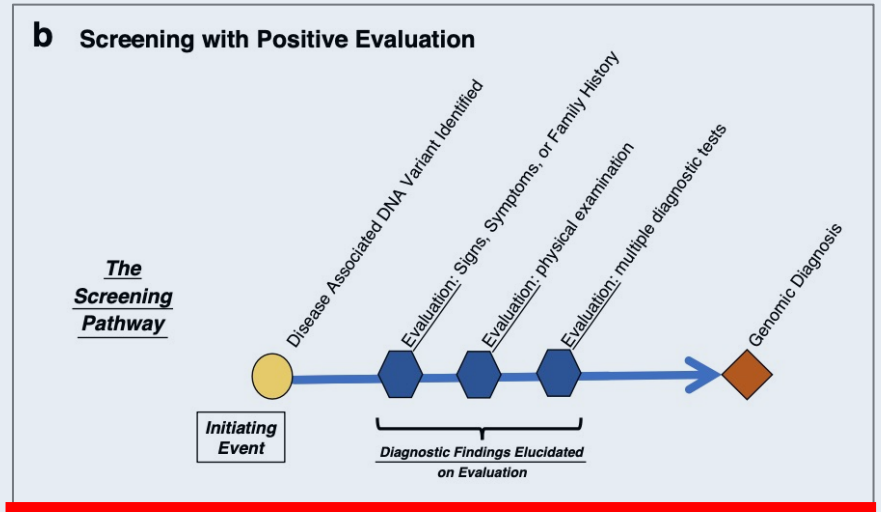
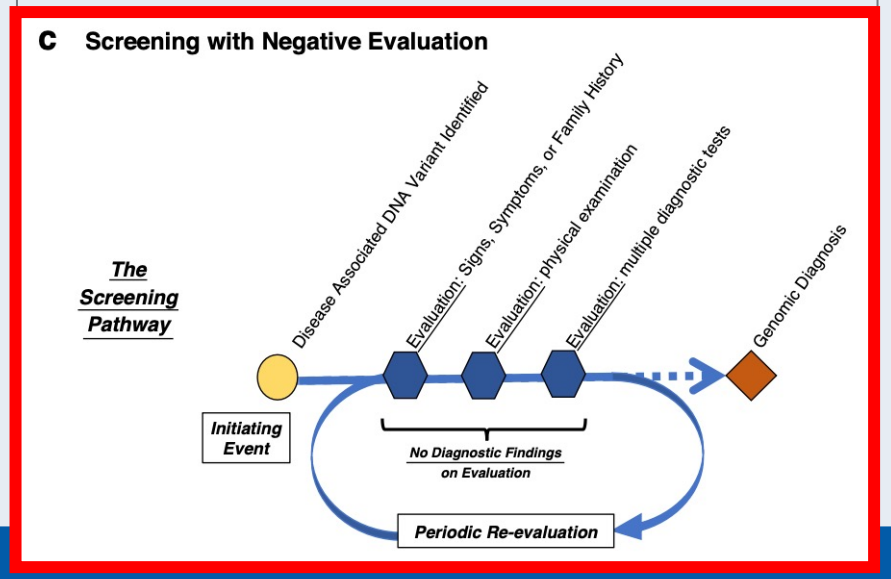


Diagnostic genetic test v. Screening genetic test







DNA-based screening and population health: a points to consider statement from the ACMG. Genet Med. 2021 Jun;23(6):989-995.

CDC

Oak Ridge Institute For Science and Education

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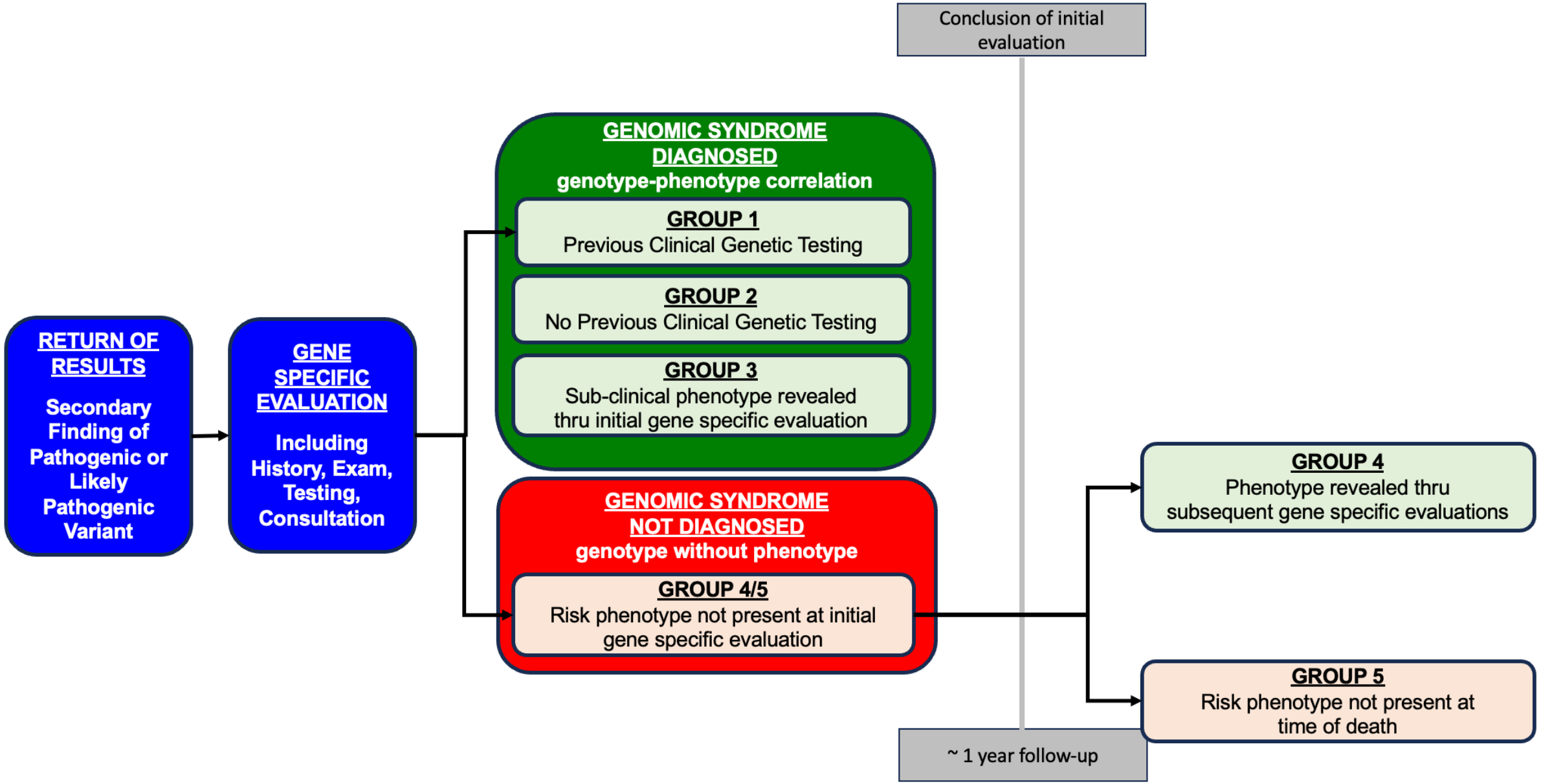

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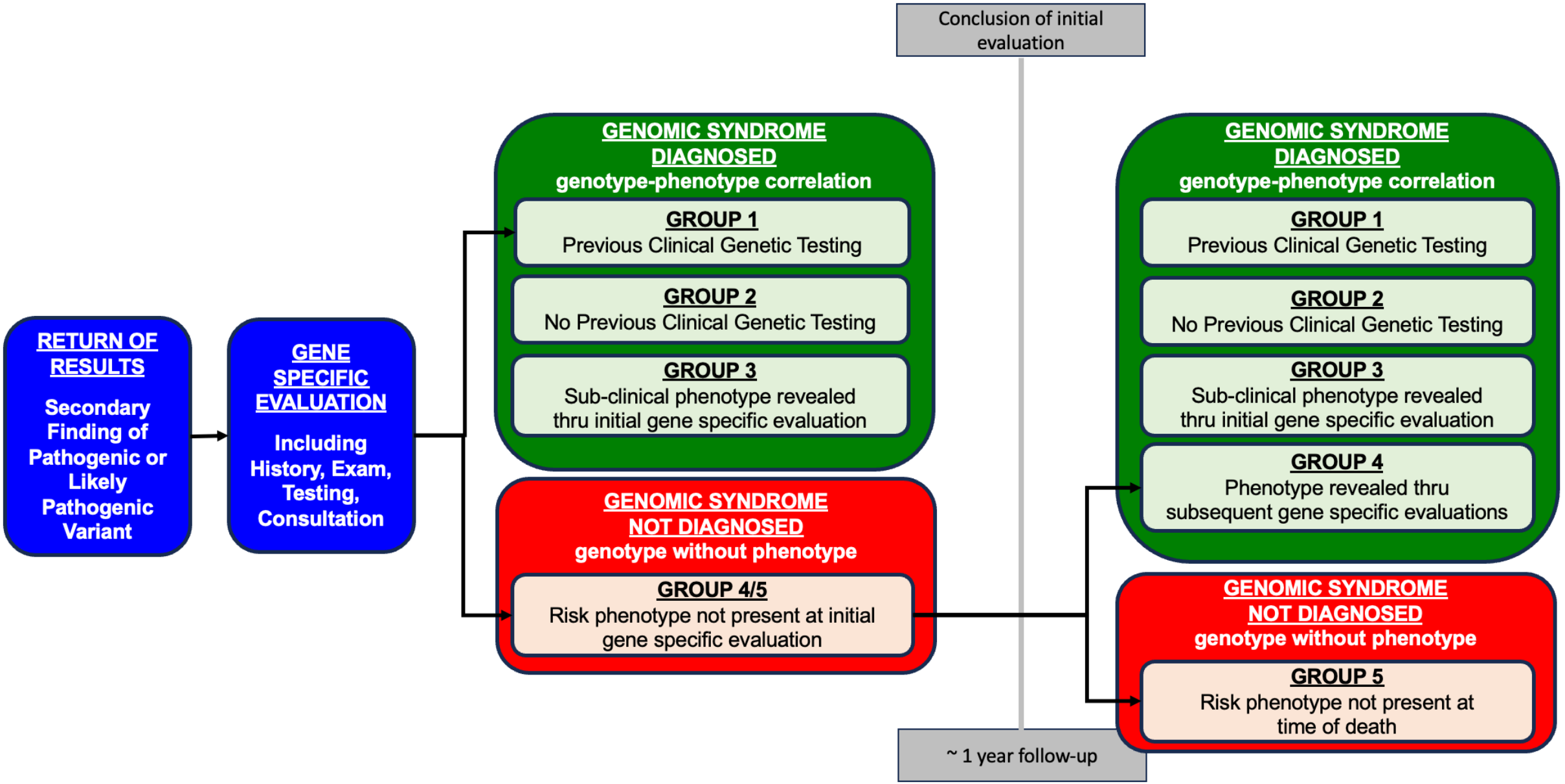

Population Based Genomic Screening – Are We Ready?

Key Genomic Screening Concepts covered:

1. Diagnostic genetic/genomic tests differ from screening genetic/genomic tests.
2. In general, health screening can reveal either disease or disease risk
3. “Incomplete genotype-phenotype correlations” and “non-penetrant risk” are the norm.
4. Cascade testing can act as a multiplier of health screening benefit.
5. Currently, pilot screening programs reveal 5 “diagnostic groups” within those with risk.
6. A screening test by itself has no clinical utility.
7. Using genomic screening to identify “monogenic disease risk” ascertains more “at risk individuals” than those who are identified as “positive for risk” through other means. More study needed to understand outcomes for genomic screen positive groups.

TWO QUESTIONS TO ANSWER

1. **Why do >80% of individuals with *BRCA1/2* cancer risk remain unidentified, despite USPSTF recommendations (in 2005, 2014, 2019) that primary care providers screen women in order to identify this cancer risk?**
    - **A. Failure to apply the endorsed "risk identification strategy" *(i.e., medical history based screening)***
    - **B. Lack of sensitivity of the endorsed "risk identification strategy" *(i.e., medical history based screening)***
    - **C. Both (a) and (b)**
    - **D. Neither (a) nor (b)**
    - **E. The condition sought is not an important health problem.**

2. **The aggregate frequency of genetic risk for the "CDC Tier 1 Genomic Health Priority Conditions" (i.e., hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia) is "1 in ___ people in the population":**
    - **A. 1 in 750,000**
    - **B. 1 in 75,000**
    - **C. 1 in 7,500**
    - **D. 1 in 750**
    - **E. 1 in 75**

Let’s end with a thought experiment

Let's end with a thought experiment about screening and data-sets in the 21st Century …

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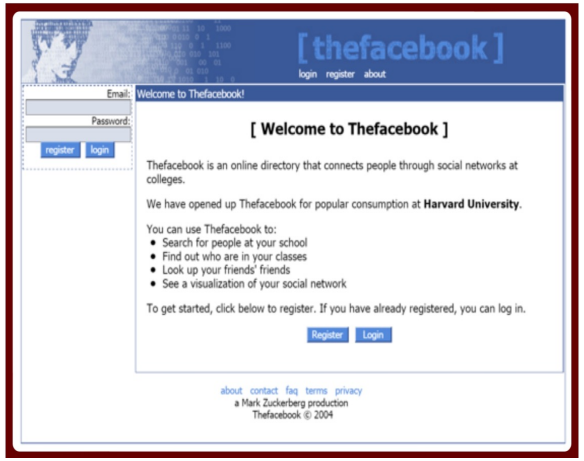
70 years ago



20 years ago

12 years ago

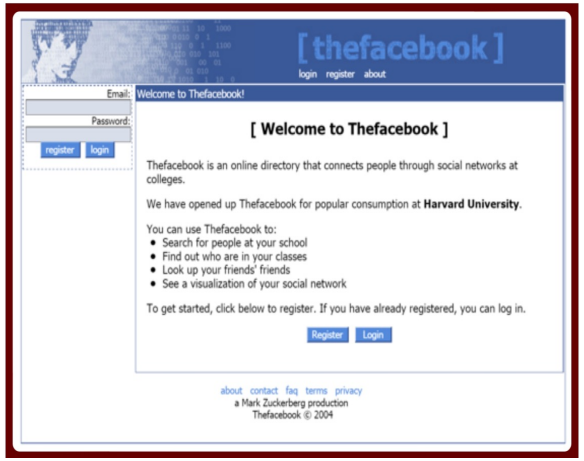
Prediction

There will be unexpected and/or currently unpredicted ways to use population-wide deep genomic data sets

? years from now

Let's end with a thought experiment about screening and data-sets in the 21st Century … and a caution related to the question "are we ready?":

70 years ago



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Prediction
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All of our work regarding Genomic Screening and Precision Public Health could be undermined in the years ahead unless there are preemptive actions to get rules in place that will be needed for things like data control & data uses.

Thank you!

Questions/Comments

Mike Murray (michael.murray@mssm.edu)