National Comprehensive Cancer Network®

NCCN 2026 Breast Cancer Congress with Updates from the 2025 San Antonio Breast Cancer Symposium

Breast Cancer Screening and Genetic Testing:
Who Is at High Risk and How Do We Optimize Their Care?

Tuya Pal, MD

Vanderbilt-Ingram Cancer Center

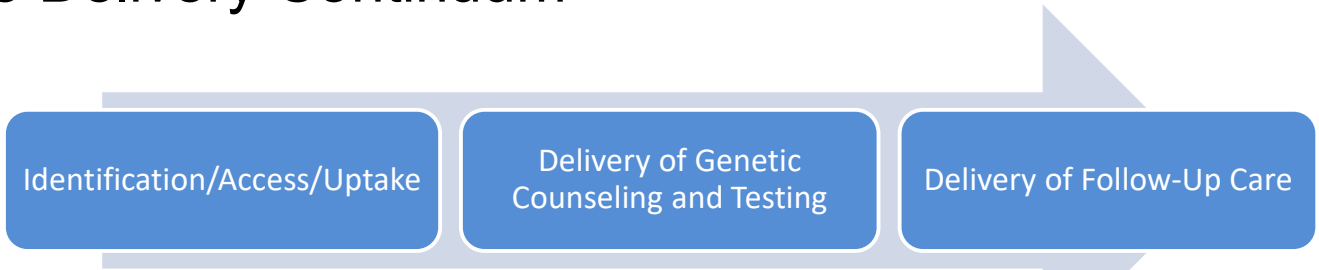
Objectives

- *Identify recent updates and recommendations regarding **eligibility for germline genetic testing** in patients with breast cancer and their close blood relatives.*

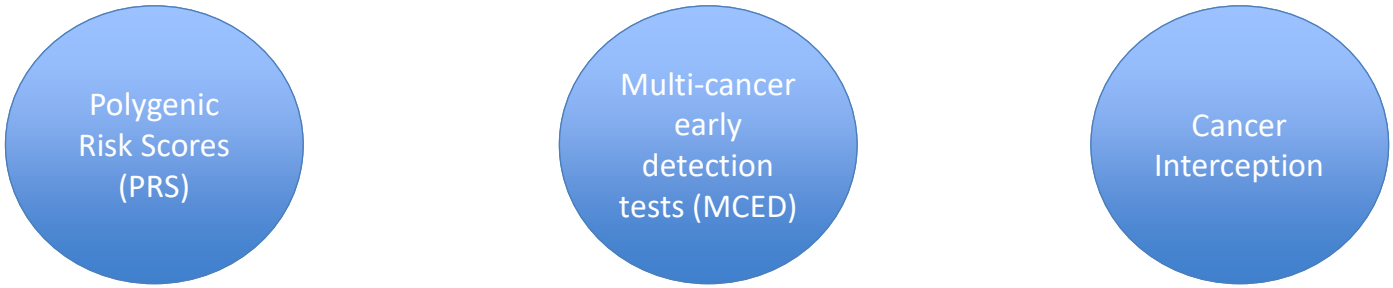
- *Outline breast **cancer risk management** recommendations in carriers of breast cancer susceptibility genes.*

Overview

- Care Delivery Continuum

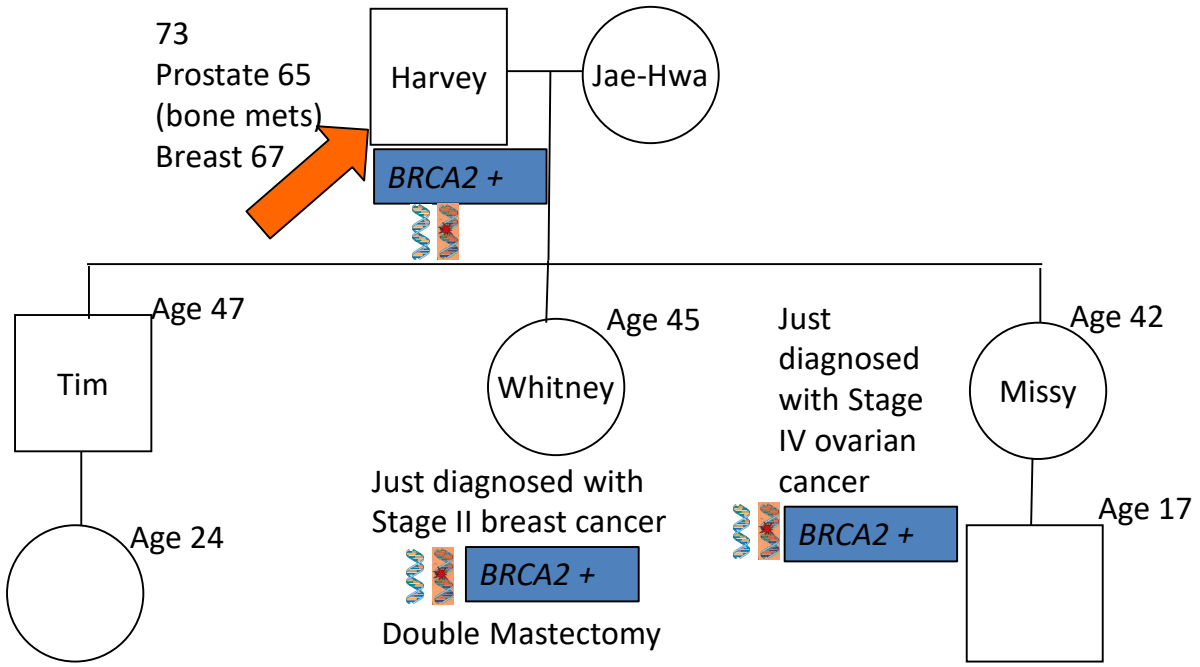


- What's Next?



A real scenario to demonstrate how identification of a *BRCA* mutation may impact a family…

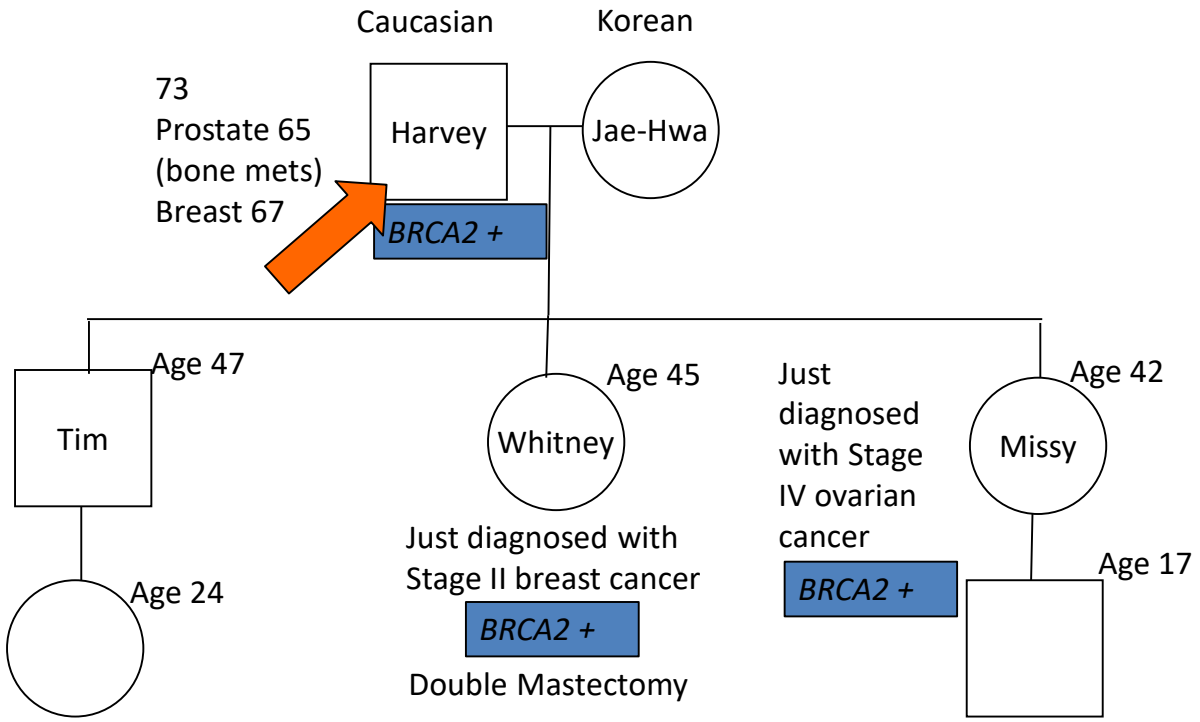
Family 1



If this family had a *BRCA* mutation identified 6 years ago, how could that have changed their lives?

If Harvey had testing 6 years ago…

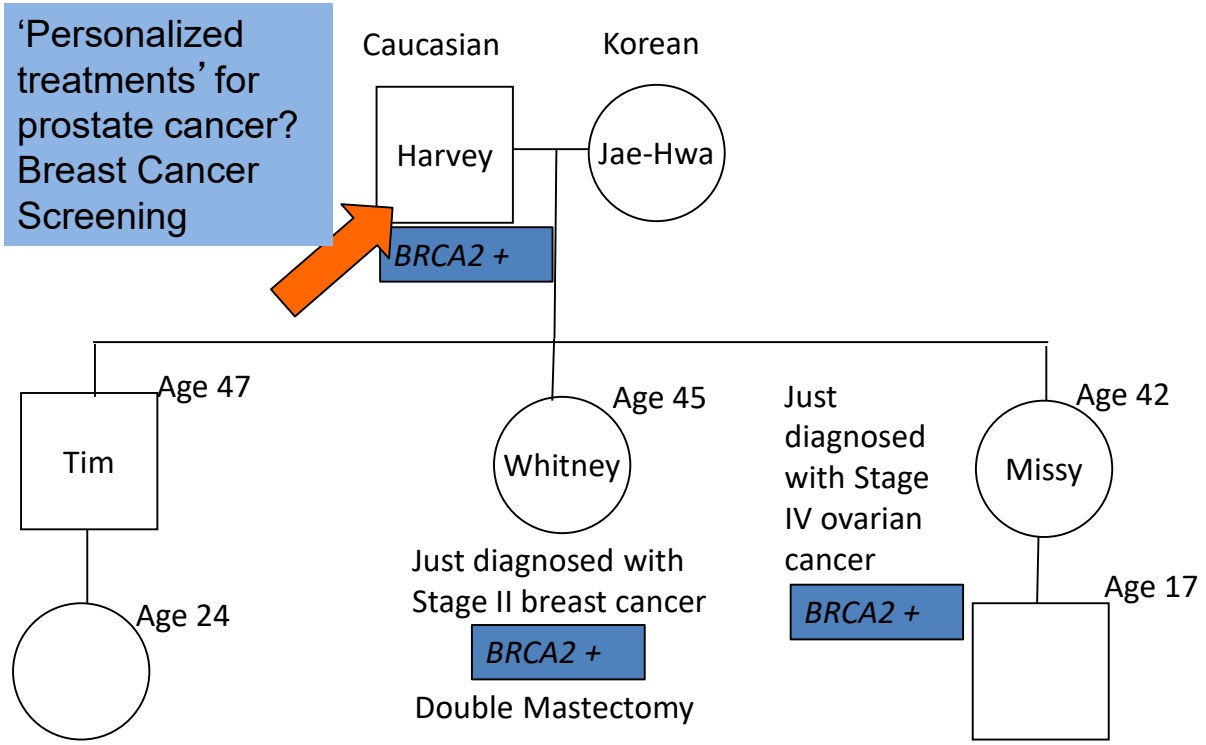
Family 1



If Harvey had testing 6 years ago…

Family 1

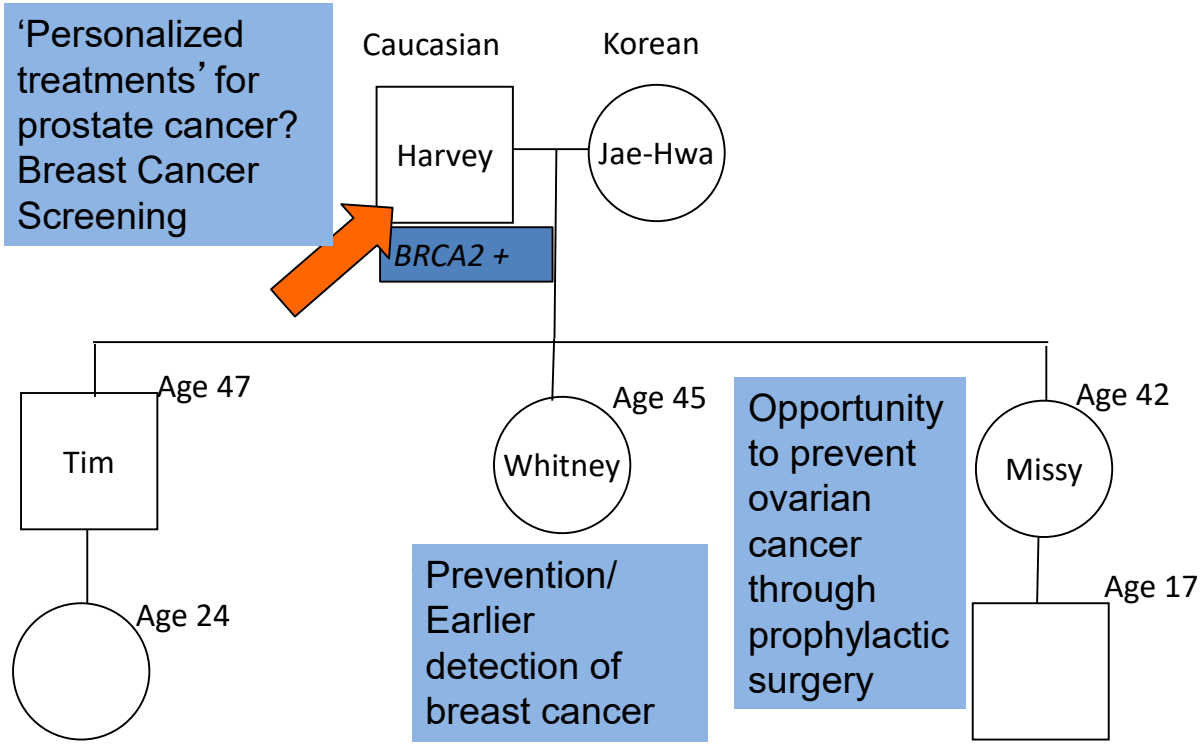
‘Personalized treatments’ for prostate cancer? Breast Cancer Screening



If Harvey had testing 6 years ago…

Family 1

‘Personalized treatments’ for prostate cancer? Breast Cancer Screening

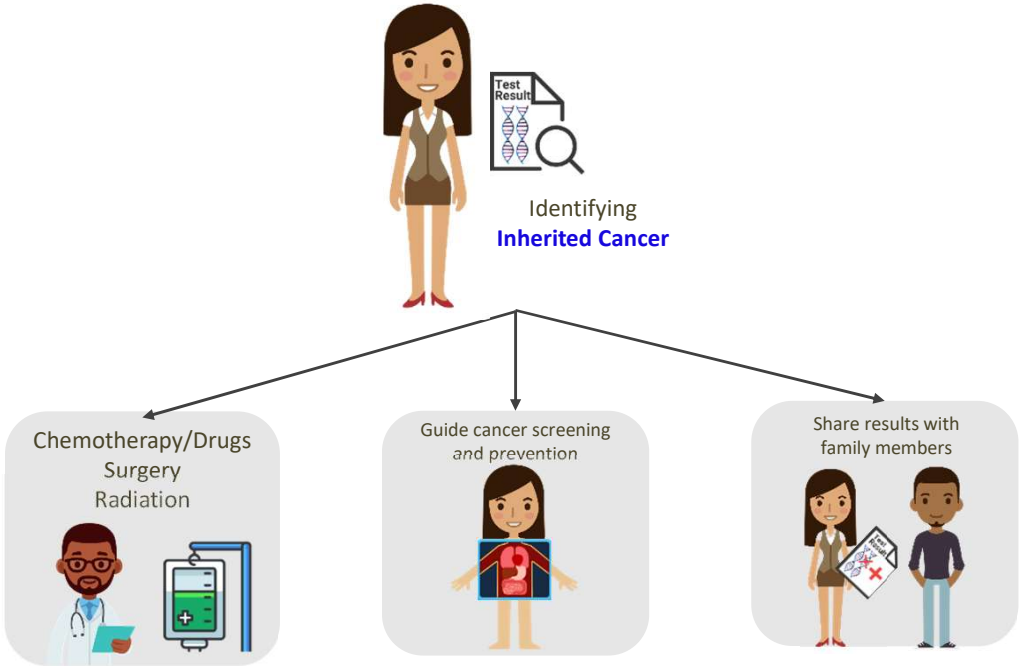


Prevention/ Earlier detection of breast cancer

Opportunity to prevent ovarian cancer through prophylactic surgery

The Bottom Line

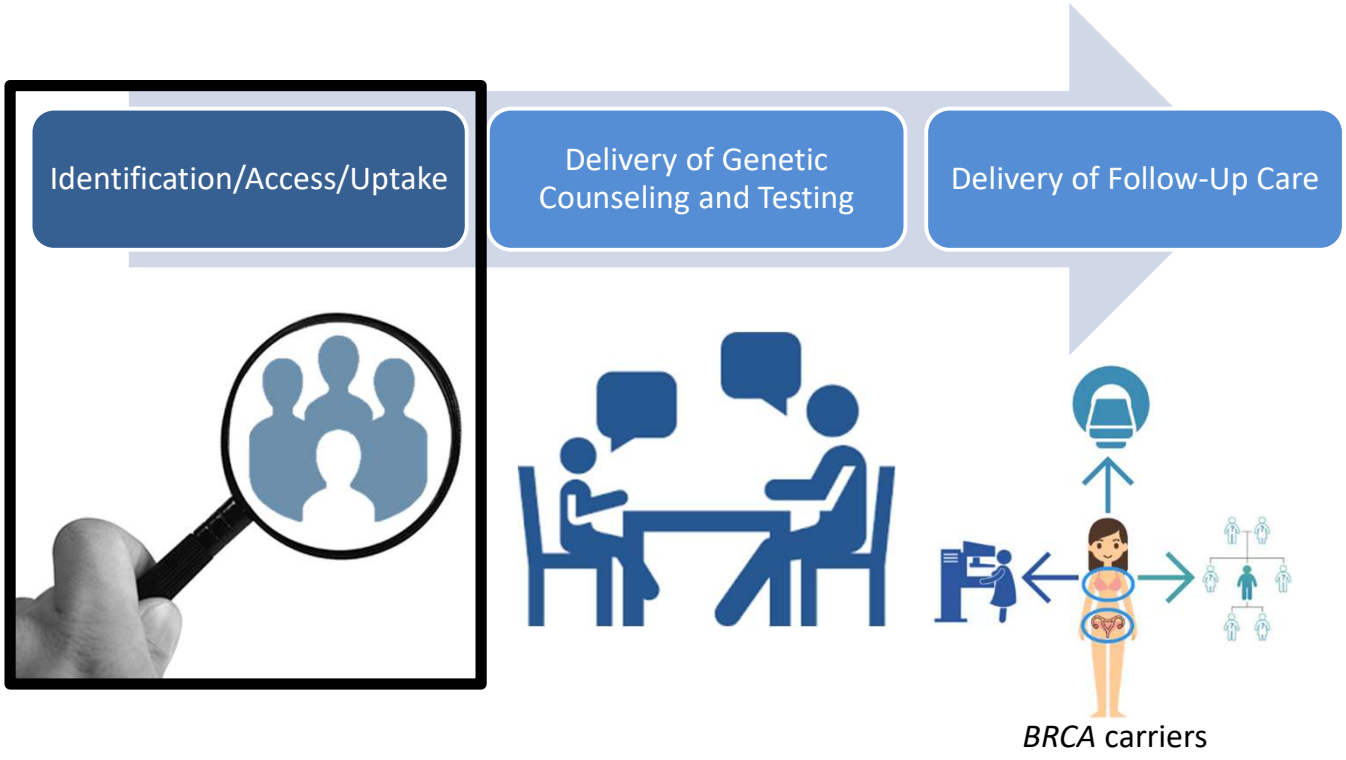
KNOWING ABOUT INHERITED CANCER CAN SAVE LIVES!



NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

VANDERBILT-INGRAM CANCER CENTER

Care Delivery Continuum



Polling Question

What proportion of adult women in the United States with a *BRCA1/2* mutation have been identified?

A. <20%

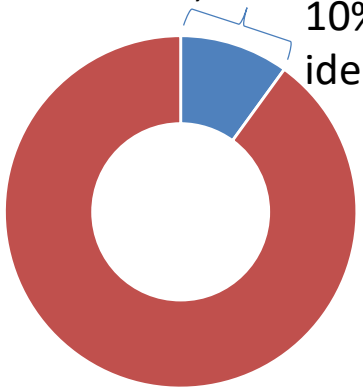
B. ~40%

C. ~60%

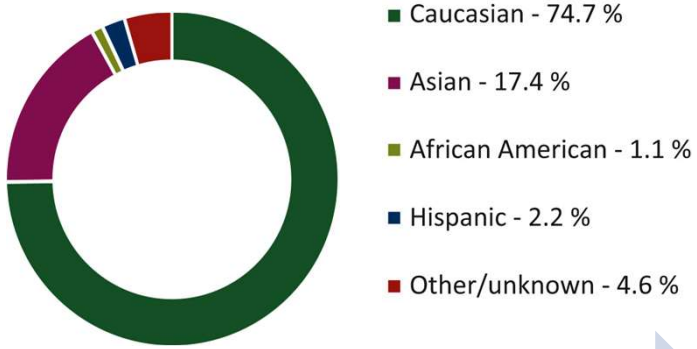
D. ~80%

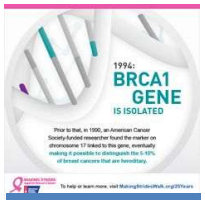
Identification of *BRCA1* or *BRCA2*?

Adult female *BRCA* carriers
350,000



Testing rates not equal across populations:





Discovery of the BRCA genes

1993 | 1998 | 2003 | 2008 | 2013 | 2018 | 2023

Drohan B, et al. Ann Surg Oncol. 2012 Jun;19(6):1732-7. PMID: 22427173.

Paiella S, ESMO Open. 2023 Apr;8(2):PMID: 36822114.

VANDERBILT-INGRAM CANCER CENTER

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate (V.2.2026)

Personal history criteria

- Age
- Treatment indications
- Pathology
- Sex
- Ancestry
- Family history

Family history criteria

- Family cancer history
- Predictive models (>5% risk)

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,g,h,i,j]

Testing is clinically indicated in the following scenarios:

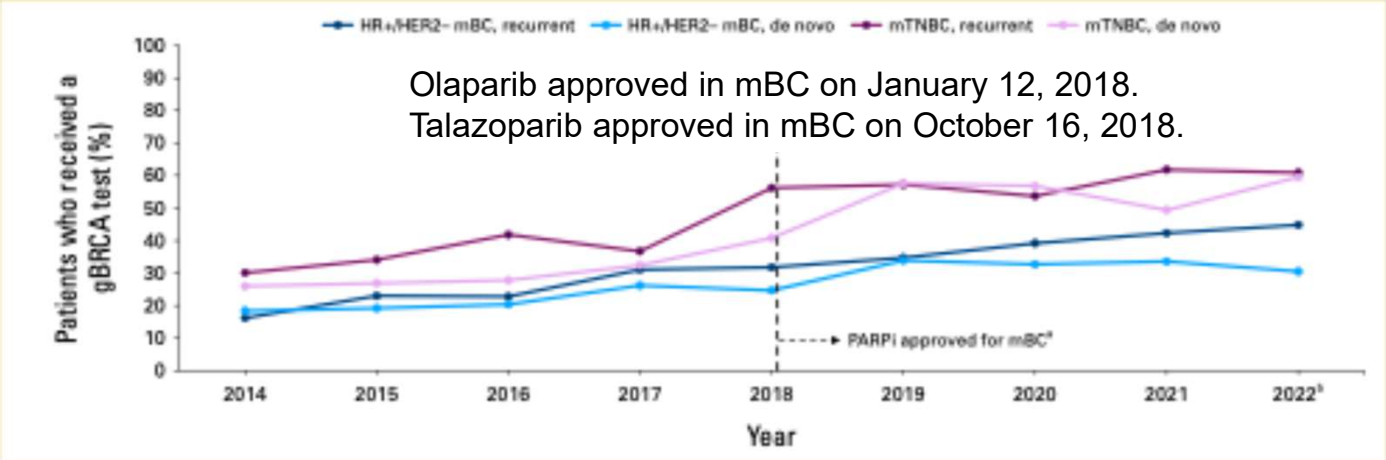
- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[k,l] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[m] HER2-negative breast cancer[j]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[n]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric)
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish
  - Any age (continued):
    - Family history[o]
      - ≥1 close blood relative[p] with ANY:
        - breast cancer at age ≤50 y
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[q] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history criteria: unaffected; or affected but does not meet above criteria
  - Individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[r]
  - Individuals who have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[s]

VANDERBILT-INGRAM CANCER CENTER

Real-World Germline BRCA Testing, Poly(ADP-ribose) Polymerase Inhibitor Utilization, and Survival Outcomes in Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

Siddhartha Yadav, MD, FACP[1]; Fergus J. Couch, PhD[1]; Sam Hillman, PhD[2]; Linlin Luo, PhD[2]; Weiyan Li, PhD, MPH[3]; Qixin Li, PharmD, MS[3]; Jennifer Fallas Hayes, PhD[3]; Jagadeswara R. Earla, PhD, PharmD, MBA[4]; and Xiaoqing Xu, PhD, MPH[3]

US Flatiron Health database: adults with HER2– mBC



Olaparib approved in mBC on January 12, 2018.
Talazoparib approved in mBC on October 16, 2018.

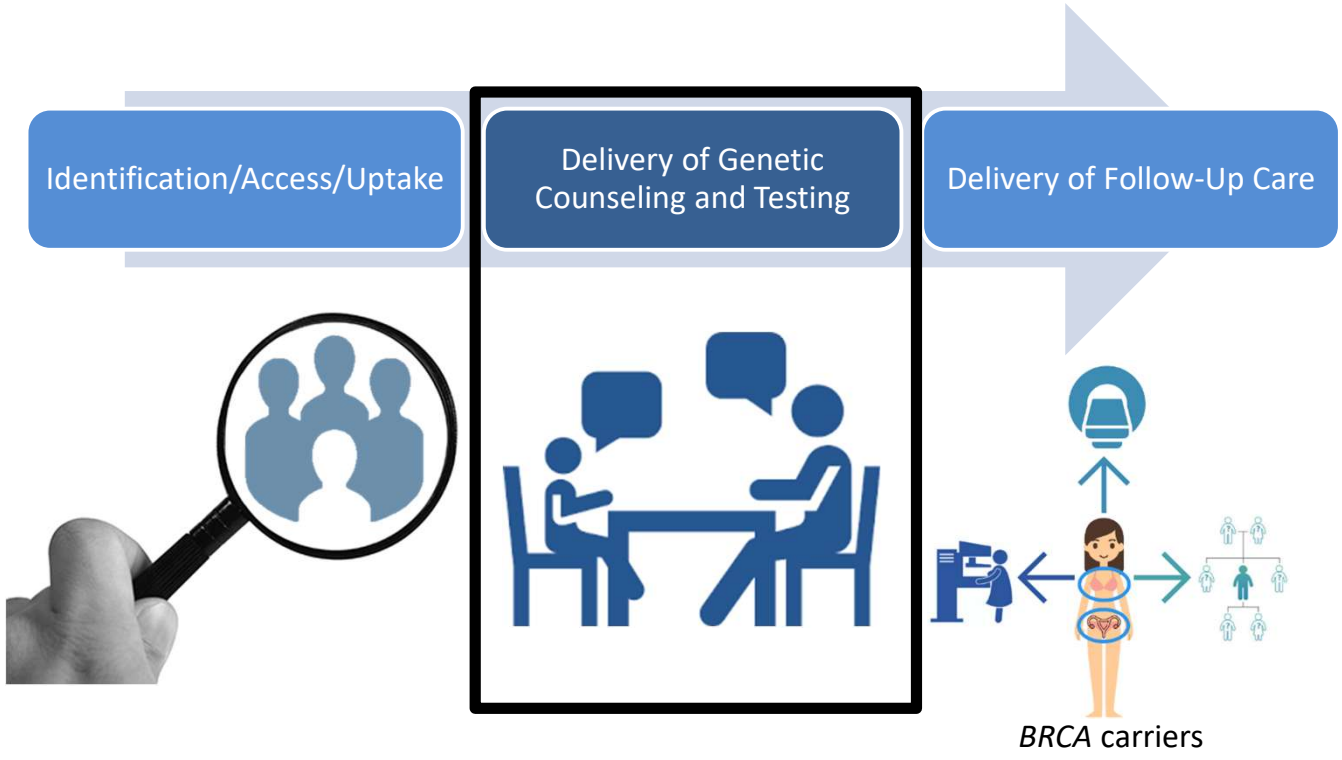
2014-2022:
- 31% received *BRCA* testing

2018 onward:
- < 50% of *BRCA*+ patients with metastatic breast cancer received PARP inhibitor

Yadav S, et al. JCO Precis Oncol. 2025 Jul;9:Epub 2025 Jul 16. PMID: 40669020.

VANDERBILT-INGRAM CANCER CENTER

Care Delivery Continuum



’Point of Care’ (POC) Testing

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Principles of genetic testing for patients with cancer (active diagnoses and previous history) when testing is performed outside of specialty genetics setting (often referred to as “point of care” testing)
There are clinical situations in which germline genetic testing is critical to therapeutic decision-making but comprehensive risk assessment and genetic counseling are not feasible. In these situations, the treating clinician (eg, oncologist, surgeon) may order germline genetic testing. They should be aware that there may be feasibility and cost limits on the type and number of genetic tests ordered for each individual patient.

To maximize the value of the testing experience they should ensure that they include in their discussion with the patient the following points:

- **Pre-test**
  - **Documentation**
    - **Family history collection of both maternal and paternal relatives who have been diagnosed with cancer of any type, ideally from three generations**
    - **Pertinent medical and surgical history**
    - **Informed consent for genetic testing**
  - **Understanding of the germline genetic test ordered and preparedness to counsel patients about any possible result outcomes, including future cancer risks**
    - **There are many testing options and the choice of which multigene panel test to order can be complicated, eg, when the personal and/or family history may suggest more than one cancer syndrome (EVAL-A 3 of 11)**
    - **Result outcomes: positive (EVAL-A 7 of 11), negative (EVAL-A 8 of 11), uncertain variant (EVAL-A 9 of 11), possible mosaic, and/or clonal hematopoiesis of indeterminate potential (LIFR-A 3 of 6)**
- **Post-test**
  - **Discussion of result including interpretation of result in the context of the patient's diagnosis, impact on future cancer risk and management if applicable, impact on reproductive plans if applicable, and impact on family members if applicable**
  - **Referral to clinical genetics services should be offered in the following situations:**
    - **for a P/LP variant result or one for which clinical management is uncertain. Local clinical genetics providers and those that provide telehealth services nationally can be located at https://findageneticcounselor.nsgc.org. Some genetic testing laboratories also offer this service.**
    - **when a patient has complex personal and/or family history suggestive of inherited risk, or has a result that may be difficult to interpret (EVAL-A 6 of 11)**
    - **For patients of reproductive age, see EVAL-A 7 of 11.**
  - **Patients should be given a physical and/or electronic copy of their germline genetic test results, as this is often not available to patients through electronic medical record (EMR) portals, if the testing was sent to an outside laboratory. This document is an important reference for the patient and their relatives in the future.**
  - **For patients who test positive or need other genetics follow-up, consider revisiting this information over time, such as when initial treatment is completed and patient is entering a phase of maintenance or surveillance. This is a time when patients may have more ability to follow up on long-term implications of their genetic testing, such as increased screening for other cancers and informing family members.**
  - **It is expected for the ordering clinician to communicate a change in the status of a VUS to the patient, especially if it is an upgrade to pathogenic.**

References on EVAL-A 11 of 11

Note: All recommendations are category 2A unless otherwise indicated.

EVAL-A 10 OF 11

’Point of Care’ (POC) Testing

Principles of genetic testing for patients with cancer (active diagnoses and previous history) when testing is performed outside of specialty genetics setting (often referred to as “point of care” testing)

- ◊ Pertinent medical and surgical history
- ◊ Informed consent for genetic testing

▸ Understanding of the germline genetic test ordered and preparedness to counsel patients about any possible result outcomes, including future cancer risks
- ◊ There are many testing options and the choice of which multigene panel test to order can be complicated, eg, when the personal and/or family history may suggest more than one cancer syndrome (EVAL-A 3 of 11)
- ◊ Result outcomes: positive (EVAL-A 7 of 11), negative (EVAL-A 8 of 11), uncertain variant (EVAL-A 9 of 11), possible mosaic, and/or clonal hematopoiesis of indeterminate potential (LIFR-A 3 of 6)

• Post-test

▸ Discussion of result including interpretation of result in the context of the patient's diagnosis, impact on future cancer risk and management if applicable, impact on reproductive plans if applicable, and impact on family members if applicable

▸ Referral to clinical genetics services should be offered in the following situations:
- ◊ for a P/LP variant result or one for which clinical management is uncertain. Local clinical genetics providers and those that provide telehealth services nationally can be located at https://findageneticcounselor.nsgc.org. Some genetic testing laboratories also offer this service.
- ◊ when a patient has complex personal and/or family history suggestive of inherited risk, or has a result that may be difficult to interpret (EVAL-A 6 of 11)
- ◊ For patients of reproductive age, see EVAL-A 7 of 11.

▸ Patients should be given a physical and/or electronic copy of their germline genetic test results, as this is often not available to patients through electronic medical record (EMR) portals, if the testing was sent to an outside laboratory. This document is an important reference for the patient and their relatives in the future.

▸ For patients who test positive or need other genetics follow-up, consider revisiting this information over time, such as when initial treatment is completed and patient is entering a phase of maintenance or surveillance. This is a time when patients may have more ability to follow up on long-term implications of their genetic testing, such as increased screening for other cancers and informing family members.

▸ It is expected for the ordering clinician to communicate a change in the status of a VUS to the patient, especially if it is an upgrade to pathogenic.

References on EVAL-A 11 of 11

Note: All recommendations are category 2A unless otherwise indicated.

EVAL-A
10 OF 11

POC Testing (Minimal Components Outlined)

Instances where germline genetic testing is critical to therapeutic decision-making but comprehensive risk assessment and genetic counseling are not feasible.

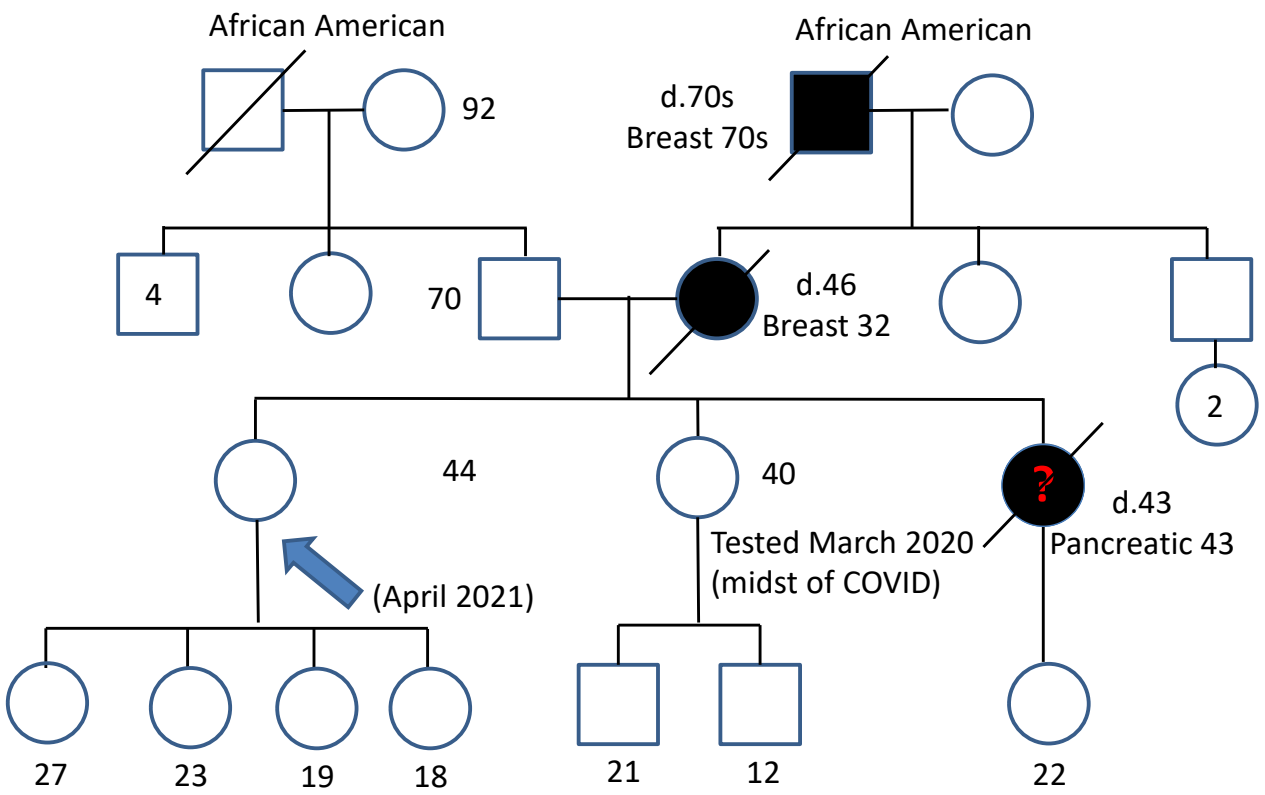
Pre-Test

- Maternal and Paternal **family history** collection (3-generations)
- **Understand** test ordered and **prepare** for any possible test results
  - Positive, negative, VUS, possible mosaic, and/or CHIP
- Overview of **nuances of test options**, as choice of which multigene panel test to order can be complicated

Post-Test

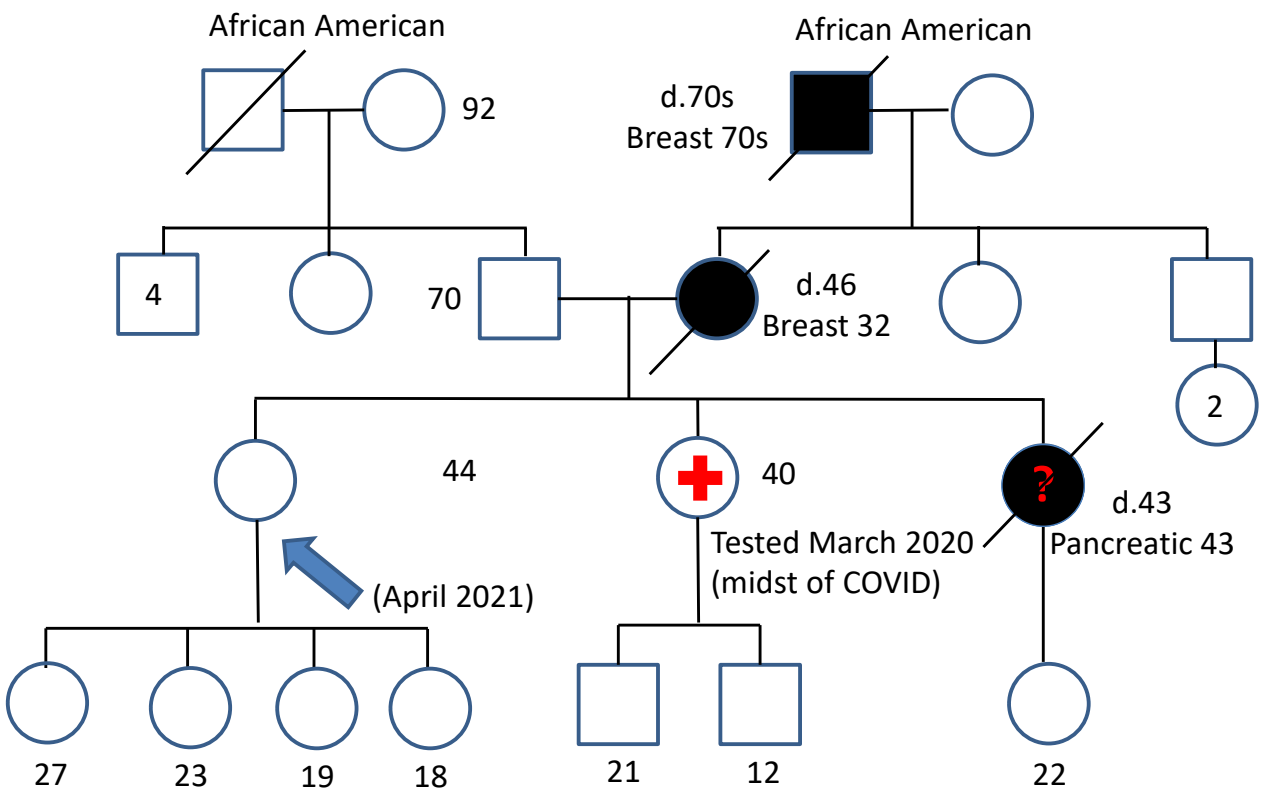
- **Interpret** results in the context of diagnosis
- **Impact** on **future** cancer risk and management, **reproductive** plans and/or **family members**
- Offer **referral** in the following situations:
  - Positive results, management uncertain
  - Complex personal and/or family history
  - Difficult to interpret results
- Provide **copy of results**
- **Revisit information** over time
- **Communicate a change in the status** of a VUS to the patient (especially upgrades)

Family 2



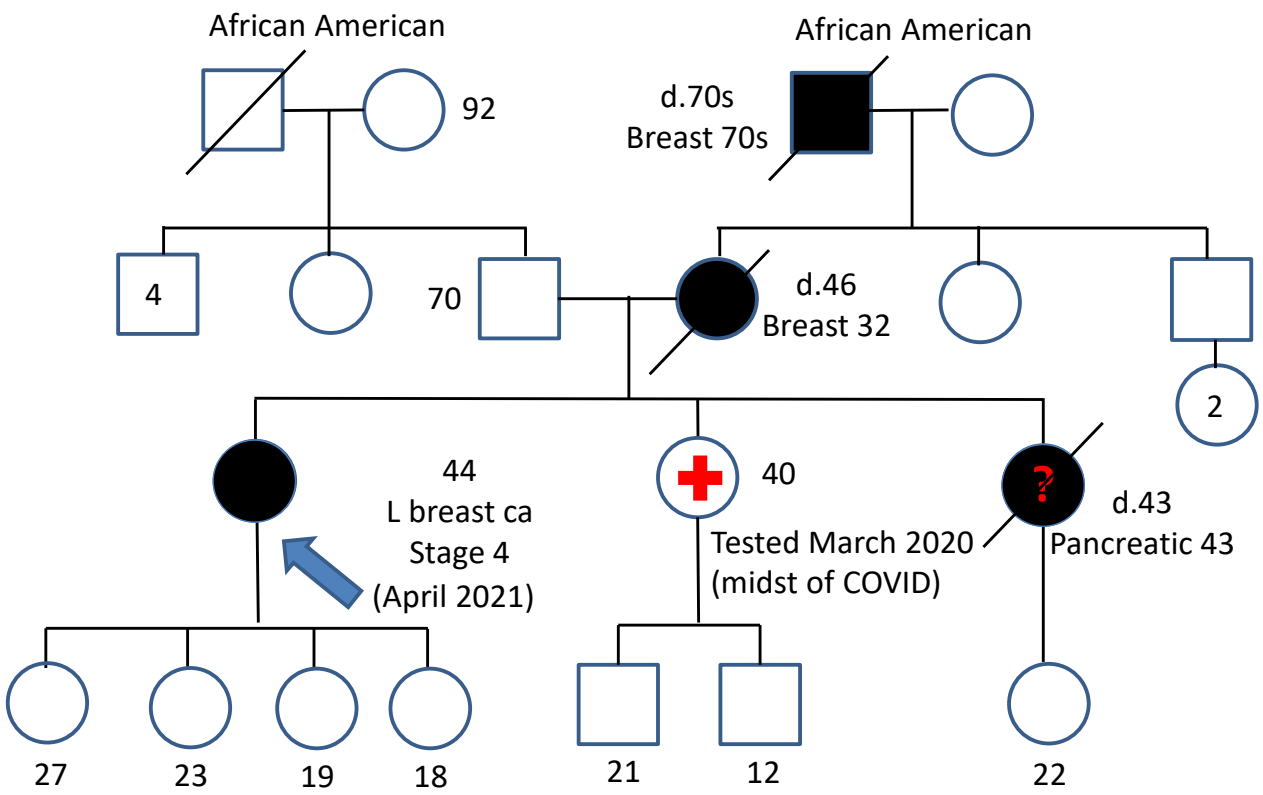
+ *BRCA2* c.3967A>T

Family 2



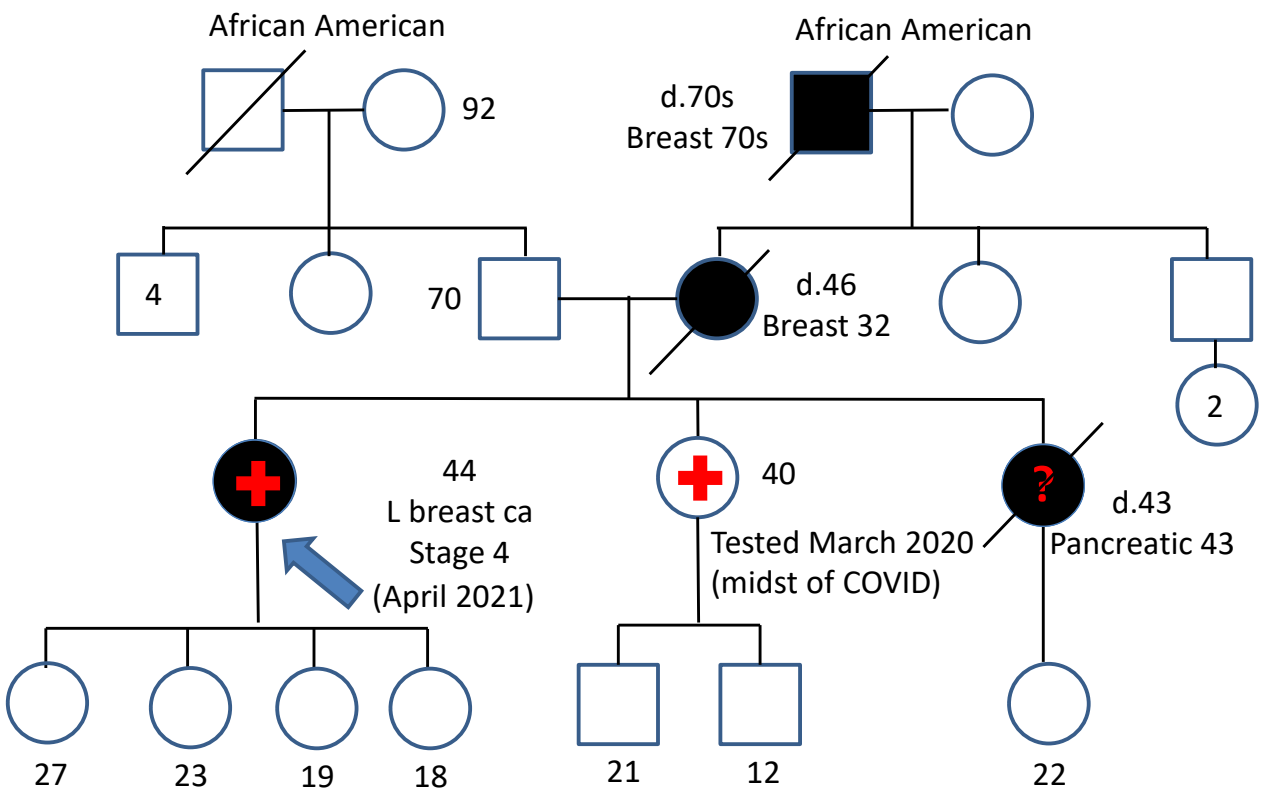
+ *BRCA2* c.3967A>T

Family 2



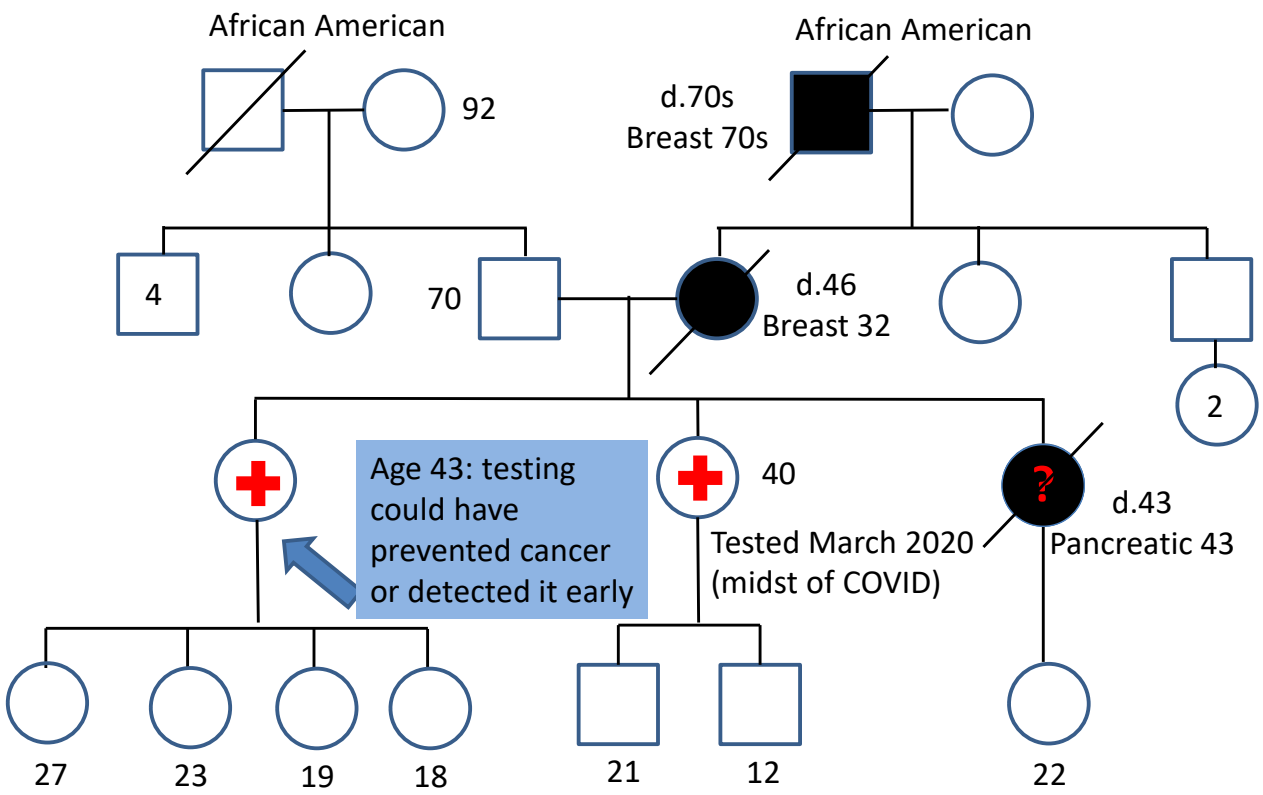
+ *BRCA2* c.3967A>T

Family 2



+ *BRCA2* c.3967A>T

Family 2



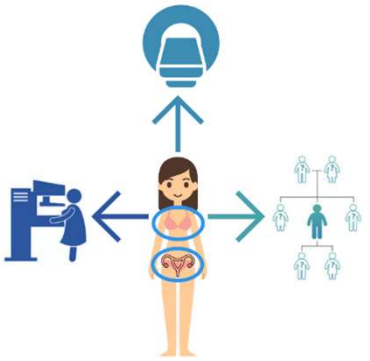
+ *BRCA2* c.3967A>T

Care Delivery Continuum

Identification/Access/Uptake

Delivery of Genetic Counseling and Testing

Delivery of Follow-Up Care



BRCA carriers

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

VANDERBILT-INGRAM CANCER CENTER

GENE-A (Management Table)

Gene-specific risks and management tabulated

Where available, includes risk of:
- Male breast cancer
- Contralateral breast cancer

Genes added/ removed as data evolves

Footnotes: important!!!

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

Gene	Breast Cancer[b]	Epithelial Ovarian Cancer[b]	Pancreatic Cancer,[12-21] Prostate Cancer, and Other Cancer Risks
ATM	Primary breast cancer • Absolute risk: 21%–24%[3,4] • Management:[5] ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with and without contrast starting at age 30–35 y[c,d,e,f] ▸ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history • Strength of evidence of association with cancer: Strong Contralateral breast cancer • 10-year cumulative risk: 4%[g,6] • Strength of evidence of association with cancer: Limited	• Absolute risk: 2%–3%[9-11] • Management: ▸ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history • Strength of evidence of association with cancer: Strong	Pancreatic cancer • Absolute risk: ~5%–10%[h,22] • Management: Screening, see PANC-A. • Strength of evidence of association with cancer: Strong Prostate cancer • Emerging evidence for association with increased risk.[23] Consider annual prostate cancer screening with PSA starting at age 40 y (NCCN Guidelines for Prostate Cancer Early Detection) Colorectal cancer • NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric
	Comments: Heterozygous *ATM* P/LP variants should not lead to a recommendation to avoid RT at this time. *ATM* missense c.7271T>G variant is an example of a higher penetrance allele (60% by age 80 y; Goldgar DE, et al. Breast Cancer Res 2011;13:R73; Hall MJ, et al. Cancer Prev Res (Phila) 2021;14:433-440; Southey MC, et al. J Med Genet 2016;53:800-811) and risk appropriate management should be considered. Management should be based on best estimates of cancer risk for the specific P/LP variant in conjunction with personal and family history. See GENE-B for reproductive implications/recessive disease and partner testing considerations.		
BARD1	Primary breast cancer • Absolute risk:17%–30%[4] • Management: ▸ Screening: Annual mammogram and consider breast MRI with and without contrast starting at age 40 y[c,d,e,f] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • Strength of evidence of association with cancer: Strong[4,6-8]	Evidence of increased risk: No established association	Other cancers • Unknown or insufficient evidence

VANDERBILT-INGRAM CANCER CENTER

Why is breast cancer risk prediction important?

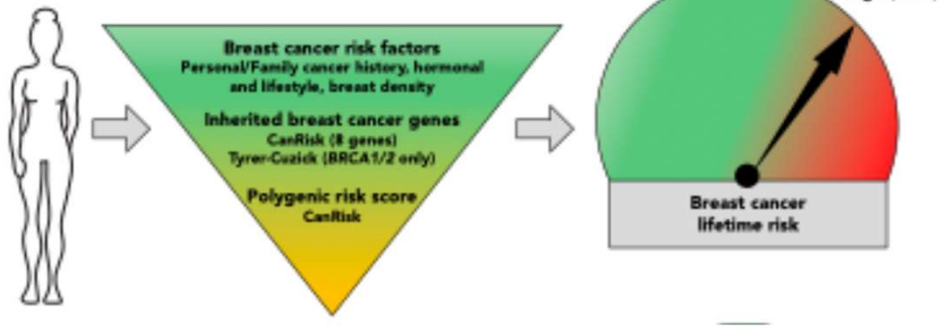
Level of risk elevation	Lifetime Risk	Odds Ratio
Low	<20%	<2
Moderate	20-40%	2-4
High	>40%	>4

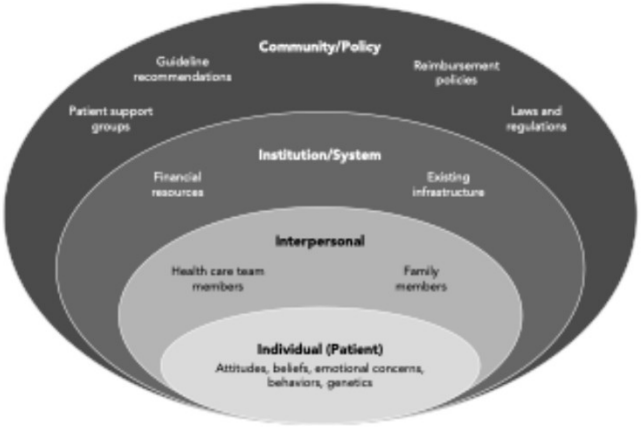
- Moderate risk: high risk screening, including breast MRI
- High risk: consider surgical risk reduction

REVIEW

Breast Cancer Risk Stratification in Black Women: Current Status and Potential Solutions to Improve Accuracy

Sonya Reid, MD, MPH[1,2,*]; Lucy Spalluto, MD[1,3,4,*]; and Tuya Pal, MD[1,2]





Reid, S., Spalluto, L., & Pal, T. (2026). Breast Cancer Risk Stratification in Black Women: Current Status and Potential Solutions to Improve Accuracy. Journal of the National Comprehensive Cancer Network, 24(1), Article e257079. https://doi.org/10.6004/jnccn.2025.7079

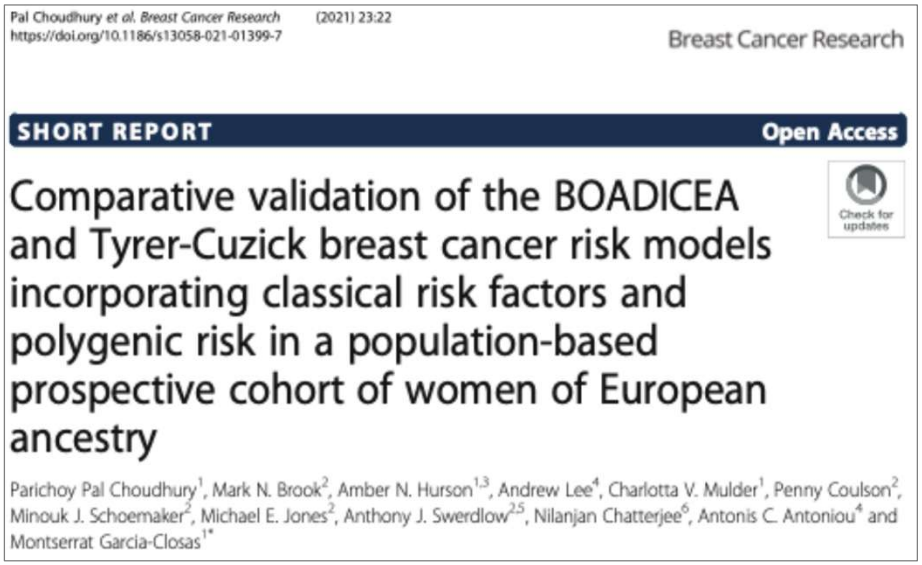
Overview of Current Breast Cancer Prediction Models

Table 1: Overview of Current Breast Cancer Risk Prediction Models: Impact on Racial Disparities

	Gail/BCRAT	BCSC Risk Calculator	Boadicea/CanRisk	Tyrer-Cuzick/IBIS version 8
Development/Validation	Developed in white females and revised in 2015 (BCRAT) to incorporate race	Developed in a geographically, racially and ethnically diverse population representative of US	Largely validated in females of European ancestry	Largely validated in females of European ancestry
Elements included in model:				
Race/Ethnicity	Yes	Yes	No	No
Ashkenazi Inheritance	No	No	Yes	Yes
Family history	First degree female relatives only (not at individual level, but as none, one, or more than one first degree)	First and second degree female relatives only (not at indiviudal level, but as at least one or at least two first or second degree)	Includes individual first, second, and third degree relatives, age of cancer onset, laterality of breast cancer, ovarian cancer and male breast cancer	Includes individual first, second, and third degree relatives, age of cancer onset, laterality of breast cancer, ovarian cancer and male breast cancer
Body Mass Index	No	Yes	Yes	Yes
Breast Density	No	Yes	Yes	Yes
Hormonal/reproductive risk factors	Limited to age at menarche, age at first live birth	Limited to age at first live birth, menopausal status	Includes age at menarche, age at first live birth, age at menopause and HRT and OCP use	Includes age at menarche, age at first live birth, age at menopause, and HRT use
Genetic Test Results	No - not recommended in patients with BRCA mutation	No	results of genetic tests, SNP, polygenic risk score	BRCA mutation
Impact on Disparities	Underestimates risk in Black females	Underestimates risk in non-Hispanic Black females	Further model validation needed prior to use in non-European ancestry populations	Underestimates risk in Black females

Reid, S., Spalluto, L., & Pal, T. (2026). Breast Cancer Risk Stratification in Black Women: Current Status and Potential Solutions to Improve Accuracy. JNCCN, 24(1), Article e257079. https://doi.org/10.6004/jnccn.2025.7079

VANDERBILT-INGRAM CANCER CENTER



Pal Choudhury et al. Breast Cancer Research (2021) 23:22
https://doi.org/10.1186/s13058-021-01399-7

Breast Cancer Research

SHORT REPORT Open Access

Comparative validation of the BOADICEA and Tyrer-Cuzick breast cancer risk models incorporating classical risk factors and polygenic risk in a population-based prospective cohort of women of European ancestry

Parichoy Pal Choudhury[1], Mark N. Brook[2], Amber N. Hurson[1,3], Andrew Lee[4], Charlotta V. Mulder[1], Penny Coulson[2], Minouk J. Schoemaker[2], Michael E. Jones[2], Anthony J. Swerdlow[2,5], Nilanjan Chatterjee[6], Antonis C. Antoniou[4] and Montserrat Garcia-Closas[1*]

- BOADICEA model identified high risk women at elevated breast cancer risk more accurately than the Tyrer-Cuzick model with PRS
- Tyrer-Cuzick model with PRS showed evidence of overestimation at the highest risk decile

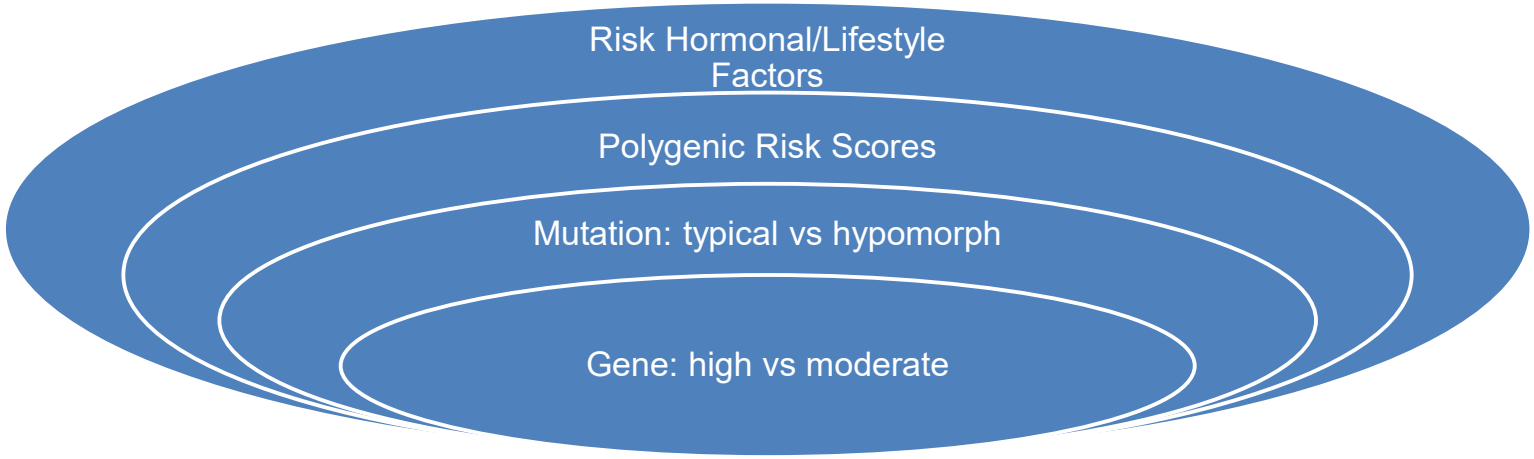
Pal Choudhury P, et al. Comparative validation of the BOADICEA and Tyrer-Cuzick breast cancer risk models incorporating classical risk factors and polygenic risk in a population-based prospective cohort of women of European ancestry. Breast Cancer Res. 2021 Feb 15;23(1):22. PMID: 33588869; PMCID: PMC7885342.

Our Goal…Personal Risks!

- What does that entail?
  - Gene
  - Genotype/Phenotype
  - Polygenic Risk Scores
  - Risk Factors (hormonal, breast density, family history, etc)

Risk Models:

- CanRisk: HBOC Genes and PRS
- Tyrer-Cuzick/IBIS: BRCA only

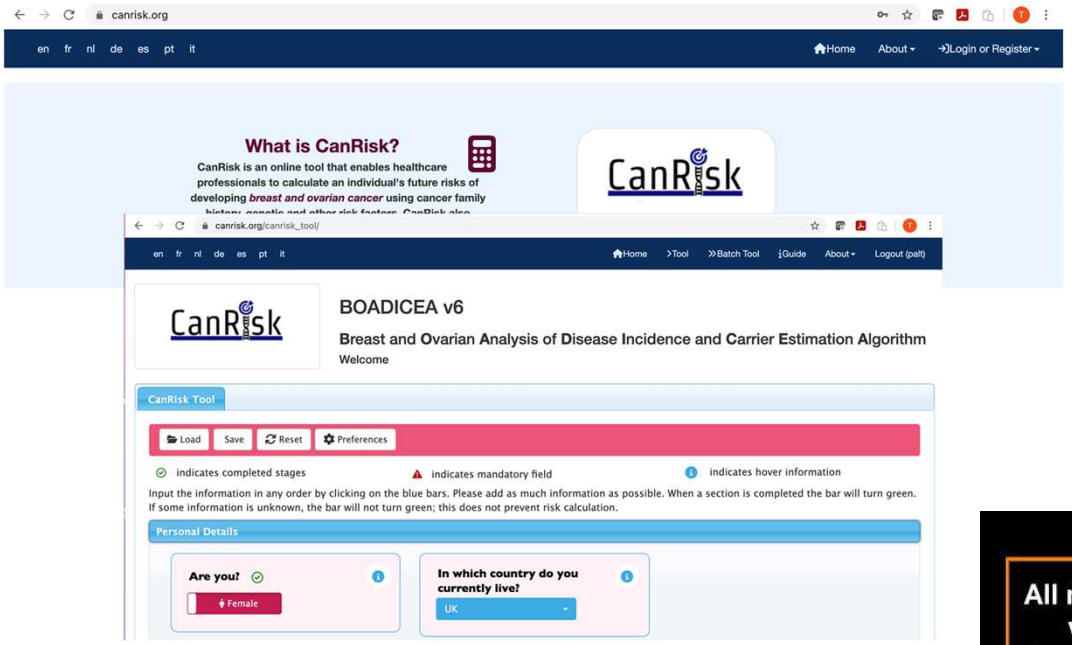


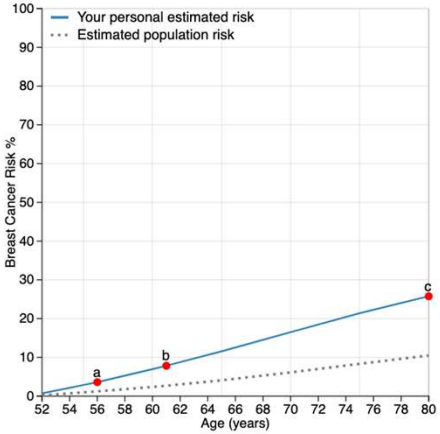
CanRisk.org Online Tool

- Freely available online tool to calculate personalized future risks of developing breast and ovarian cancer using the BOADICEA v6 model
- Can include:
  - personal risk factors
  - cancer family history
  - genetic testing for high- and moderate-risk genes
  - polygenic scores
  - mammographic density

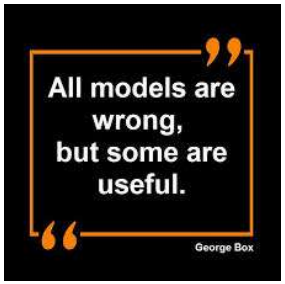
Risk Factor	Breast Cancer	Ovarian Cancer
Family and personal-proband history of breast, ovarian, prostate and pancreatic cancer	x	x
Rare pathogenic variants in moderate and high risk susceptibility genes	x	x
Age information on unaffected family members	x	x
Ashkenazi Jewish origin	x	x
Information on year of birth to capture birth cohort	x	x
Age of menarche	x	
Parity	x	x
Age at first live birth	x	
Use of oral contraception	x	x
Use of menopause hormone therapy	x	x
Body mass index	x	x
Daily alcohol intake	x	
Mammographic density	x	
Height	x	x
Tubal ligation procedure		x
Endometriosis		x
Common cancer genetic susceptibility variants (PRS)	x	x

Breast cancer genes: BRCA1/2, PALB2, CHEK2, ATM, RAD51C/D,
Ovarian cancer genes: BRCA1/2, PALB2, RAD51C/D, BRIP1)





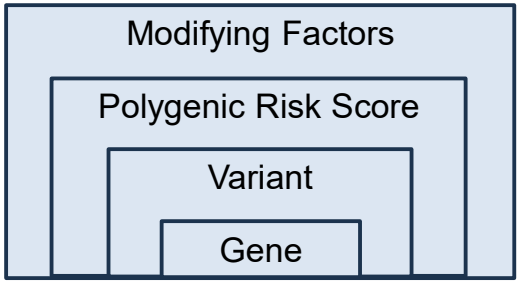
Estimated breast cancer risk
a Next 5 year risk is 3.6%
b Next 10 year risk is 7.8%
c Risk between now and the age of 80 is 25.8%

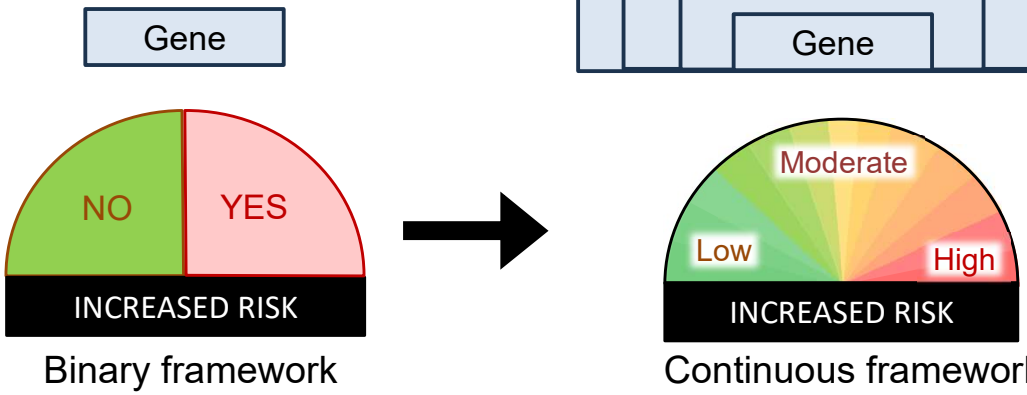


CanRisk v4 recently released
Now includes prostate cancer!

Shifting: binary to continuous framework

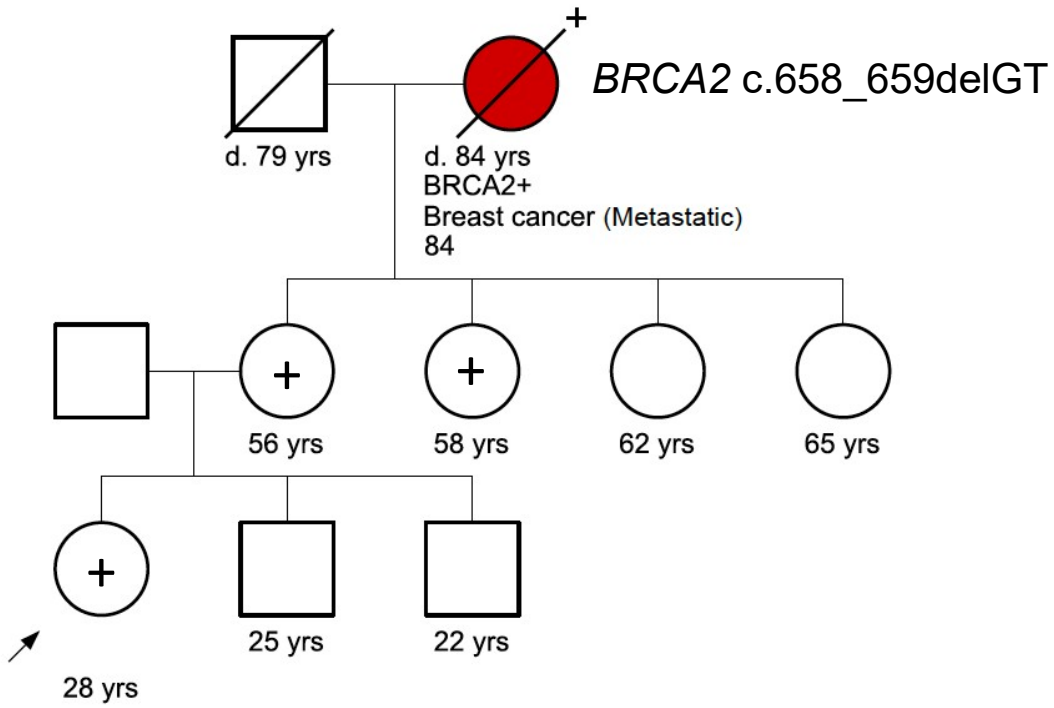
Risk continuum based on **interactions** between:

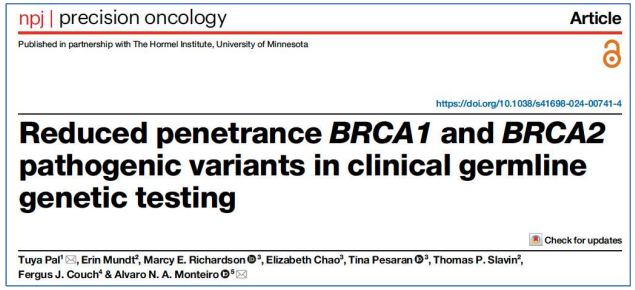




Adapted from Pal T, et al. Consideration of inherited cancer risk on a continuum: An international and multidisciplinary perspective: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2026 Jan 30:101659. Epub ahead of print. PMID: 41618953.

Family 3





npj | precision oncology

Article

Published in partnership with The Hormel Institute, University of Minnesota

https://doi.org/10.1038/s41698-024-00741-4

Reduced penetrance *BRCA1* and *BRCA2* pathogenic variants in clinical germline genetic testing

Check for updates

Tuya Pal[1] ✉, Erin Mundt[2], Marcy E. Richardson[3], Elizabeth Chao[3], Tina Pesaran[3], Thomas P. Slavin[2], Fergus J. Couch[4] & Alvaro N. A. Monteiro[5] ✉

www.ncbi.nlm.nih.gov/clinvar/variation/9342/

NM_000059.4(BRCA2):c.658_659del (p.Val22... Cite Follow

Germline

Top reviewed classifications are shown here. Submission summary: 54 submissions 45 submitters 18 conditions

Reviewed by expert panel

Pathogenic
Apr 2016 by Evidence-based...

for Breast-ovarian cancer, familial, susceptibility to, 2

Buried in one of the entries:
…However, because this variant is identified in one or more patients with Fanconi Anemia it **may be hypomorphic** and thus, carriers of this variant and their families **may present with reduced risks**, and not with the typical clinical characteristics of a high-risk pathogenic *BRCA2* alteration.

List of 16 consensus *BRCA1/2* reduced penetrance pathogenic variants

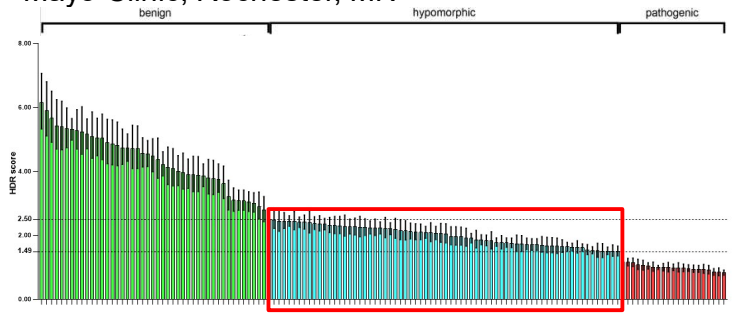
RPPV[a]	Variant Type
BRCA1 c.5096 G > A; p.(Arg1699Gln)	Missense
BRCA1 c.671-1delins6	Splice
BRCA1 c.671-2 A>T	Splice
BRCA1 c.671-2 A>G	Splice
BRCA1 c.671-2 A>C	Splice
BRCA1 c.671-1 G>T	Splice
BRCA1 c.671-1 G>C	Splice
BRCA1 c.671-1 G>A	Splice
BRCA2 c.658_659del; p.(Val220Ilefs*4)	Frameshift
BRCA2 c.9672dup; p.(Tyr3225Ilefs*30)	Frameshift
BRCA2 c.9699_9702del; p.(Cys3233Trpfs*15)	Frameshift
BRCA2 c.7878 G > C; p.(Trp2626Cys)	Missense
BRCA2 c.7878 G > T; p.(Trp2626Cys)	Missense
BRCA2 c.9302 T > G; p.(Leu3101Arg)	Missense
BRCA2 c.8488-1 G > A	Splice
BRCA2 c.8488-1 G > T	Splice

Pal T, Mundt E, Richardson ME, Chao E, Pesaran T, Slavin TP, Couch FJ, Monteiro ANA. Reduced penetrance BRCA1 and BRCA2 pathogenic variants in clinical germline genetic testing. NPJ Precis Oncol. 2024 Nov 2;8(1):247. PMID: 39488595; PMCID: PMC11531542.

VANDERBILT-INGRAM CANCER CENTER

Partially functional (hypomorphic) missense variants in *BRCA2* are reduced penetrance pathogenic variants

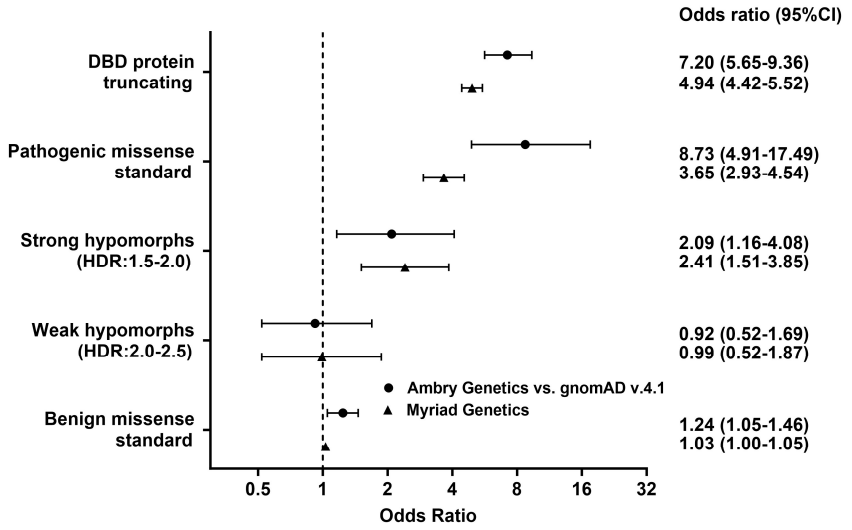
Huaizhi (Gilbert) Huang, B.S.
Mayo Clinic, Rochester, MN



Homology-directed DNA repair assay

Functionally hypomorphic missense variants:

- 49 of 70 candidate hypomorphs showed partial endogenous functional effects
- 14 were classified as pathogenic variant using ClinGen *BRCA1/2* VCEP guidelines



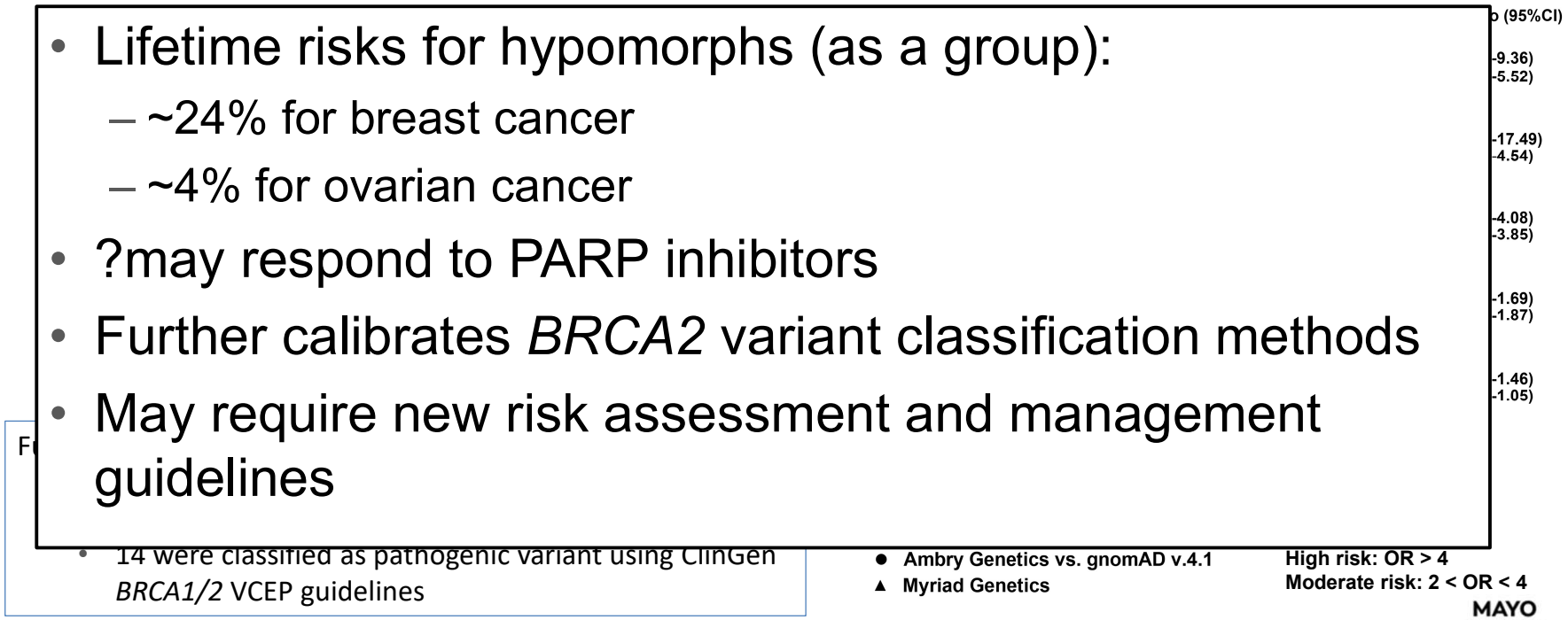
● Ambry Genetics vs. gnomAD v.4.1
▲ Myriad Genetics

High risk: OR > 4
Moderate risk: 2 < OR < 4

Presented at the SABCS 2025 Meeting

Partially functional (hypomorphic) missense variants in *BRCA2* are reduced penetrance pathogenic variants

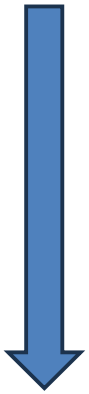
- Lifetime risks for hypomorphs (as a group):
  - ~24% for breast cancer
  - ~4% for ovarian cancer
- ?may respond to PARP inhibitors
- Further calibrates *BRCA2* variant classification methods
- May require new risk assessment and management guidelines



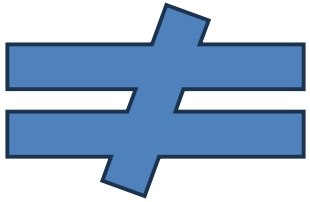
- 14 were classified as pathogenic variant using ClinGen *BRCA1/2* VCEP guidelines

Terminology

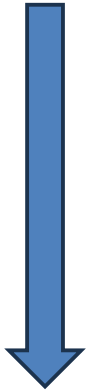
Hypomorph



Refers to gene function



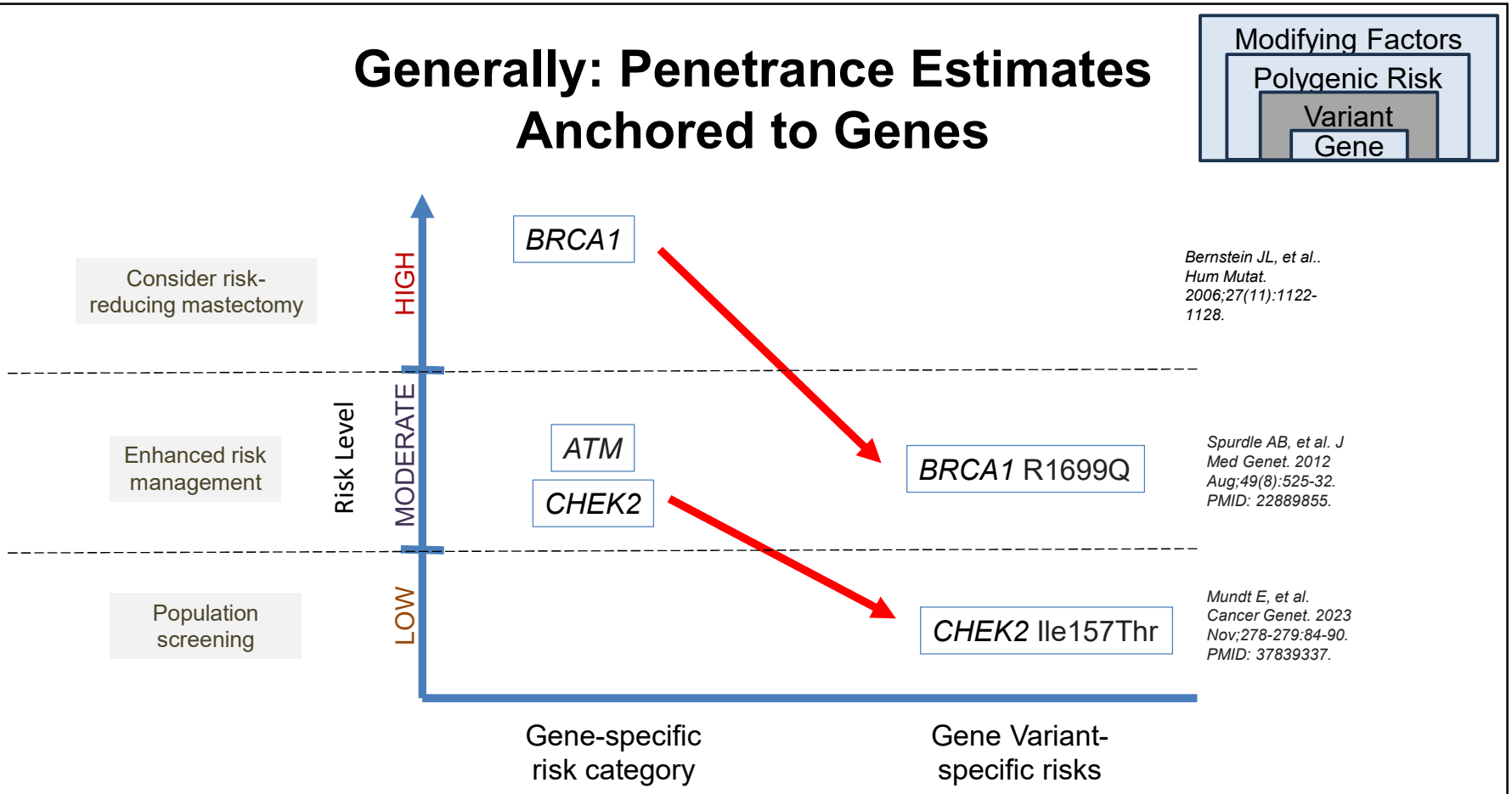
Reduced Penetrance Pathogenic Variant (RPPV)



Refers to resulting risks (clinical relevance)

Clinical relevance based on: INCREASED Risks ≠ Treatment Response

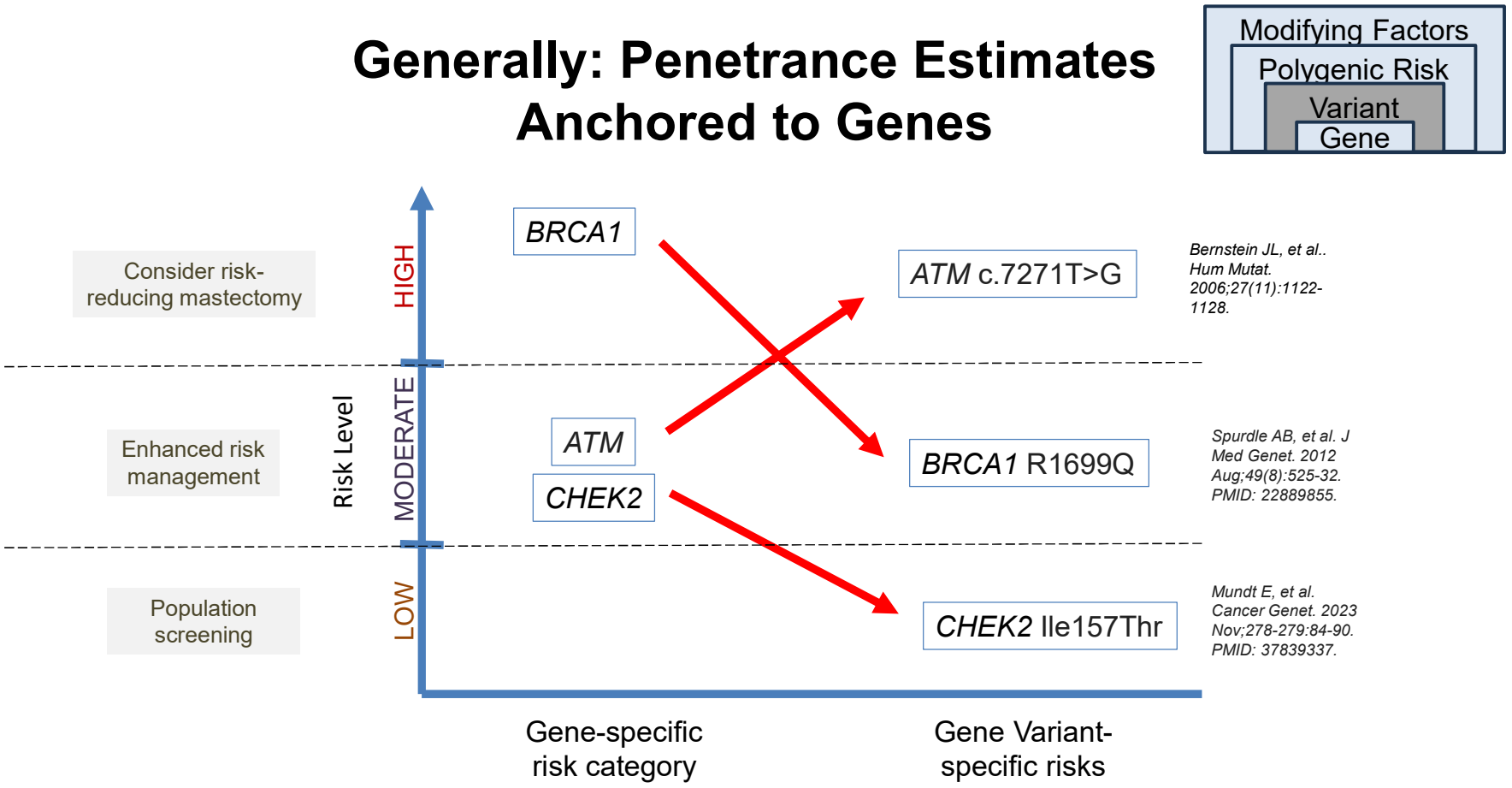
Generally: Penetrance Estimates Anchored to Genes



Adapted from Pal et al. Consideration of inherited cancer risk on a continuum ACMG PTC Document. Accepted, GIM

VANDERBILT-INGRAM CANCER CENTER

Generally: Penetrance Estimates Anchored to Genes



Adapted from Pal et al. Consideration of inherited cancer risk on a continuum ACMG PTC Document. Accepted, GIM

VANDERBILT-INGRAM CANCER CENTER

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS (GENE-A Table): Footnotes…

ATM

Comments: Heterozygous *ATM* P/LP variants should not lead to a recommendation to avoid RT at this time. *ATM* missense c.7271T>G variant is an example of a higher penetrance allele (60% by age 80 y; Goldgar DE, et al. Breast Cancer Res 2011;13:R73; Hall MJ, et al. Cancer Prev Res (Phila) 2021;14:433-440; Southey MC, et al. J Med Genet 2016;53:800-811) and risk appropriate management should be considered. Management should be based on best estimates of cancer risk for the specific P/LP variant in conjunction with personal and family history.

BRCA1

Comment: See GENE-B for reproductive implications/recessive disease and partner testing considerations. The risk for breast cancer appears to be lower for certain variants (eg, *BRCA1* R1699Q) (Spurdle AB, et al. J Med Genet 2012;49:525-532; Pal T, et al. NPJ Precis Oncol 2024;8:247) and risk appropriate management should be considered. Management should be based on best estimates of cancer risk for the specific P/LP variant in conjunction with personal and family history.

BRCA2

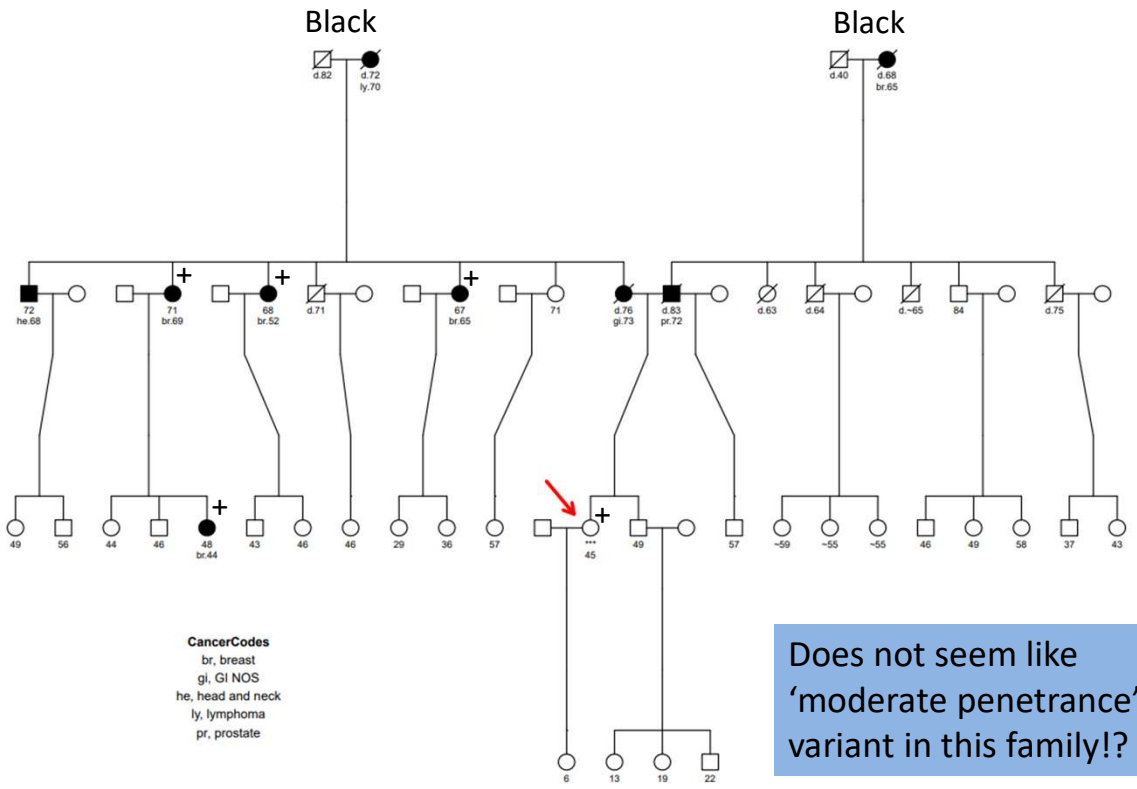
Comment: See GENE-B for reproductive implications/recessive disease and partner testing considerations. The risk for breast cancer appears to be lower for certain missense and splicing variants (Pal T, et al. NPJ Precis Oncol 2024;8:247; Huang H, et al. Nature 2025;638:528-537) and risk appropriate management should be considered. Management should be based on best estimates of cancer risk for the specific P/LP variant in conjunction with personal and family history.

CHEK2

Comments: The above risk data are based only on frameshift and missense P/LP variants other than Ile157Thr, Ser428Phe, and Thr476Met. There is emerging evidence that not all missense P/LP variants are low penetrance. For Ile157Thr, Ser428Phe, and Thr476Met, the risk for breast cancer appears to be lower. Additional cancer risk management based on these variants is not recommended. Management should be based on best estimates of cancer risk for the specific P/LP variant and family history.

BRCA2 c.658_659delGT (RPPV)…?

Family 4



Does not seem like 'moderate penetrance' variant in this family!?

RPPV[a]	Variant Type
BRCA1 c.5096 G > A; p.(Arg1699Gln)	Missense
BRCA1 c.671-1delins6	Splice
BRCA1 c.671-2 A>T	Splice
BRCA1 c.671-2 A>G	Splice
BRCA1 c.671-2 A>C	Splice
BRCA1 c.671-1 G>T	Splice
BRCA1 c.671-1 G>C	Splice
BRCA1 c.671-1 G>A	Splice
BRCA2 c.658_659del; p.(Val220Ilefs*4)	Frameshift
BRCA2 c.9672dup; p.(Tyr3225Ilefs*30)	Frameshift
BRCA2 c.9699_9702del; p.(Cys3233Trpfs*15)	Frameshift
BRCA2 c.7878 G > C; p.(Trp2626Cys)	Missense
BRCA2 c.7878 G > T; p.(Trp2626Cys)	Missense
BRCA2 c.9302 T > G; p.(Leu3101Arg)	Missense
BRCA2 c.8488-1 G > A	Splice
BRCA2 c.8488-1 G > T	Splice

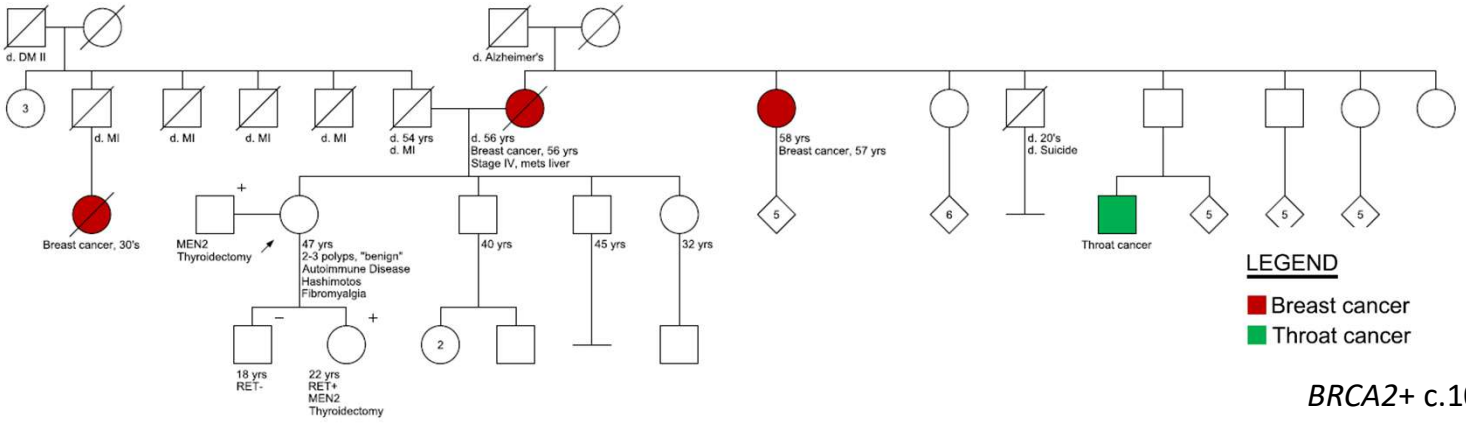
Pal T, Mundt E, Richardson ME, Chao E, Pesaran T, Slavin TP, Couch FJ, Monteiro ANA. Reduced penetrance BRCA1 and BRCA2 pathogenic variants in clinical germline genetic testing. NPJ Precis Oncol. 2024 Nov 2;8(1):247. PMID: 39488595; PMCID: PMC11531542.

VANDERBILT-INGRAM CANCER CENTER

Family 5

47 yo female - *BRCA2*+ with family history of breast cancer

- s/p **total abdominal hysterectomy/bilateral salpingo-oophorectomy:**
  - severe menopausal symptoms – and could not get HRT
  - encouraged to take Tamoxifen – but concerned about making symptoms worse
  - started taking gabapentin
  - also had episode of recurrent major depressive disorder
- Incidentally, husband and daughter – MEN2, s/p thyroidectomy



BRCA2+ c.1037delA

Polling Question

What are the options for hormone replacement therapy (HRT) in this premenopausal BRCA+ woman status post TAH/BSO?

A. HRT is not an option

B. Would consider Estrogen + Progesterone

C. Would consider Estrogen only

D. None of the above

Is it safe to use menopausal hormone therapy (MHT) after oophorectomy

Presented by Dr. Joanne Kotsopoulos

MHT and Risk of Breast Cancer

MHT type	*BRCA1* and *BRCA2* (n = 676 pairs)			*BRCA1* (n = 548 pairs)		*BRCA2* (n = 128 pairs)	
	Cases/Total	HR (95% CI)*	*P*	HR (95% CI)*	*P*	HR (95% CI)*	*P*
Any MHT use							
Unexposed	128/676	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Exposed	87/676	0.48 (0.36-0.63)	<0.0001	0.50 (0.37-0.66)	<0.0001	0.35 (0.15-0.82)	0.02
E alone							
Unexposed	58/291	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Exposed	35/291	0.37 (0.24-0.57)	<0.0001	0.36 (0.23-0.58)	<0.0001	0.39 (0.13-1.22)	0.11
E+P							
Unexposed	42/244	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Exposed	37/244	0.94 (0.54-1.63)	0.82	0.95 (0.53-1.59)	0.75	n/a	n/a

*Adjusted for parity and country of residence

Kotsopoulos J, et al. Menopausal hormone therapy and the risk of breast cancer in women with a pathogenic variant in BRCA1 or BRCA2. J Natl Cancer Inst. 2025 Dec 17: Epub ahead of print. PMID: 41403285.

Risk of breast cancer: Evaluating Route and Type of MHT

Estrogen Only

MHT type	Cases (n)/ Total (n)	HR (95% CI)*	*P*
Any Estrogen (E)			
Unexposed	58/291	1.00 (ref)	
Exposed	35/291	0.37 (0.24-0.57)	<0.0001
Transdermal estradiol			
Unexposed	36/169	1.00 (ref)	
Exposed	21/169	0.46 (0.25-0.82)	0.008
Oral estradiol			
Unexposed	13/60	1.00 (ref)	
Exposed	9/60	0.57 (0.20-1.62)	0.29
Oral CEE			
Unexposed	10/69	1.00 (ref)	
Exposed	6/69	0.40 (0.11-1.55)	0.19
Oral synthetic E			
Unexposed	7/36	1.00 (ref)	
Exposed	4/36	0.32 (0.04-2.38)	0.27

*Adjusted for parity and country of residence

Estrogen + Progesterone

MHT type	Cases (n)/ Total (n)	HR (95% CI)*	*P*
Any Progestogen (P)			
Unexposed	46/266	1.00 (ref)	
Exposed	41/266	0.90 (0.54-1.49)	0.67
E+P			
Unexposed	42/244	1.00 (ref)	
Exposed	37/244	0.94 (0.54-1.63)	0.82
E+Synthetic P			
Unexposed	30/179	1.00 (ref)	
Exposed	25/179	0.89 (0.48-1.64)	0.70
E+Natural P			
Unexposed	13/64	1.00 (ref)	
Exposed	11/64	1.19 (0.24-5.87)	0.83
P alone			
Unexposed	3/18	1.00 (ref)	
Exposed	3/18	1.14 (0.21-6.22)	0.88

*Adjusted for parity and country of residence

Summary

- No adverse effect of MHT on *BRCA* breast cancer risk
  - E alone = lower risk, irrespective of route and type
  - E+P = no increased risk
- Use of MHT in *BRCA* cohort is low (37% of potentially eligible)

Limitations:
- Small strata & did not stratify by tumor receptor status
- Need for longer follow-up

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

AFTER RRSO: HRT is generally not contraindicated and thus should be discussed with premenopausal patients who do not have a personal history of breast cancer

Hormone replacement options after risk-reducing surgery	• In conjunction with a gynecologist or other qualified health care professional with expertise in menopause management: ▸ HRT recommendations should be tailored depending on each patient's personal history of breast cancer and/or breast cancer risk reduction strategies. ▸ HRT is an important consideration for premenopausal patients who do not carry a diagnosis of breast cancer or do not have other contraindications for HRT. ▸ Premature menopause due to RRSO can cause detriments to bone health, cardiovascular health, psychosocial health, neurologic health, sexual health, and generalized quality-of-life. HRT can reduce these risks. • Studies examining the risk of subsequent breast cancer associated with HRT use after RRSO have primarily focused on average durations of HRT use up to 3–5 years, and the safety of longer-term use remains uncertain. • If uterus is left in place at time of RRSO, consider options for hormone replacement ▸ LNG-IUD for uterine protection with oral or transdermal estrogen. LNG-IUD may have benefits over combined HRT including potential decreased risk for breast cancer.[22] ▸ Combination E/P HRT with counseling regarding bleeding precautions and endometrial cancer risk/awareness. ▸ Combination estrogen with selective estrogen receptor modulator (such as bazedoxifene).[23] ▸ Combination OCPs that can be taken continuously without placebo week.

JNCCN Insights article (February 2026 Issue)

Cheng H, Giri V, Goggins M, Yurgelun M, Karlan B, Norquist B, Daly M, Pal T...Dwyer M, Darlow S., Diwan, Z.

Prostate Cancer Screening

- Review of genes/risks: BRCA1/2, *HOXB13, ATM, CHEK2, MSH2, PALB2, TP53*
- PSA
- Prostate MRI
  - recommended screening done in experienced high-volume centers after an in-depth discussion

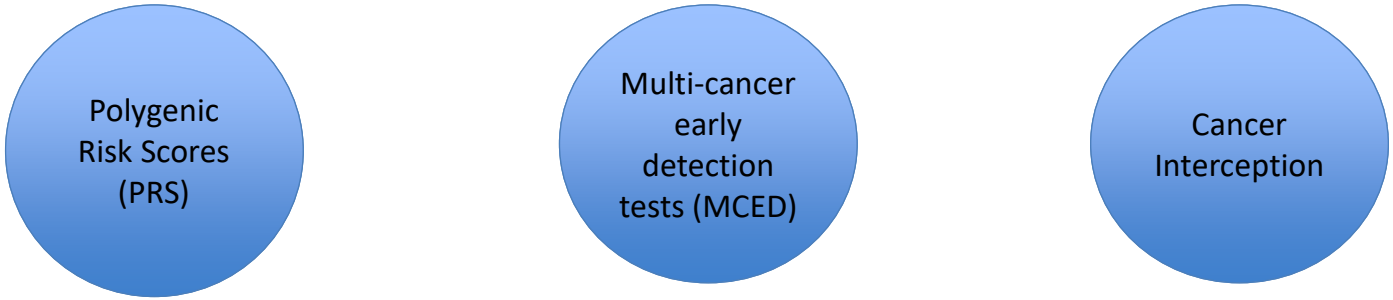
Pancreatic Cancer Screening

- Screening without need for family history: *CDKN2A*, *STK11*, *ATM*, or *BRCA2*
- Family history needed: *BRCA1, MSH2, MLH1, MSH6, EPCAM, PALB2, TP53*

Testing for non-epithelial ovarian cancer

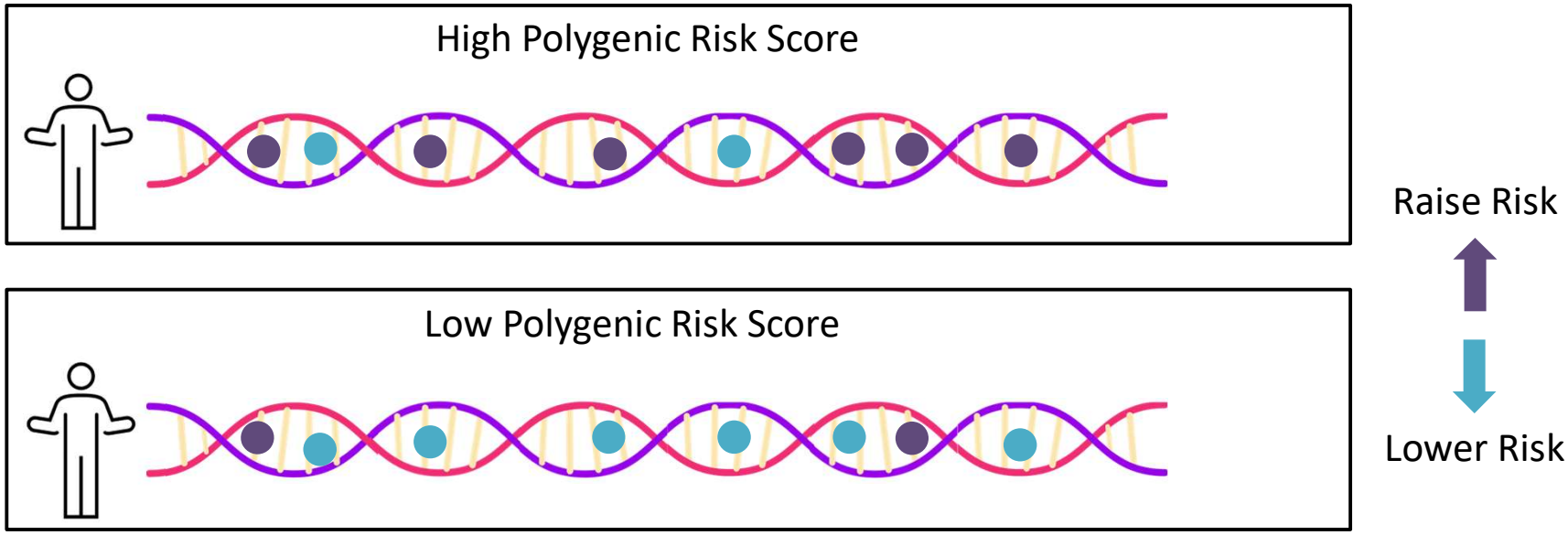
- *DICER1*: SCCOHT
- *STK11* (Peutz-Jeghers): SCTAT
- Given rarity, consultation with expert may be considered

What's next?



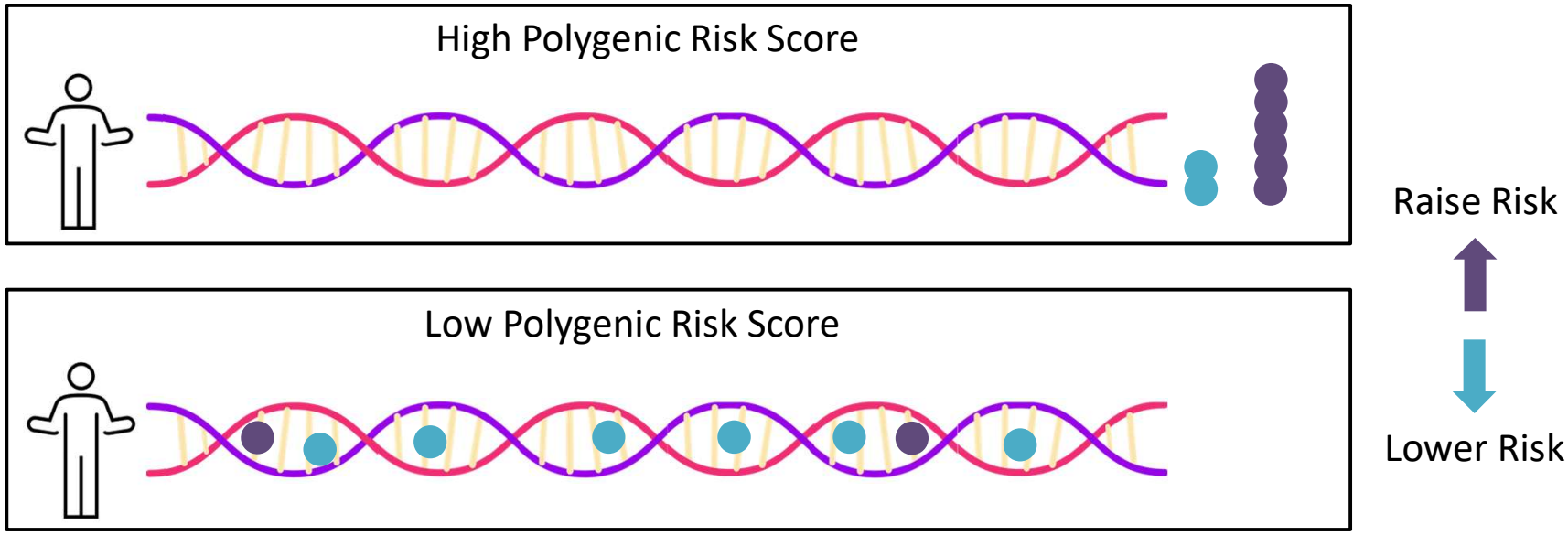
Polygenic Risks Scores (PRS)

- DNA variants can be used to calculate a “polygenic risk score”.
- Some variants raise disease risks. Other variants lower these risks.



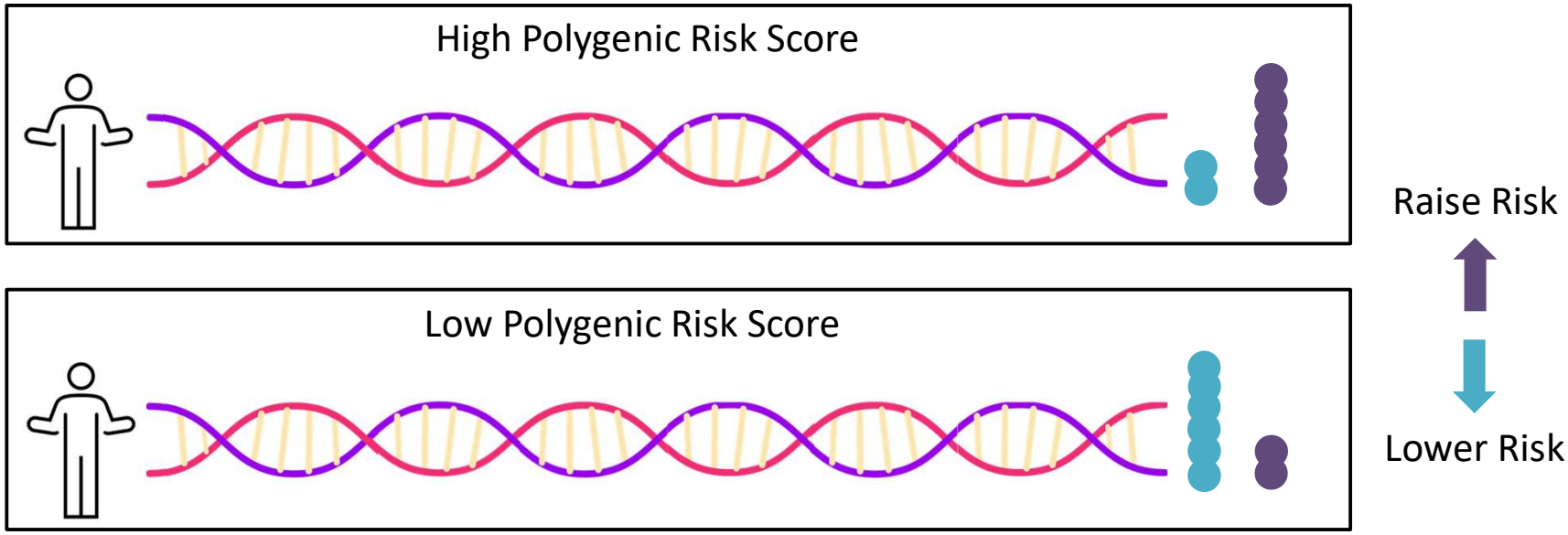
Polygenic Risks Scores (PRS)

- DNA variants can be used to calculate a “polygenic risk score”.
- Some variants raise disease risks. Other variants lower these risks.



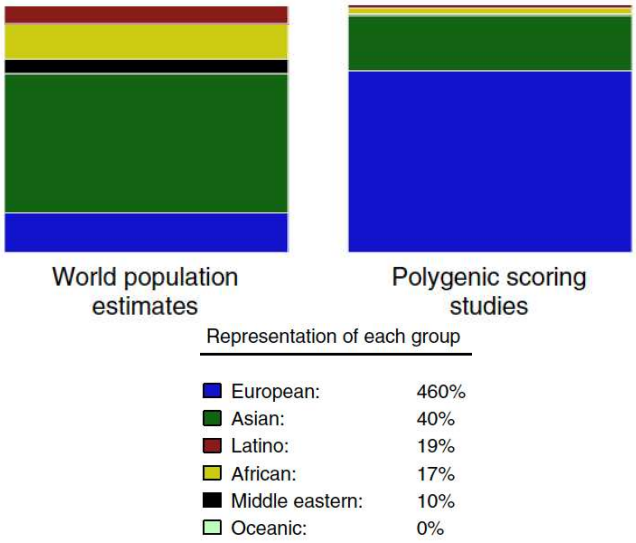
Polygenic Risks Scores (PRS)

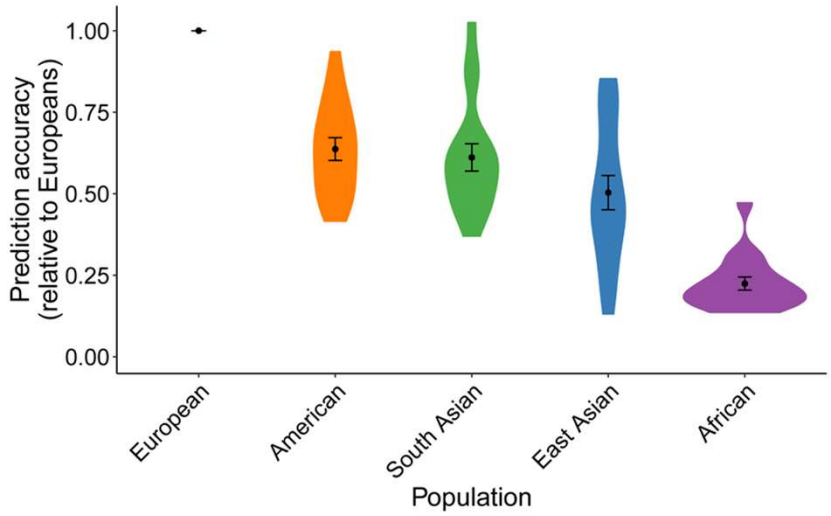
- DNA variants can be used to calculate a “polygenic risk score”.
- Some variants raise disease risks. Other variants lower these risks.



Disparities in Polygenic Risk Scores

Under-representation → ↓ Prediction Accuracy





Duncan L, et al. Analysis of polygenic risk score usage and performance in diverse human populations. Nat Commun. 2019 Jul 25;10(1):3328. PMID: 31346163.

Martin AR, et al. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019 Apr;51(4):584-591. PMID: 30926966.

JAMA | Original Investigation | WOMEN'S HEALTH

Risk-Based vs Annual Breast Cancer Screening
The WISDOM Randomized Clinical Trial

Laura J. Esserman, MD, MBA; Allison S. Fiscalini, MPH; Arash Naeim, MD, PhD; Laura J. van't Veer, PhD; Andrea Kaster, MD; Maren T. Scheuner, MD; Andrea Z. LaCroix, PhD; Alexander D. Borowsky, MD; Hoda Anton-Culver, PhD; Olufunmilayo I. Olopade, MD; James Esserman, MD; Rachael Lancaster, MD; Lisa Madlensky, PhD; Amie M. Blanco, MS; Katherine S. Ross, MS; Deborah L. Goodman, MD, PhD; Barry S. Tong, MS; Michael Hogarth, MD; Diane Heditsian, BA; Susie Brain, BSc; Vivian Lee, BA; Kelly Blum, MS; Mi-Ok Kim, PhD; Leah P. Sabacan, MBA; Kirkpatrick B. Fergus, MD; Christina Yau, PhD; Hannah L. Park, PhD; Barbara A. Parker, MD; Celia Kaplan, DrPH; Kim F. Rhoads, MD; Suzanne Eder, CFNP; Kelly Adduci, MPH; Jeffrey B. Matthews, PhD; Neil S. Wenger, MD; Yiwey Shieh, MD; Robert A. Hiatt, MD, PhD; Elad Ziv, MD; Jeffrey A. Tice, MD; Martin Eklund, PhD

Esserman LJ, et al. Risk-Based vs Annual Breast Cancer Screening: The WISDOM Randomized Clinical Trial. JAMA. 2025 Dec 12:Epub ahead of print. PMID: 41385349.

- **OBJECTIVE** To determine whether risk-based breast cancer screening is a feasible alternative to annual mammography.
- **Methods: 2-arms:**
  - Risk-based arm vs Annual Age-based Mammography
- **Results:** Rate of stage >IIB cancers in risk-based group noninferior to annual screening

Personalized Screening Group

RISK FACTORS

Breast Density
(mammogram)

Health Questionnaire
family history, age, race/ethnicity, comorbidities, previous biopsies

Genomic Profiling
9 gene panel SNPs
Saliva collection

SCREENING RECOMMENDATIONS

LOWEST RISK
No Screening until age 50

AVERAGE RISK
Biennial mammograms

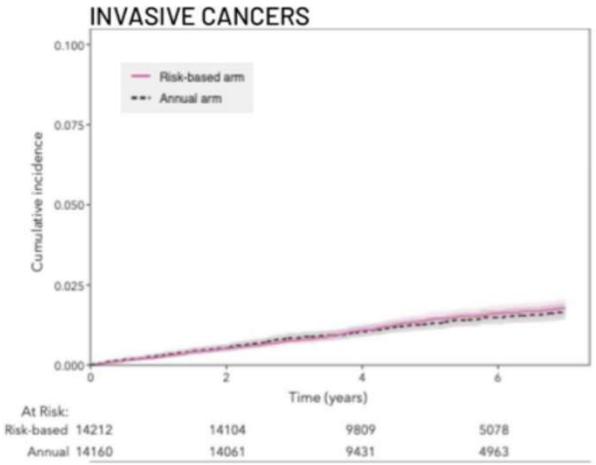
ELEVATED RISK
Annual mammograms
+ 1:1 Breast Health Specialist
+ Breast Health Decisions Tool

HIGHEST RISK
Annual mammograms + MRI
+ 1:1 Breast Health Specialist
+ Breast Health Decisions Tool

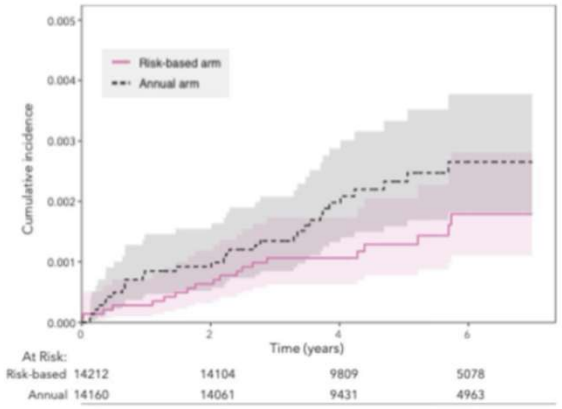
Pathogenic variants

To generate PRS

Invasive Breast Cancers: Risk-Based vs Annual Arms

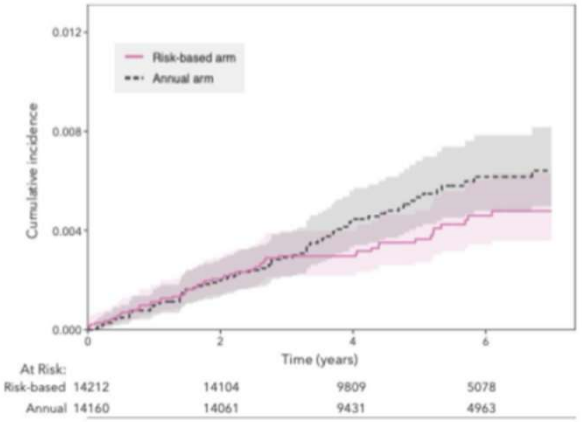


Same number of cancers in each arm



Fewer Stage≥2B cancer in RISK BASED

Clearly met non-inferiority



Rate of Stage ≥2A cancer in risk-based arm not higher

Author Conclusion:

RISK-BASED should become the new standard of care

More for those that need it, less for those who do not

Impact of Polygenic Risk Scores on Breast Cancer Risk Assessment and Clinical Decision Making in Carriers of Germline Pathogenic Variants in *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2*: Results from the Prospective Multisite GENRE-2 Clinical Trial

Siddhartha Yadav, et al
Mayo Clinic

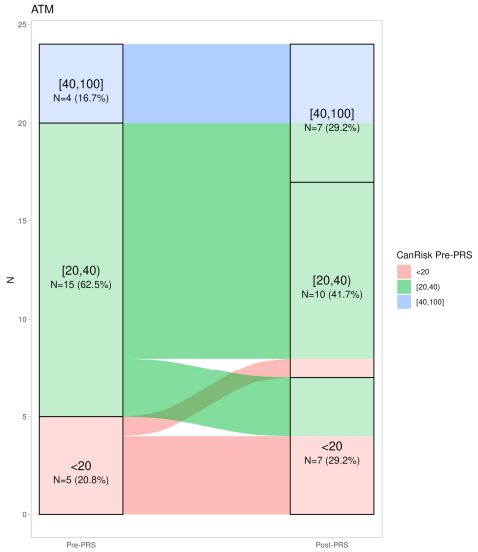
933 women enrolled in the trial
Results on 633 available

214 (33.8%) PV Carriers with median age of **41 years** at assessment

ATM: 24 *CHEK2:* 54
BRCA1: 54 *BRCA2:* 73
PALB2: 9

CanRisk based lifetime and 10-year breast cancer risk estimated before and after PRS

Lifetime risk categorized as average (<20%), moderate (20-40%) and high (>40%) risk



PRS:

Most helpful for ATM and *CHEK2*

Limited clinical utility in high-risk genes such as *BRCA1* or *BRCA2.*

	ATM, n=24	*BRCA1, n=54*	*BRCA2, n=73*	*CHEK2, n=54*	*PALB2, n=9*
N (%) of Individuals with shift in risk categories	7 (29%)	0	3 (4%)	9 (17%)	1 (11%)

Presented at the SABCS 2025 Meeting

VANDERBILT-INGRAM CANCER CENTER

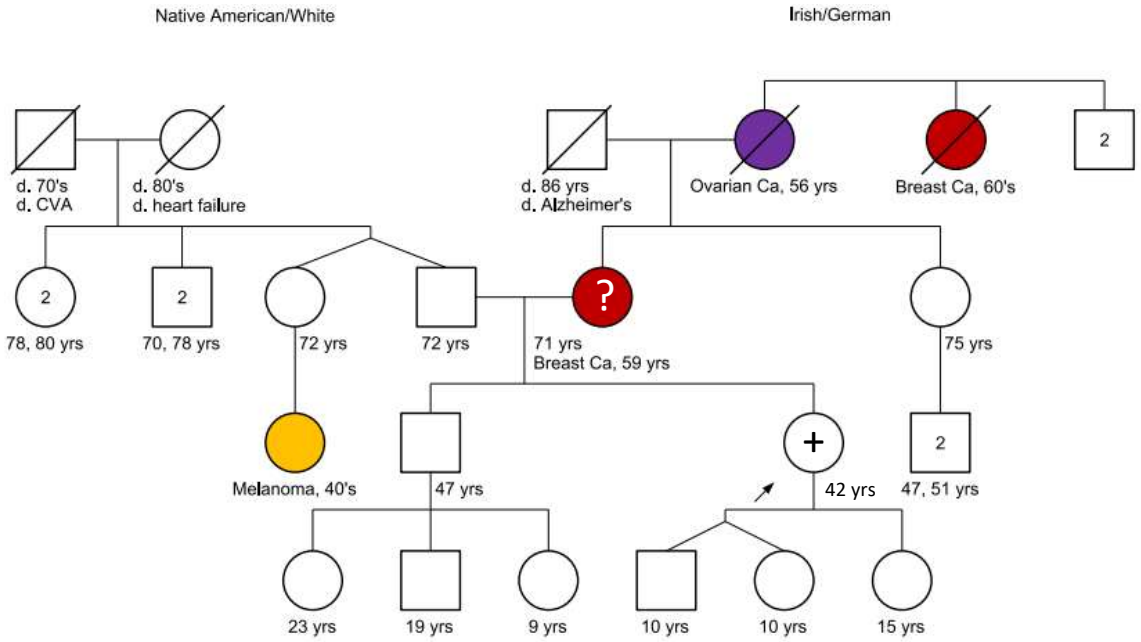
Current NCCN Guidelines:

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- There are significant limitations in interpretation of polygenic risk scores (PRS). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including diverse populations. See Discussion.

Family 6

- 42 y.o. unaffected female with family history of breast and ovarian cancers
- Genetic testing: *ATM+*
- Mother not yet tested (would be useful to refine risks)
- Management:
  - High risk breast screening
- CanRisk: ~30% lifetime risk of breast cancer (with mother's variant status unknown)



ATM c.6976-2A>C (pathogenic)

Polling Question

Which of the following could affect breast cancer risks in this *ATM* carrier?

A. Breast density

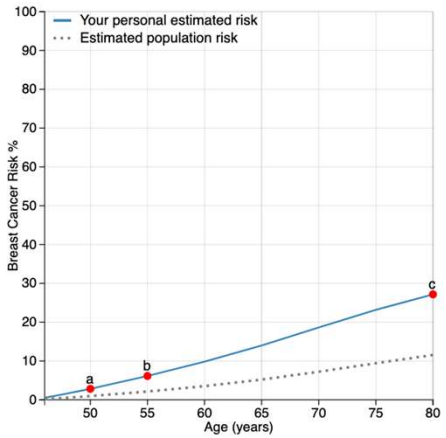
B. Polygenic risk score

C. Family history of breast cancer

D. All of the above

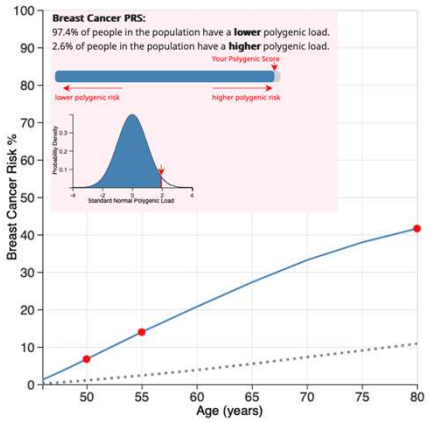
CanRisk Estimates in ATM

Mother – *ATM* Unknown



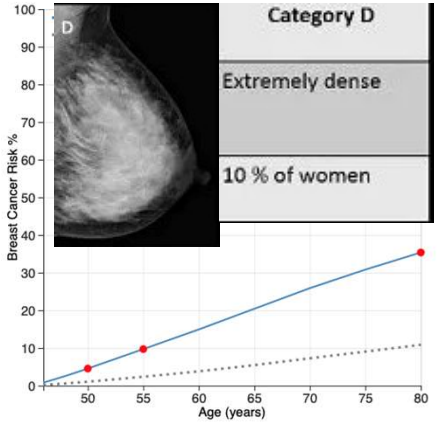
Estimated breast cancer risk:
a) Next 5-year risk is 2.8%
b) Next 10-year risk is 6.1%
c) Risk to 80 is 27.2%

Mother – *ATM* Unknown, high PRS



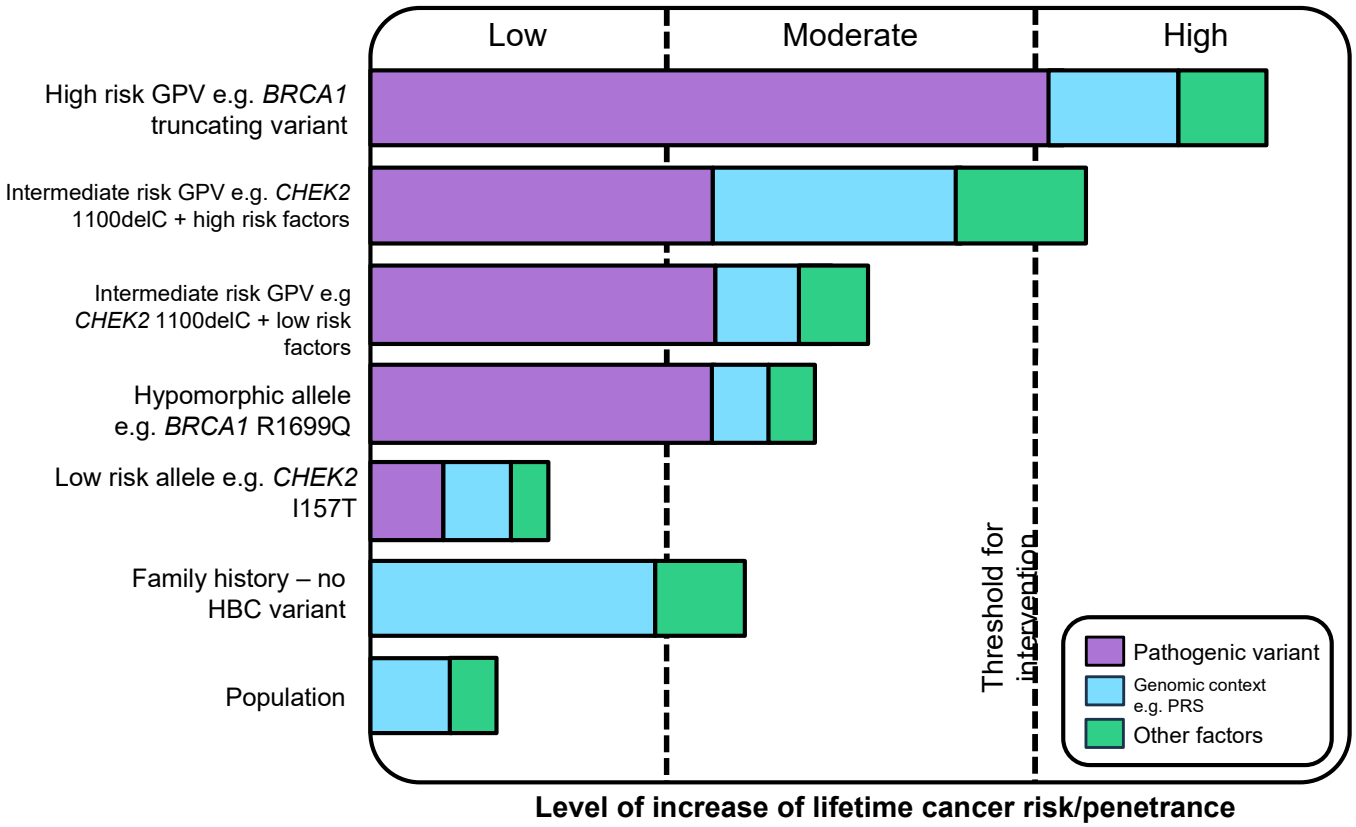
Estimated breast cancer risk:
a) Next 5-year risk is 6.7%
b) Next 10-year risk is 13.9%
c) Risk to 80 is 41.6%

Mother – *ATM* Unknown, dense breasts



Estimated breast cancer risk:
a) Next 5-year risk is 4.5%
b) Next 10-year risk is 9.7%
c) Risk to 80 is 35.4%

Individualized cancer risk assessment based on multiple factors



Pal T, et al. Consideration of inherited cancer risk on a continuum: Genet Med. 2026 Jan 30:101659. Epub ahead of print. PMID: 41618953.

VANDERBILT-INGRAM CANCER CENTER

ctDNA (MCED)…early detection?

Clinical Validation
- positive predictive value has been validated

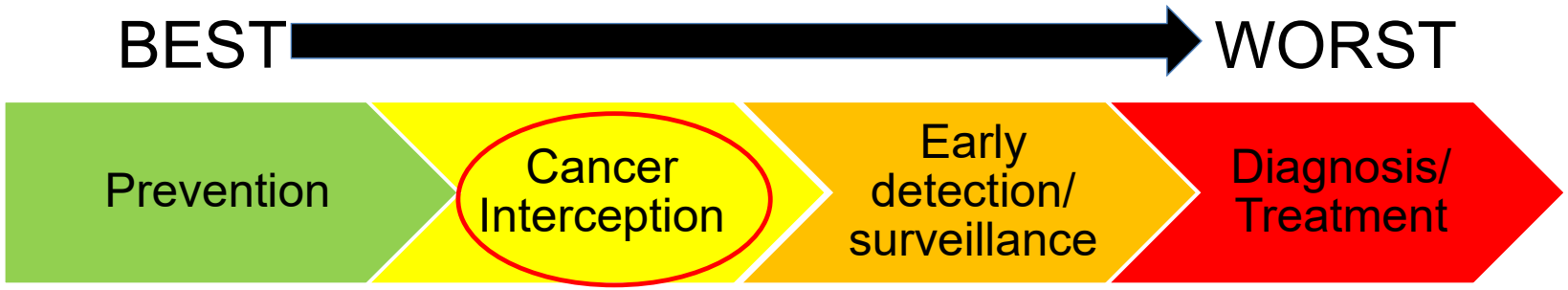
≠

Clinical Utility
- show that we can do something useful with this information

NCCN Principles of Cancer Risk Assessment and Counseling

For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered in the setting of prospective clinical trials, because the **sensitivity, false-positive rates, and positive predictive value** of ctDNA tests for early-stage disease, which are **needed to derive clinical utility** and determine clinical validity, are **not fully defined**.
The psychological impact of ctDNA testing remains unknown.

The Best Way to Treat Cancer



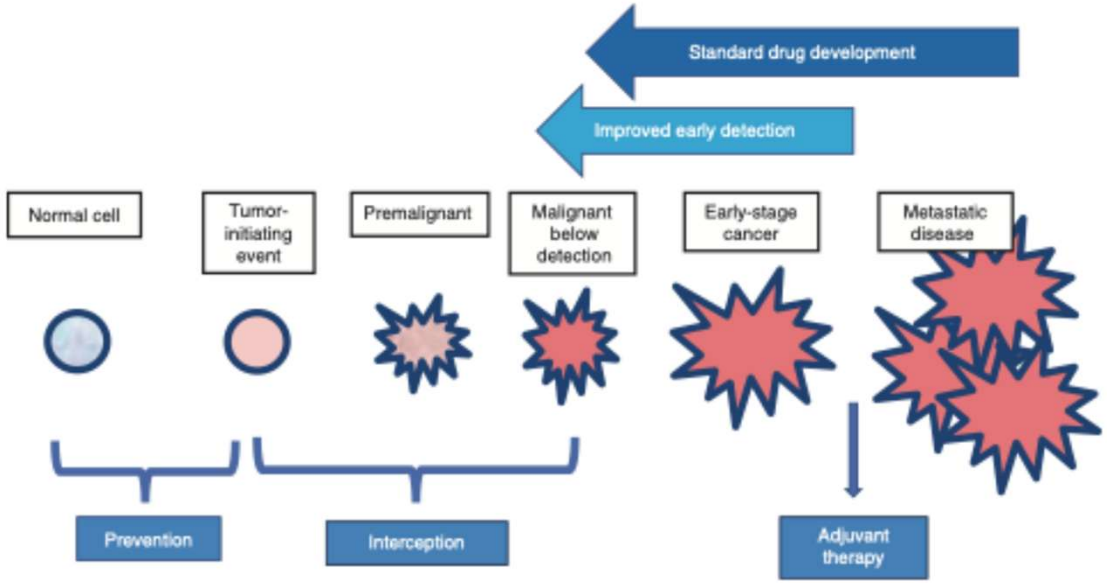
…an emerging field that aims to stop the oncogenic process by targeting and eliminating cells during the precancerous stage, before they develop into invasive cancer

IN FOCUS

Advancing Cancer Interception

Susan M. Domchek[1,2,3] and Robert H. Vonderheide[2,3]

Summary: Rapid advances in technology and therapeutics, along with better methods to discern who is at risk for cancer by genetic testing and other means, has enabled the development of cancer interception. Targeted therapies and "immuno-interception" may eliminate premalignant lesions and require clinical trial and treatment paradigms altogether distinct from current approaches.



Phase 1 vaccine trial (for cancer interception) led by Dr. Susan Domchek completed enrollment of *BRCA1/2* carriers last year; now in observation phase…eagerly awaiting results.

Susan M. Domchek, Robert H. Vonderheide; Advancing Cancer Interception. Cancer Discov 1 April 2024; 14 (4): 600–604. https://doi.org/10.1158/2159-8290.CD-24-0015

VANDERBILT-INGRAM CANCER CENTER

In Conclusion…

Many individuals with inherited cancer remain unidentified

- Despite discovery of *BRCA1/2* over 3 decades ago!

Cancer risk management

- Personalize risks to guide management
- *BRCA1/2*: HRT can be used in unaffected carriers

Delivery of genetic counseling and testing

- Need to scale up services with expanding test indications

Expect forthcoming advances in many areas:

- E.g., PRS, MCED tests, Cancer Interception

Thank you for your attention!
Questions?

CONTACT INFO:

Tuya.Pal@vumc.org

@TuyaPalMD

Follow @inheritedcancer to stay informed:

Website: https://inheritedcancer.net

NCI CCC

VANDERBILT-INGRAM CANCER CENTER

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal