# GENETICS: Determining and Reducing the Risk of Cancer

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# Agenda/Objectives

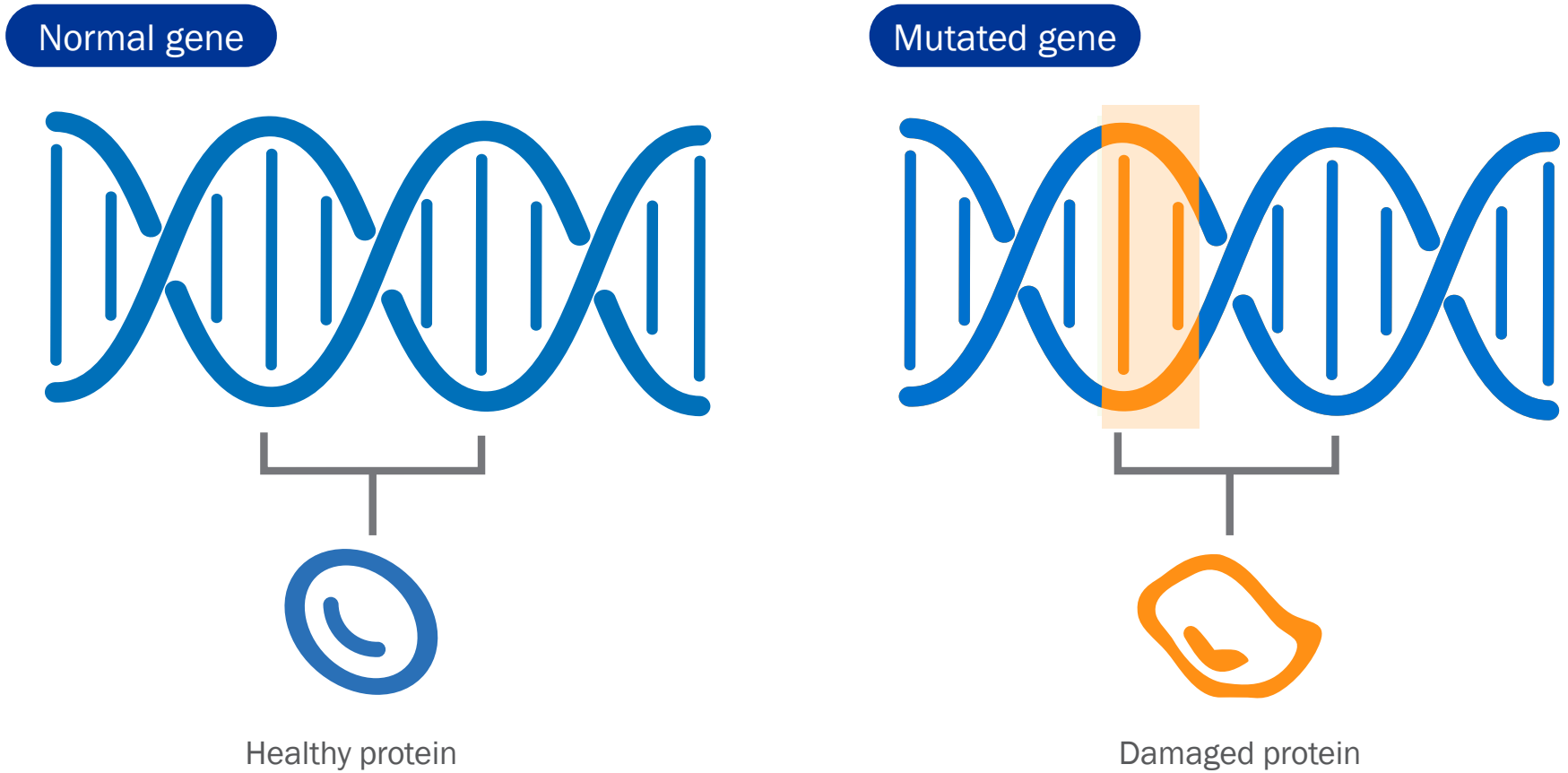
Discuss the role of genetics in cancer

Review strategies for identifying and stratifying hereditary cancer risks

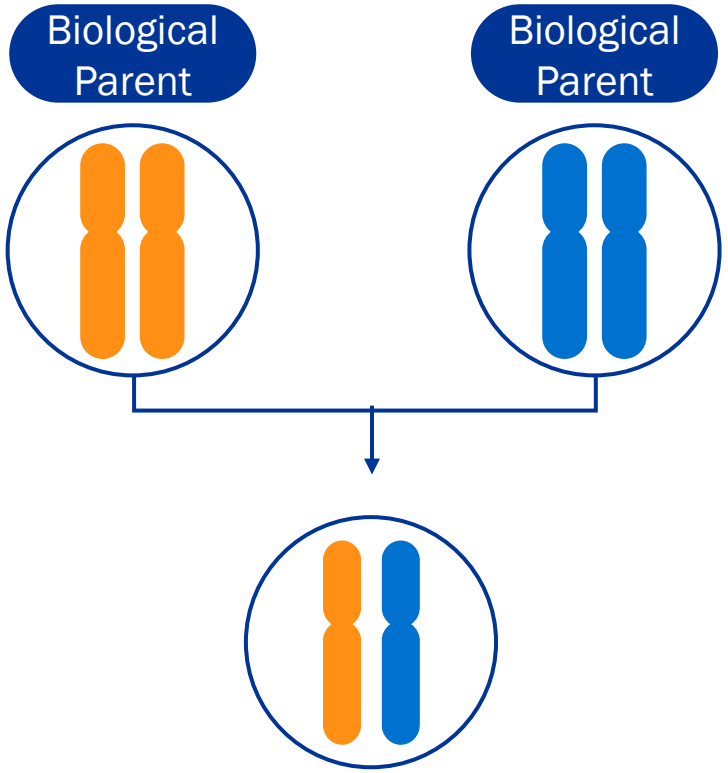
Illustrate best practices for collecting cancer history and constructing pedigrees

Summarize the process for testing and informed consent

# What happens when there is a genetic mutation?

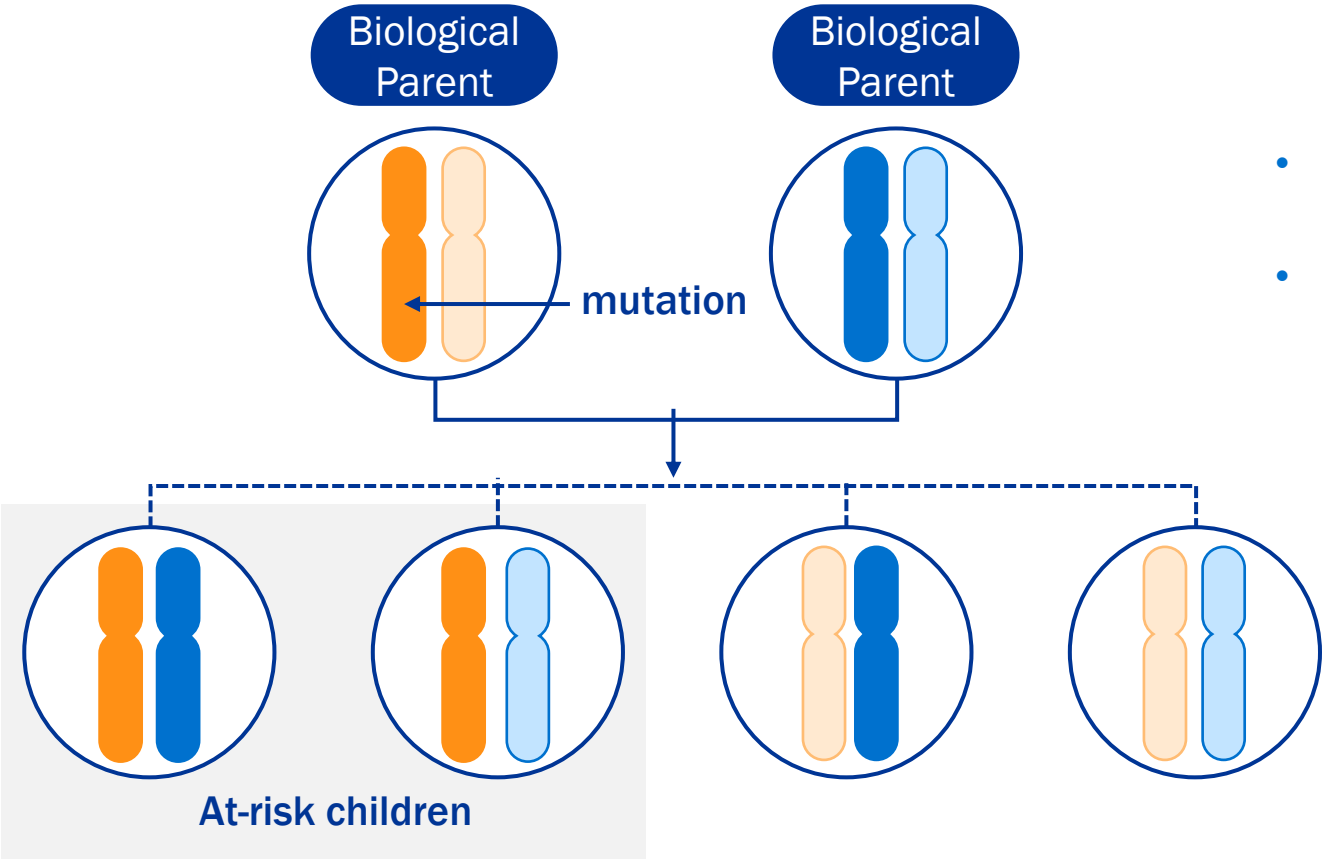


# How are genes inherited?



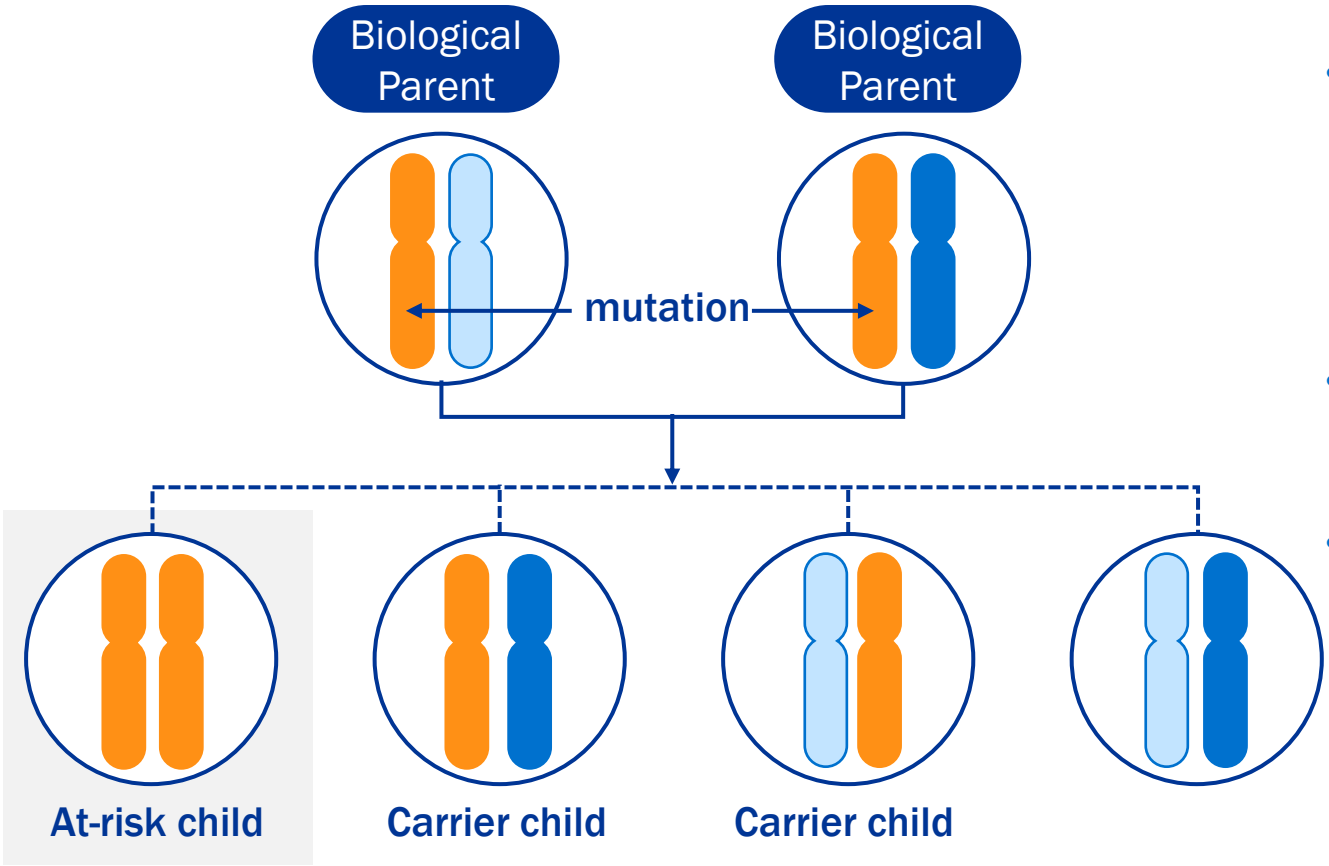

**One gene inherited from each biological parent**

# Autosomal dominant inheritance



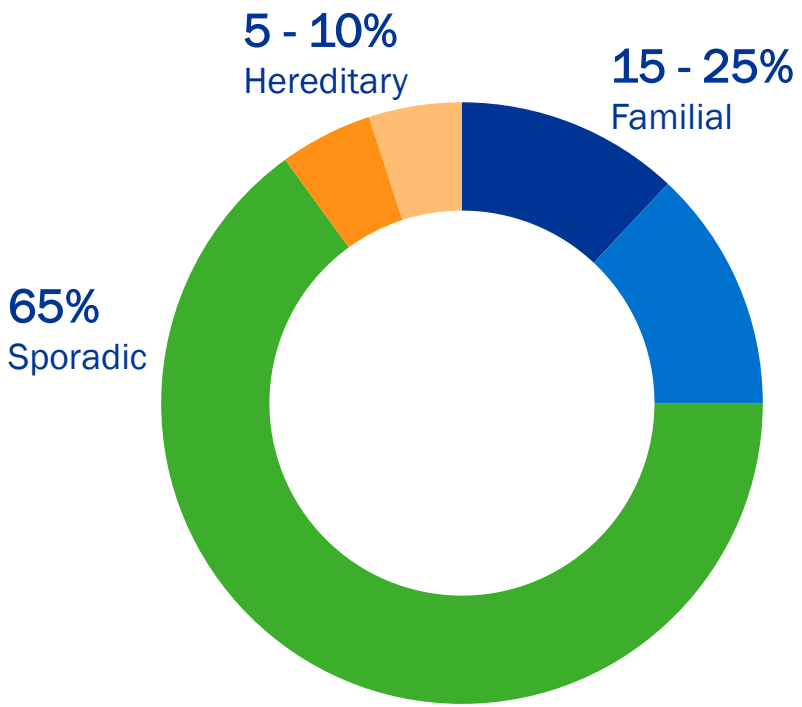

- 50% chance of child inheriting mutation
- Risk of inheritance is the same for sons and daughters

# Autosomal recessive inheritance

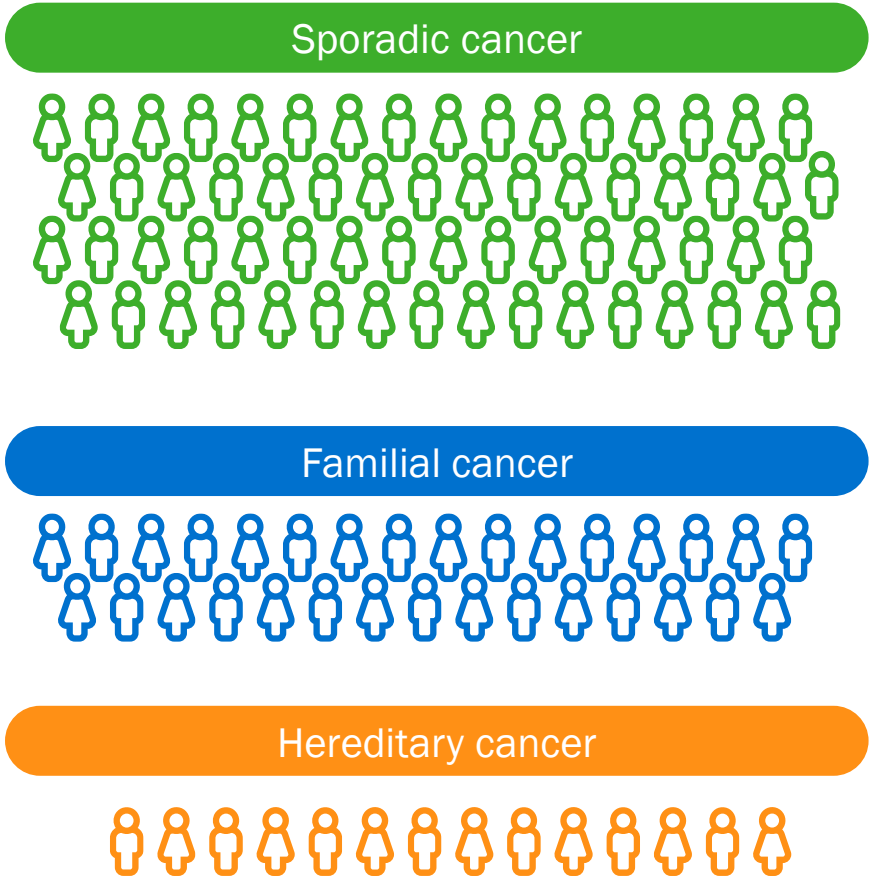



- Only at risk of inheriting the condition (“being affected”) if both parents are carriers or affected
- 25% chance of child inheriting both mutations
- Risk of inheritance is same for sons and daughters

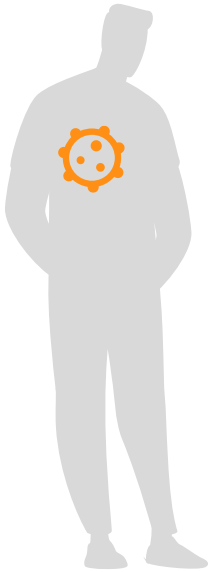
# Cancer is generally hereditary, familial, or sporadic




**Understanding which category your cancer falls into will help guide the management of your risk better.**

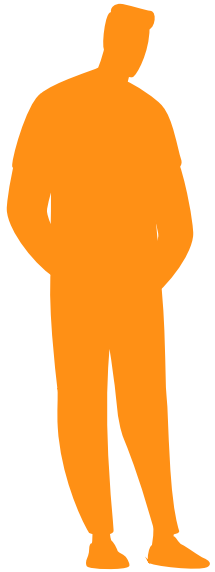


# Somatic vs. germline mutation



## Somatic mutation

- Every cancer has many somatic mutations.
- A somatic mutation is a change in the gene that arose in the tumor and is confined to the tumor.
- Most cancer is sporadic (i.e., it happened by chance).



## Germline mutation

- A germline mutation is a change in the gene that was inherited and therefore causes an increased risk for cancer.
- This is also known as hereditary cancer.
- Only around 10% of cancer is hereditary.
  - *IN THE WKCC SETTING ~18% OF PATIENTS ARE POSITIVE*

# Updated ASCO Guidelines for Germline Testing in Cancer Patients

## The American Society of Clinical Oncology (ASCO) published guidelines[1] to help guide the use of multigene germline testing for patients with cancer:

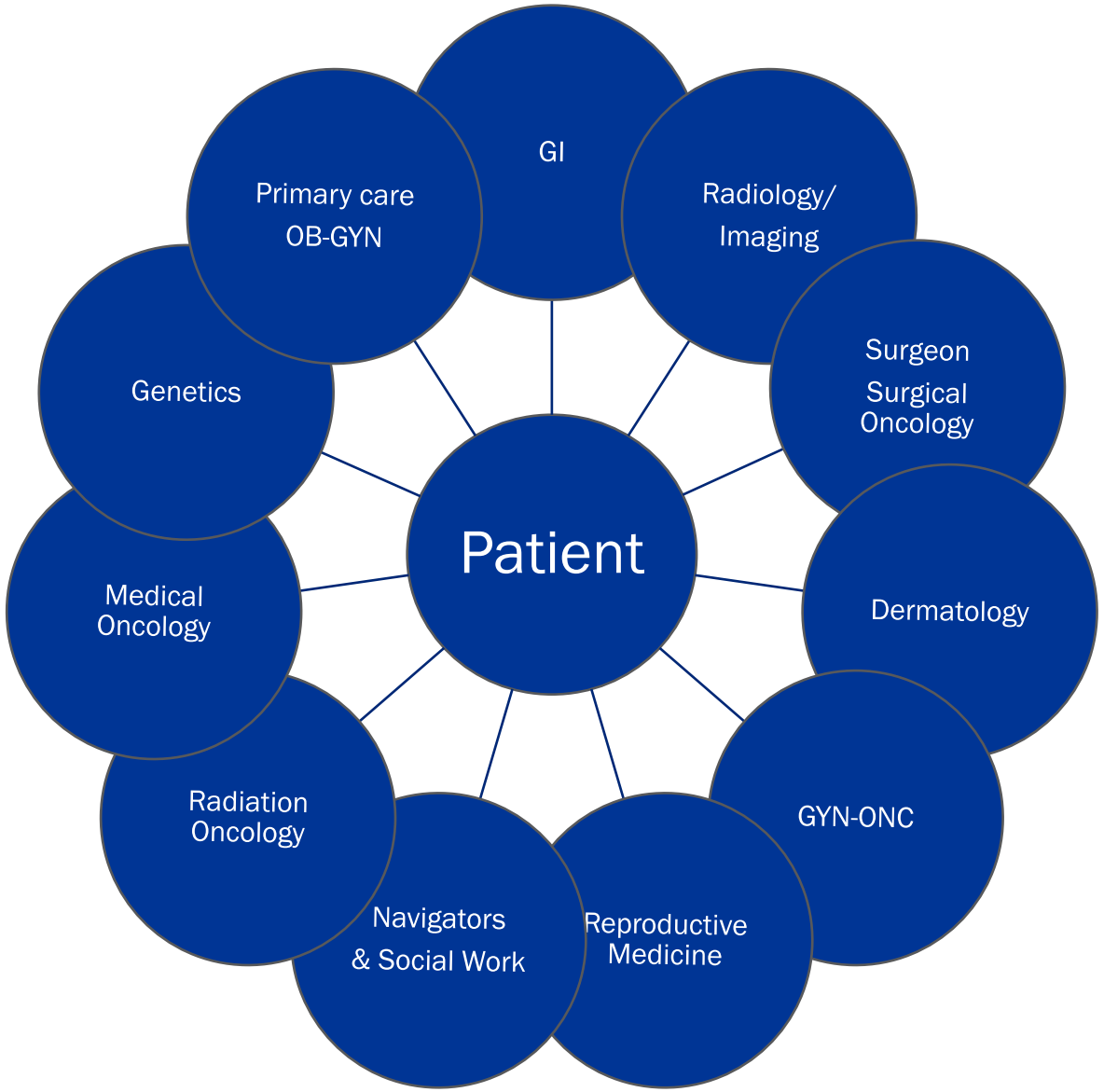
1. **Multigene Testing (MGT):** A thorough personal and family cancer history should be recorded for risk assessment and patients should undergo MGT if more than one gene is relevant.
2. **Germline Testing Importance:** Germline testing should be offered to patients who meet criteria, regardless of tumor testing results.
3. **Gene Inclusion:** ASCO "strongly recommends" most genes that are included in 11 core cancers.
4. **Germline Testing Based on Tumor Results:** Germline testing should be offered after finding a pathogenic variant (PV) in certain genes identified by tumor testing.

**8-10%**
**of germline PVs are missed on tumor testing[1]**

**The expert panel noted the increasing clinical utility of germline testing as precision oncology rapidly advances and more treatments targeting germline mutations are approved and recommended. These experts encouraged more oncologist-driven testing to better ensure that patients and their family members receive appropriate and beneficial testing.**

1. Nadine Tung et al., Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. JCO 42, 2599-2615(2024). DOI:10.1200/JCO.24.0066

# Circle of Care



# WHY Genetic testing?

- Provides more precise answers
- Potentially reduces the risk of "delay in diagnosis" lawsuits
- Many different practice guidelines support genetic testing

**American Society of Clinical Oncology**

*"Genetic testing can have implications for management of the cancer patients, including: surgical treatment, chemotherapy choices, prognosis and risk for additional cancers. It is therefore important to assess the risk of a hereditary syndrome at diagnosis, at decision points along the cancer treatment trajectory and again when entering survivorship or surveillance."*

**The American Society of Breast Surgeons**

*"Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing...*

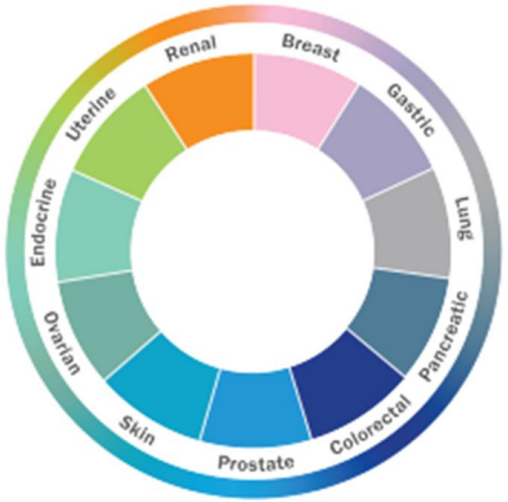
***Genetic Testing should be made available to all patients with a personal history of breast cancer"***

ASCO: https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/genetic-testing
ASBrS: https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf

# Guidelines Comparison

| ASBS | ASCO | NCCN |
|---|---|---|
| All patients with a breast cancer diagnosis should be considered for genetic testing | All patients with breast cancer diagnosed ≤65 | All patients with a breast cancer diagnosis ≤50 |
| | All patients with breast cancer and a concerning personal or family history** | All patients with a breast cancer diagnosis and concerning personal or family history:<br>• Personal: Triple-negative breast cancer, Multiple primaries, Lobular breast cancer with history of diffuse gastric cancer, Male breast cancer, Ashkenazi Jewish ancestry<br>Family:<br>• ≥1 family member with ANY: breast ≤50, male breast cancer, ovarian cancer, pancreatic cancer, metastatic/high-risk prostate cancer<br>• ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family |
| | All patients who are candidates for PARPi therapy | All patients who are candidates for PARPi therapy |
| | Informed consent for genetic testing is important, this does not need to be done by a genetic counselor | Informed consent for genetic testing is important, this does not need to be done by a genetic counselor but someone with genetics expertise |

# Common Hereditary Cancer Sites & Genes




| Genes | Breast | Ovarian | Colorectal | Uterine | Skin | Pancreatic | Gastric | Prostate | Renal | Lung | Endocrine | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *BRCA1* | ● | ● | | | | ● | | ● | | | | |
| *BRCA2* | ● | ● | | | ● | ● | | ● | | | | |
| *MLH1, MSH2, MSH6, PMS2, EPCAM* | | ● | ● | ● | ● | ● | ● | ● | | | | ● |
| *APC* | | | ● | | | ● | ● | | | | ● | ● |
| *MUTYH* | | | ● | | | | | | | | | ● |
| *CDK4, CDKN2A (p16INK4a), (p14ARF)* | | | | | ● | ● | | | | | | |
| *TP53* | ● | | ● | ● | ● | ● | ● | ● | ● | | | ● |
| *PTEN* | ● | | ● | ● | ● | | | | ● | | ● | ● |
| *STK11* | ● | ● | ● | ● | | ● | ● | | | ● | | ● |
| *CDH1* | ● | | | | | | ● | | | | | |
| *BMPR1A, SMAD4* | | | ● | | | | ● | | | | | ● |
| *PALB2* | ● | ● | | | | ● | | | | | | |
| *CHEK2* | ● | | ● | | | | | | | | | |
| *ATM* | ● | | | | | ● | | ● | | | | |
| *BARD1* | ● | | | | | | | | | | | |
| *BRIP1* | | ● | | | | | | | | | | |
| *RAD51C, RAD51D* | ● | ● | | | | | | | | | | |
| *POLD1, POLE, GREM1, AXIN2* | | | ● | | | | | | | | | |
| *HOXB13* | | | | | | | | ● | | | | |
| *NTHL1* | ● | | ● | | | | | | | | | |
| *MSH3* | | | ● | | | | | | | | | |
| *FH, FLCN* | | | | | ● | | | | ● | | | ● |
| *MET* | | | | | | | | | ● | | | |
| *TSC1, TSC2* | | | | | | | | | ● | | | ● |
| *SDHA, SDHB, SDHC, SDHD, VHL* | | | | | | | | | ● | | ● | ● |
| *BAP1* | | | | | ● | | | | ● | | | ● |
| *MITF, TERT* | | | | | ● | | | | | | | |
| *CTNNA1* | | | | | | | ● | | | | | |
| *EGFR* | | | | | | | | | | ● | | |
| *MEN1, RET* | | | | | | | | | | | ● | ● |

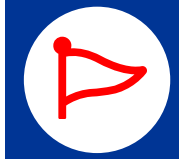
References can be found at
https://myriad.com/gene-table/

# Meeting Professional Guidelines for Genetic Testing

| | |
|---|---|
| Breast | All patients diagnosed with breast cancer |
| Ovarian | All patients diagnosed with ovarian cancer |
| Pancreatic | All patients diagnosed with pancreatic cancer |
| Prostate | All patients diagnosed with metastatic prostate cancer |
| Colorectal | All patients diagnosed with colorectal cancer |
| Endometrial | All patients diagnosed with Uterine cancer |

# Flags for genetic testing

## What are the common traits associated with hereditary cancer?



### Cancer at an early age

At an age younger than the average

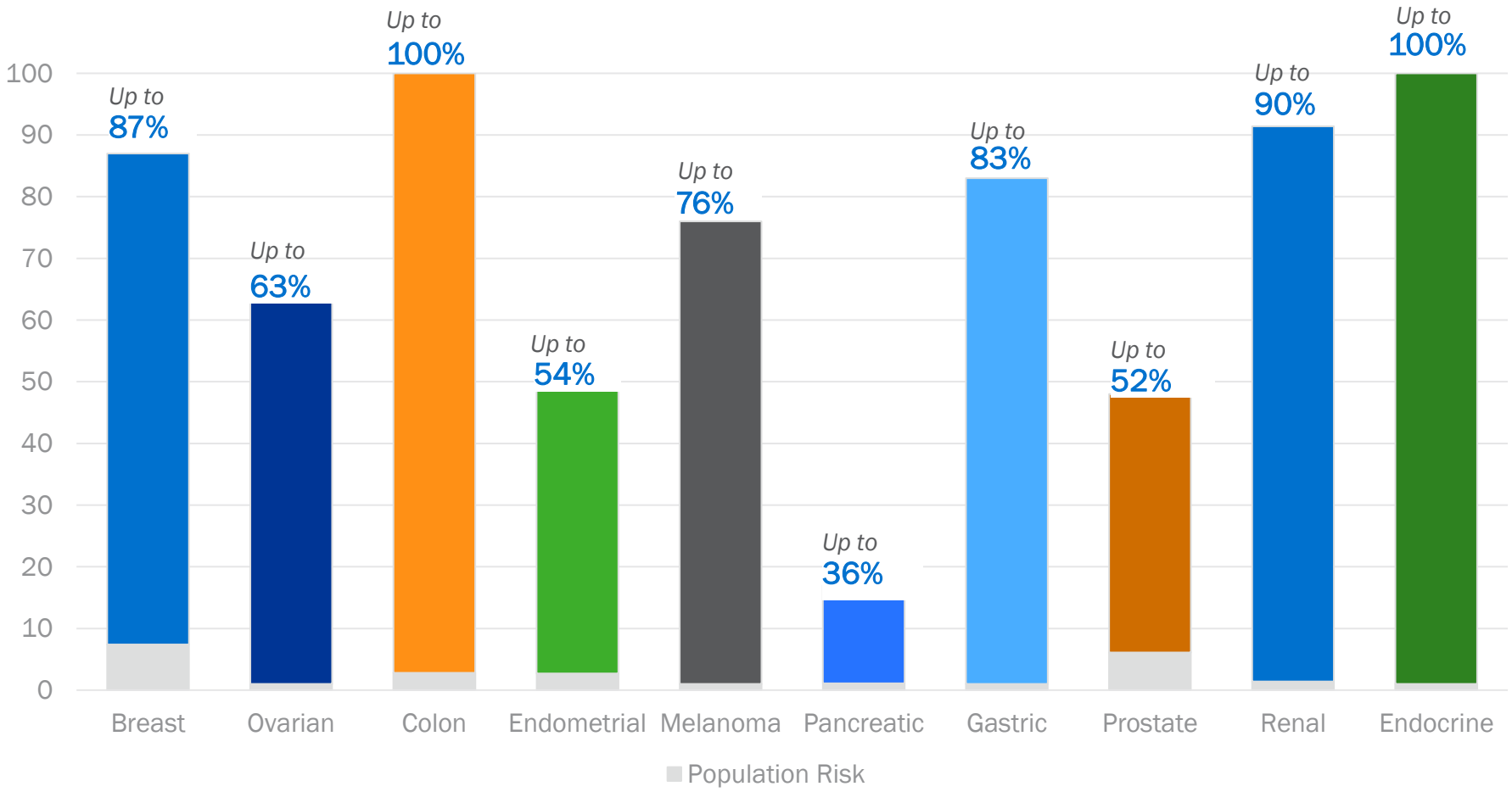
### Certain rare cancers

Such as ovarian, pancreatic, male breast cancer, sarcoma, etc.

### Multiple cancers

Multiple individuals within the family may have cancer. Or, one individual may have multiple cancers

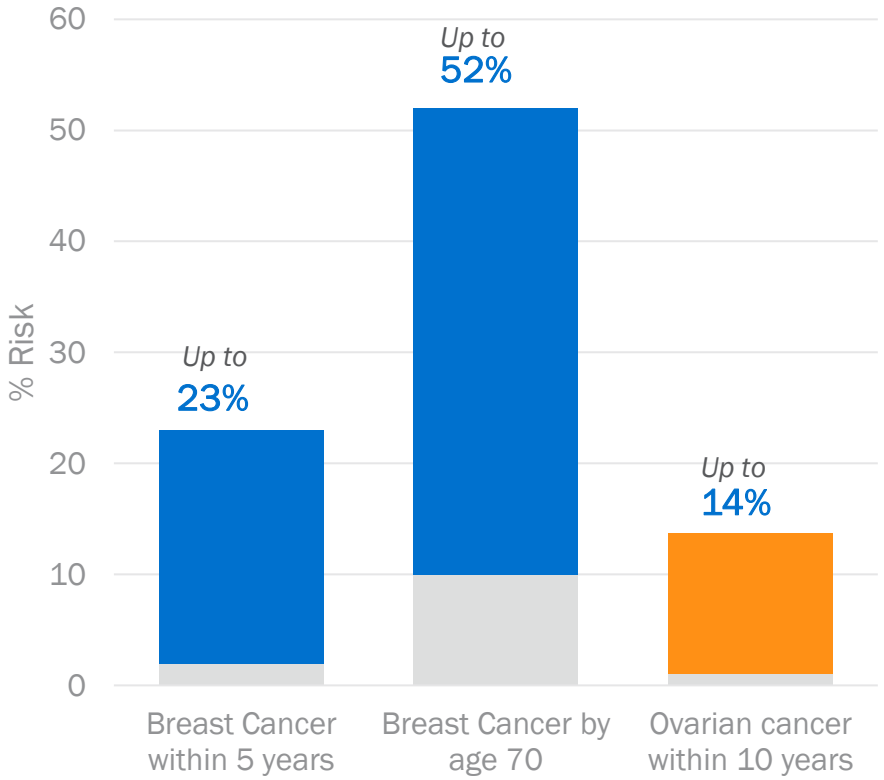
# Lifetime cancer risk for patients with hereditary cancer



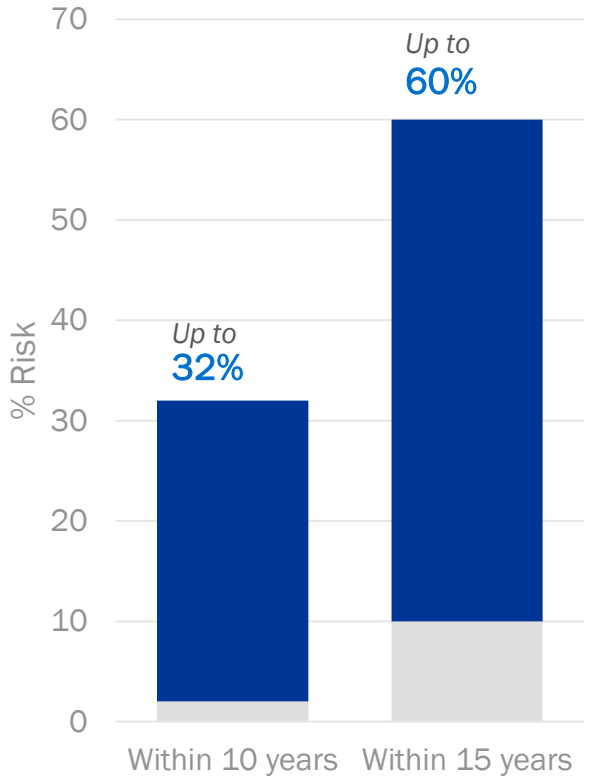

References can be found at https://myriad.com/gene-table/

# Second primary cancer risks for patients with hereditary cancer syndromes

## Patients with genetic mutations in *BRCA1/2*

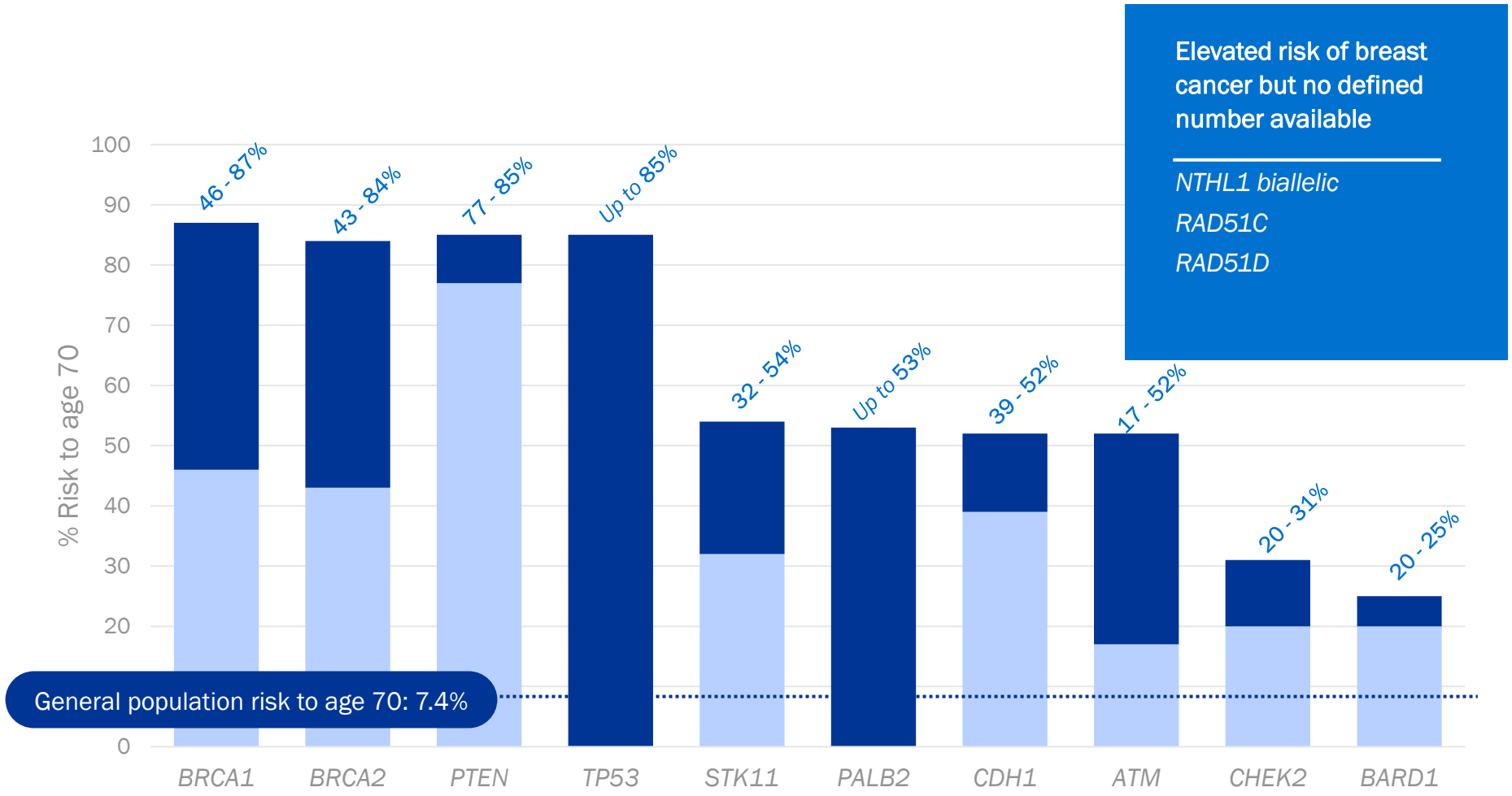



## Patients with genetic mutations in Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM)



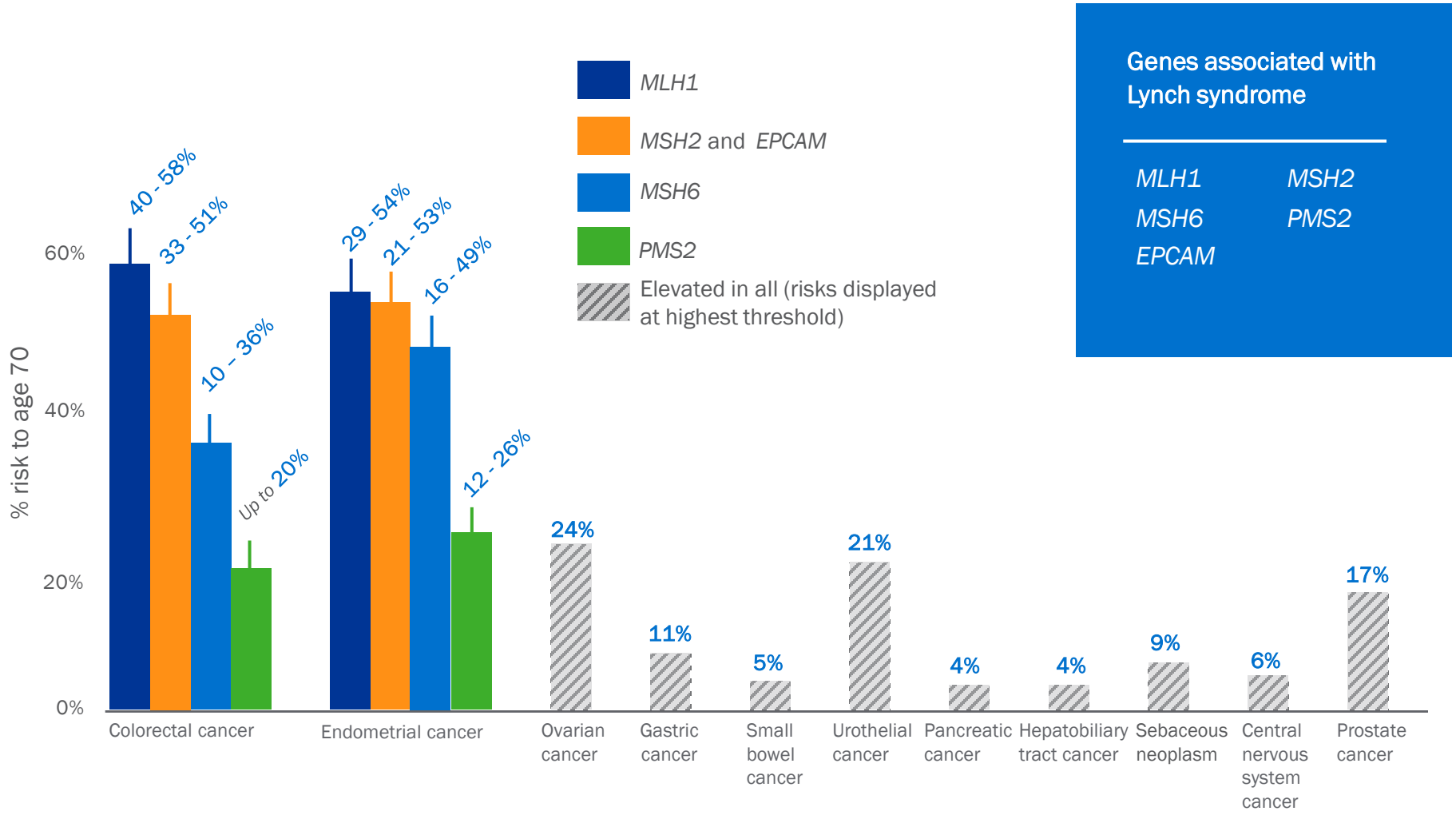

References can be found at https://myriad.com/gene-table/

# Genes associated with breast cancer risk and their associated risk ranges




References can be found at https://myriad.com/gene-table/

# Cancer risks associated with Lynch syndrome




**Genes associated with Lynch syndrome**

| | |
|---|---|
| *MLH1* | *MSH2* |
| *MSH6* | *PMS2* |
| *EPCAM* | |

References can be found at https://myriad.com/gene-table/

# NCCN Guidelines

- **Treatment by Cancer Type**
- **Detection, Prevention, and Risk Reduction**
- **Supportive Care**
- **Specific Populations**
- **Guidelines for Patients**
- **Guidelines With Evidence Blocks**
- **NCCN Framework For Resource Stratification**
- **Harmonized Guidelines**

## Detection, Prevention, and Risk Reduction

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are posted with the latest update date and version number.

**Breast Cancer Risk Reduction**
Version: 1.2025

**Breast Cancer Screening and Diagnosis**
Version: 2.2024

**Colorectal Cancer Screening**
Version: 1.2024

**Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
Version: 3.2024

**Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric**
Version: 1.2024

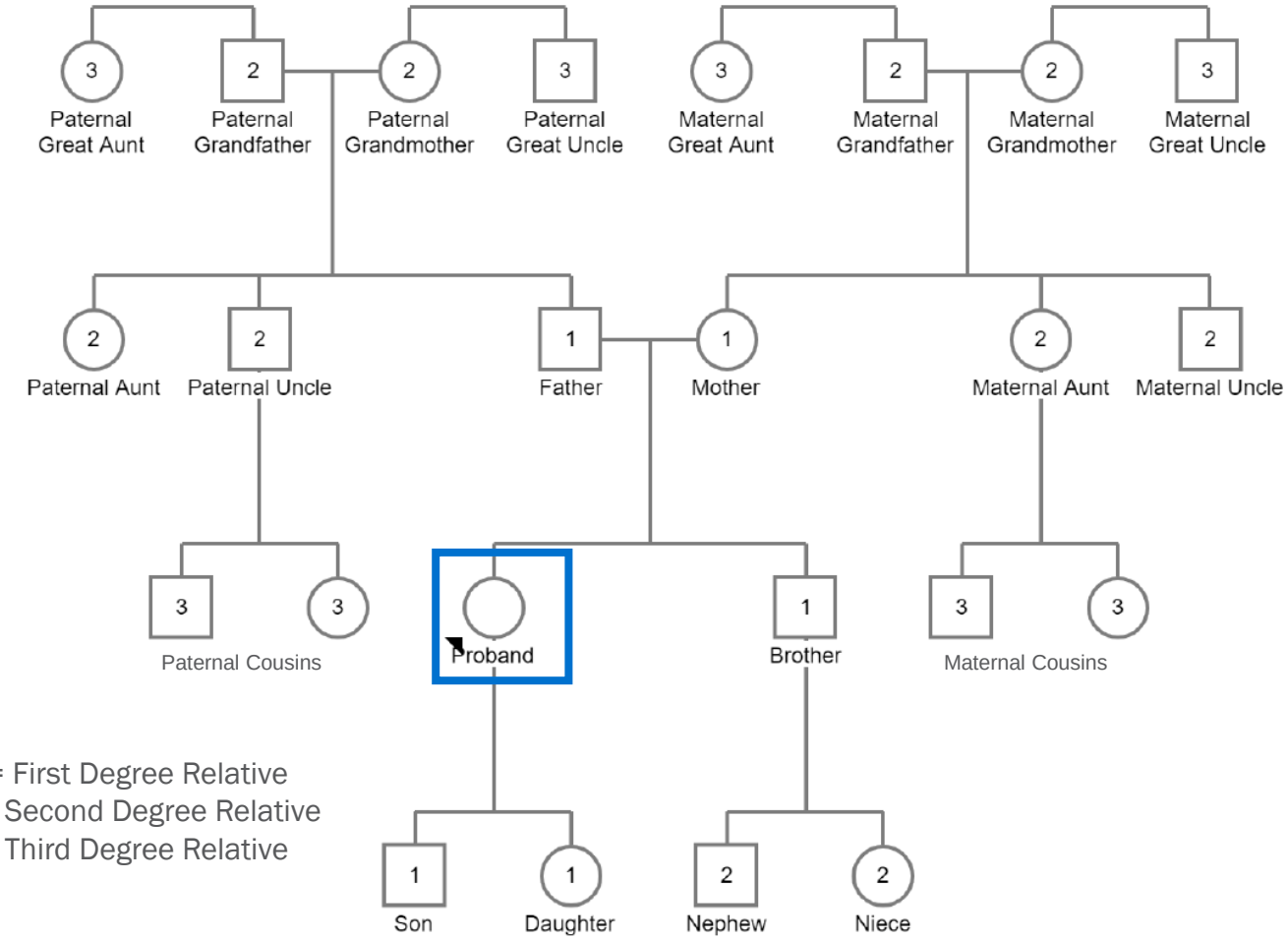
**Lung Cancer Screening**
Version: 2.2024

**Prostate Cancer Early Detection**
Version: 2.2024

# PEDIGREE RELATIONSHIPS

Collecting Family History

- ❑ 1st, 2nd & 3rd degree minimum family member
- ❑ Blood relatives only (includes half siblings)
- ❑ Male/Female (ASAB)
- ❑ Type of cancer
- ❑ Age at diagnosis
- ❑ Previous hereditary cancer testing (germline)
- ❑ Consanguinity
- ❑ Ancestry




1 = First Degree Relative
2= Second Degree Relative
3= Third Degree Relative

Image courtesy Breanna Roscow, MS, CGC

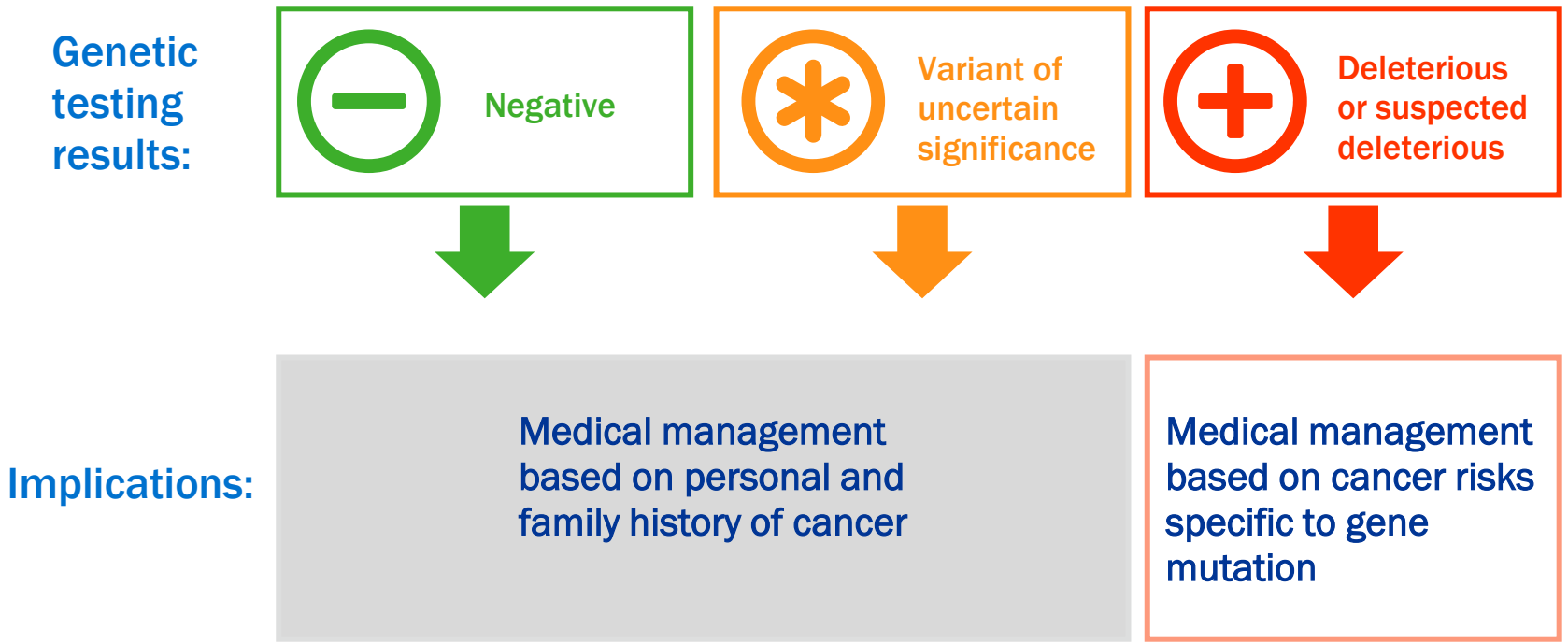
# Special Populations, Barriers to Care, Disparities

- BRCA1/2 prevalence 1 in 400 in general population vs. 1 in 40 in individuals of Ashkenazi Jewish descent.
  - Commonly “founder mutations” in BRCA1/2.
- Decreased awareness, access, referrals, and uptake for genetic testing in Black and Hispanic populations.
- Lack of genetic data in ethnically diverse populations.
- Higher rates for variants of uncertain significance (VUS) in non-white populations.
- In some cancer types, Black individuals are diagnosed younger and have lower rates of survival.

National Cancer Institute (NCI).
https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet

# GINA: Genetic Information Non-discrimination Act

# What do these results mean?



# Medical management options for consideration when the test is positive

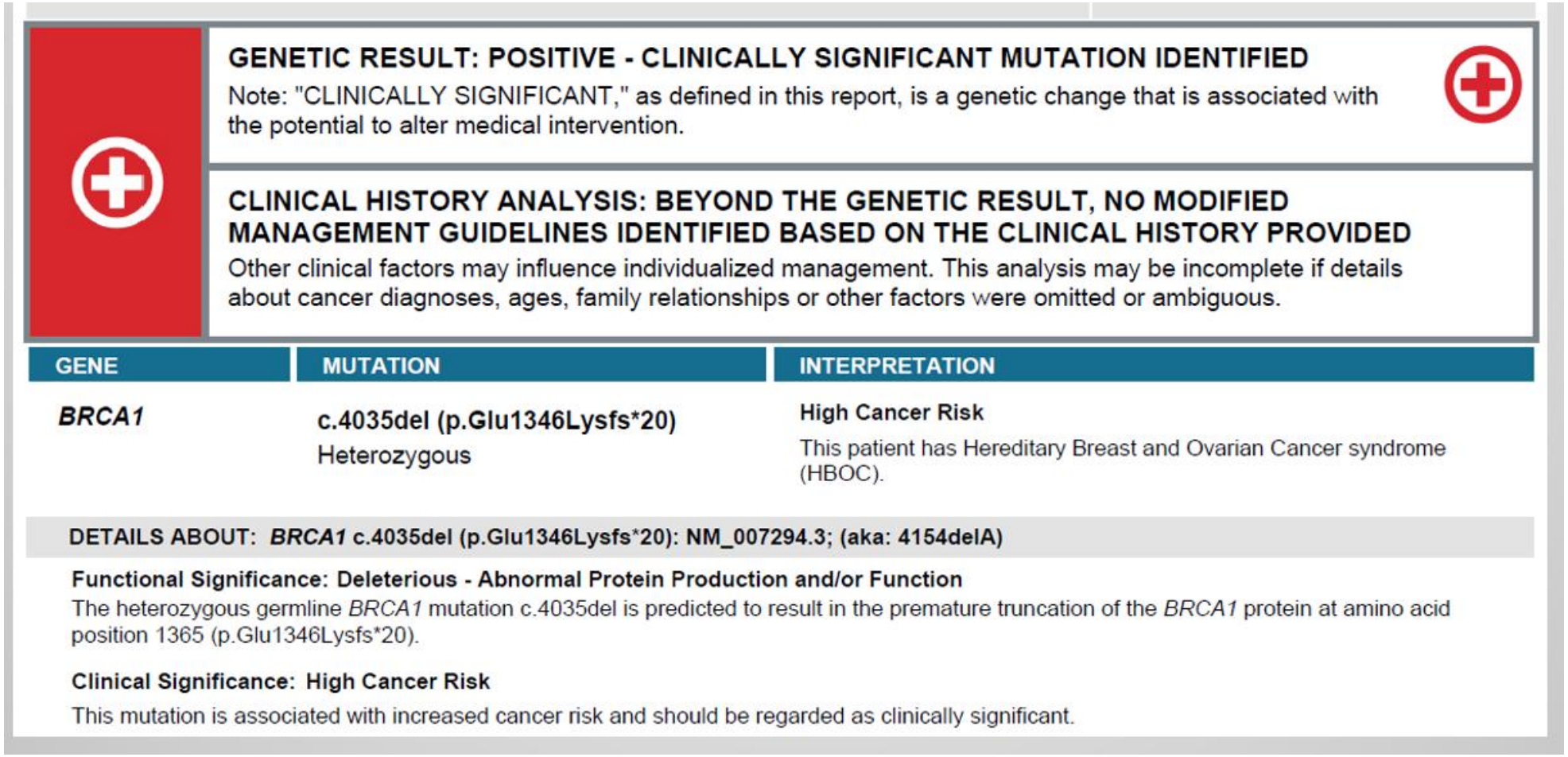
Hereditary cancer risk

Familial cancer risk

General population cancer risk

- Avoidance of risk factors
- Increased surveillance
- Risk-reducing agents
- Risk-reducing surgery

# Result – pathogenic/positive



**GENETIC RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED**

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

**CLINICAL HISTORY ANALYSIS: BEYOND THE GENETIC RESULT, NO MODIFIED MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED**

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

| GENE | MUTATION | INTERPRETATION |
|---|---|---|
| ***BRCA1*** | **c.4035del (p.Glu1346Lysfs*20)**<br>Heterozygous | **High Cancer Risk**<br>This patient has Hereditary Breast and Ovarian Cancer syndrome (HBOC). |

**DETAILS ABOUT: *BRCA1* c.4035del (p.Glu1346Lysfs*20): NM_007294.3; (aka: 4154delA)**

**Functional Significance: Deleterious - Abnormal Protein Production and/or Function**

The heterozygous germline *BRCA1* mutation c.4035del is predicted to result in the premature truncation of the *BRCA1* protein at amino acid position 1365 (p.Glu1346Lysfs*20).

**Clinical Significance: High Cancer Risk**

This mutation is associated with increased cancer risk and should be regarded as clinically significant.

# Cancer Risks

| CANCER TYPE | CANCER RISK | RISK FOR GENERAL POPULATION | RELATED TO |
|---|---|---|---|
| **FEMALE BREAST** | | | |
| To age 50 | 28%-51% | 1.9% | *BRCA1* |
| To age 70 | 46%-87% | 7.1% | *BRCA1* |
| Second primary within 5 years of first breast cancer diagnosis | 13%-20% | 2% | *BRCA1* |
| **OVARIAN** | | | |
| To age 50 | 8%-23% | 0.2% | *BRCA1* |
| To age 70 | 39%-63% | 0.7% | *BRCA1* |
| Ovarian cancer within 10 years of a breast cancer diagnosis | 12.7% | <1.0% | *BRCA1* |
| **PANCREATIC** | | | |
| To age 80 | Elevated risk | 1% | *BRCA1* |

# Breast Screening & Risk Management

| FEMALE BREAST | | | |
|---|---|---|---|
| Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent breast self-examination (BSE) may facilitate breast awareness.[2] | 18 years | NA | *BRCA1* |
| Clinical breast examination[2] | 25 years | Every 6 to 12 months | *BRCA1* |
| Breast MRI with contrast and/or Mammography with consideration of tomosynthesis[2] | Age 25 for MRI, or if MRI is unavailable, mammography with consideration of tomosynthesis. Age 30 for both MRI and mammography. Individualize to a younger age if a relative has been diagnosed younger than age 30. | Annually | *BRCA1* |
| Consider investigational screening studies within clinical trials.[2] | Individualized | NA | *BRCA1* |
| Consider risk-reducing mastectomy.[2] | Individualized | NA | *BRCA1* |
| Consider options for breast cancer risk-reduction agents (i.e. tamoxifen).[2] | Individualized | NA | *BRCA1* |

# Other Screening & Risk Management

| PROCEDURE | AGE TO BEGIN | FREQUENCY (Unless otherwise indicated by findings) | RELATED TO |
|---|---|---|---|
| **OVARIAN** | | | |
| Bilateral salpingo-oophorectomy[2] | 35 to 40 years, upon completion of childbearing | NA | *BRCA1* |
| Consider transvaginal ultrasound and CA-125 measurement. Consider investigational screening studies within clinical trials.[2] | 30 to 35 years | Individualized | *BRCA1* |
| Consider options for ovarian cancer risk-reduction agents (i.e. oral contraceptives).[1,2] | Individualized | NA | *BRCA1* |
| **PANCREATIC** | | | |
| Currently there are no specific medical management guidelines for pancreatic cancer risk in mutation carriers. | NA | NA | *BRCA1* |

# What this means for family members

Family members can use test results to help identify their own personal risks of cancer.

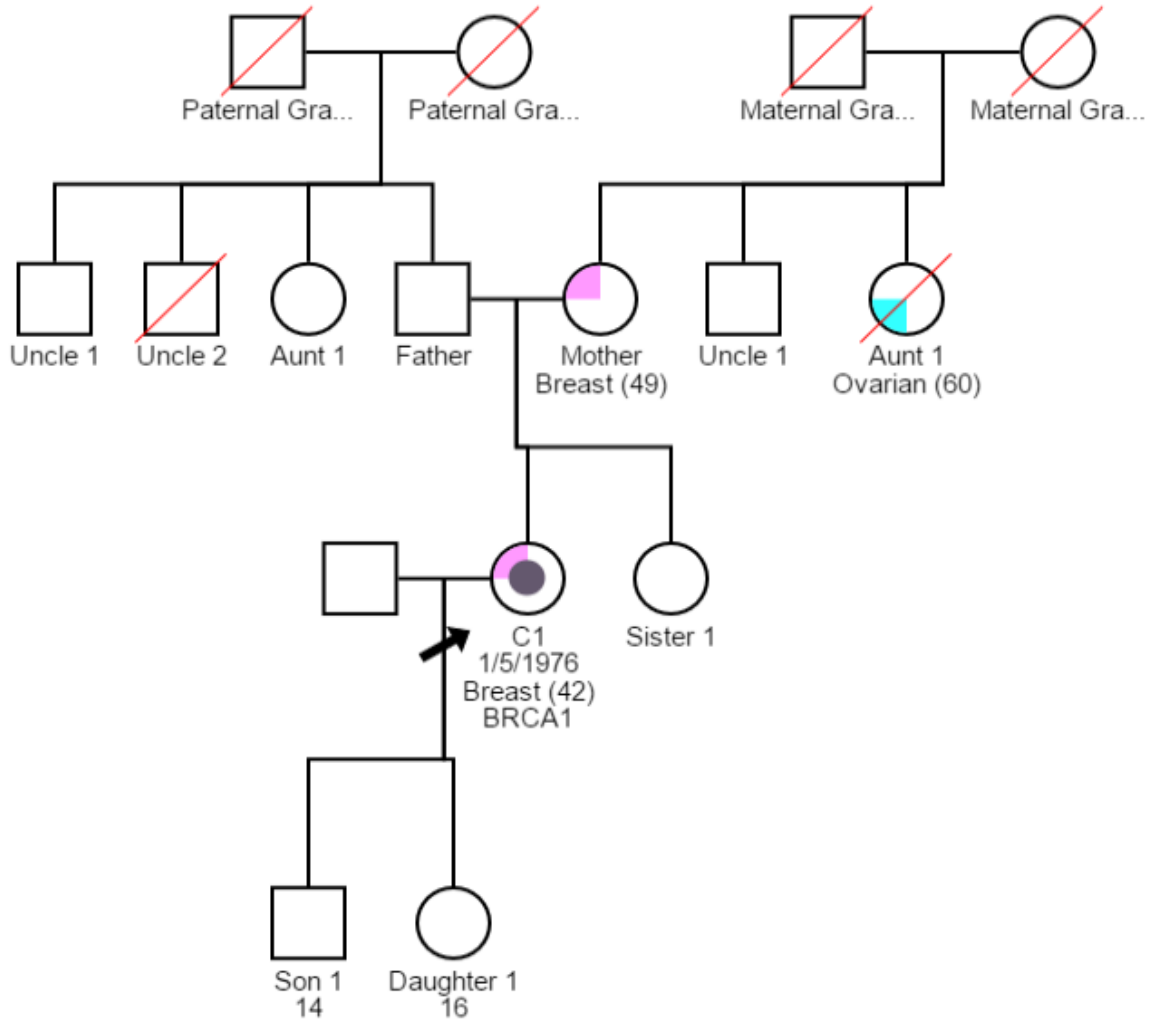
## Positive

Family members should talk to a healthcare professional with expertise in genetics about testing for the known mutation identified.

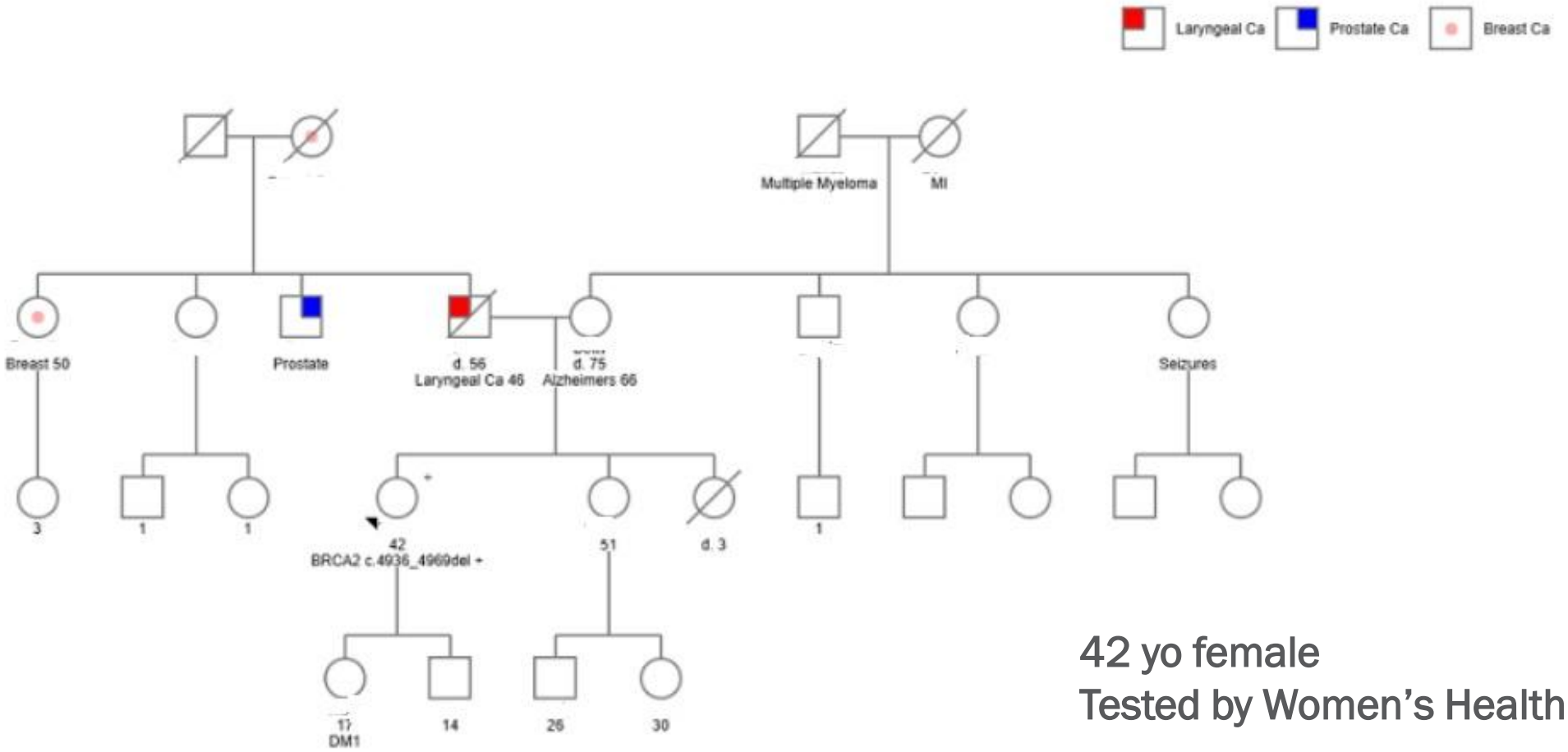
## Negative

The cause of increased cancer risk has still not been identified. Relatives should talk to a genetics professional if testing or increased surveillance is appropriate for them.

# Which family members should be offered testing?

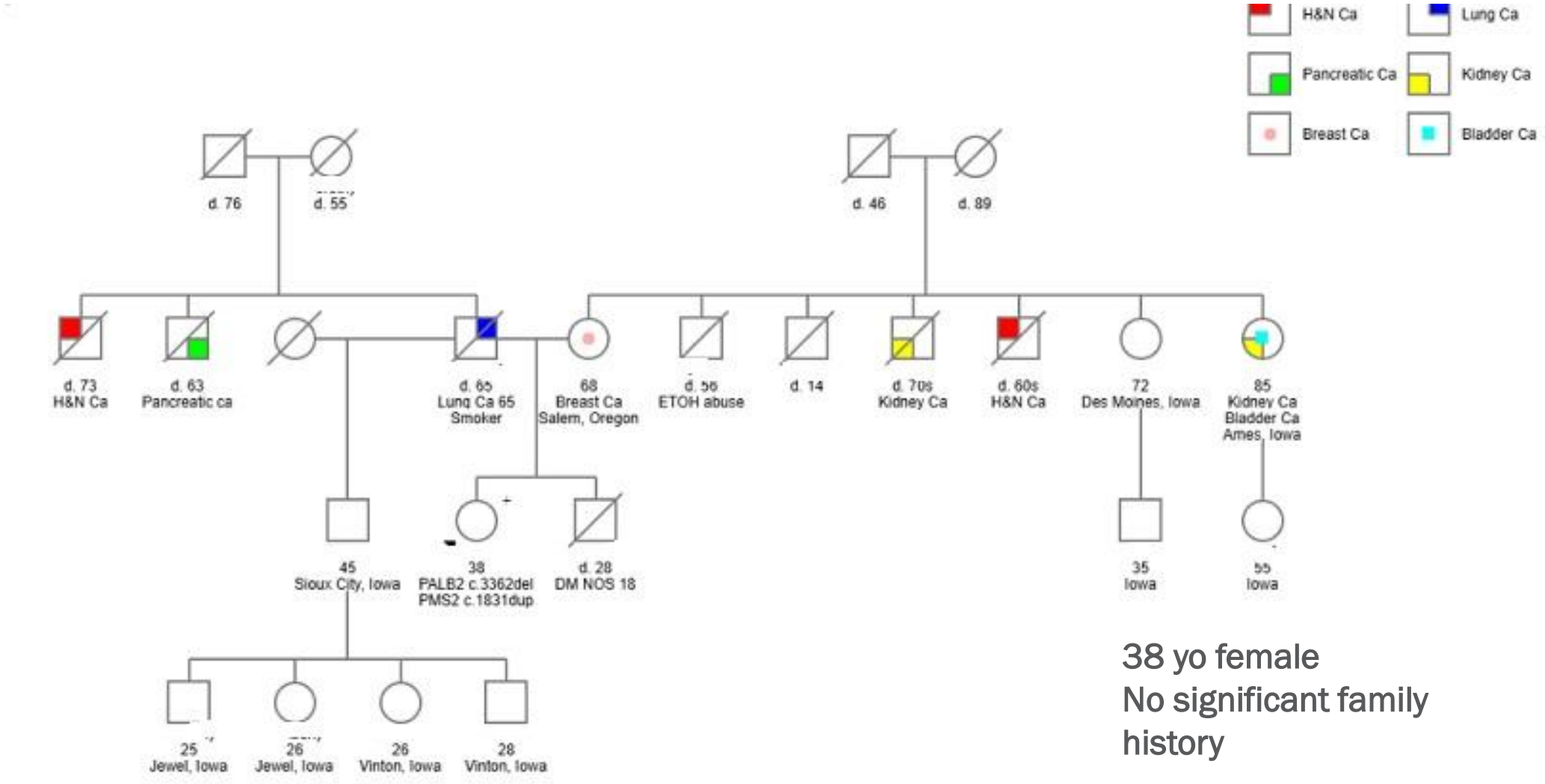


# BRCA2+ PATIENT - UNAFFECTED




42 yo female
Tested by Women's Health

# PALB2+/PMS2+ PATIENT - UNAFFECTED




38 yo female
No significant family history

# Which genes have management guidelines?

## Genes with management guidelines

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *BRCA1* | *PMS2* | *CDKN2A (p16INK4a)* | *PTEN* | *CHEK2* | *BRIP1* | *MEN1* | *FLCN* | *SDHB* | *GREM1* |
| *BRCA2* | *EPCAM* | *CDKN2A (p14ARF)* | *STK11* | *CHEK2 Biallelic* | *BMPR1A* | *BAP1* | *HOXB13* | *SDHC* | *AXIN2* |
| *MLH1* | *CTNNA1* | *CDK4* | *CDH1* | *RAD51C* | *SMAD4* | *TSC1* | *NTHL1 Biallelic* | *SDHD* | |
| *MSH2* | *APC* | *TP53* | *PALB2* | *RAD51D* | *VHL* | *TSC2* | *MET* | *POLD1* | |
| *MSH6* | *MUTYH Biallelic* | *MSH3 Biallelic* | *ATM* | *BARD1* | *RET* | *FH* | *SDHA* | *POLE* | |

Management guidelines are put forth by professional societies

## Other important genes

| | | | | | |
|---|---|---|---|---|---|
| *TERT* | *MITF* | *EGFR* | *NTHL1 Monoallelic* | *MSH3 Monoallelic* | *MUTYH Monoallelic* |

Identifying changes in these genes is still important as the information in combination with personal/family history may still warrant intervention

References can be found at https://myriad.com/gene-tables/

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

**The inclusion of a gene in this table below does not imply the endorsement either for or against multigene testing for moderate-penetrance genes.**

| Gene | Breast Cancer[b] | Epithelial Ovarian Cancer[b] | Pancreatic Cancer,[11-20] Prostate Cancer, and Other Cancer Risks |
|---|---|---|---|
| *BRCA1* | Primary breast cancer<br>• Absolute risk: 60%–72%[23,24]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong<br>Contralateral breast cancer[i,j]<br>• 20-year cumulative risk: 30%–40%[5,25]<br>• 15-year cumulative risk in premenopausal women: >20%[5,25]<br>• Strength of evidence of association with cancer: Strong<br>Male breast cancer<br>• Absolute risk: 0.2%–1.2% by age 70 y[26,27]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Strong | • Absolute risk: 39%–58%[29]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong | Pancreatic cancer<br>• Absolute risk: ≤5%[27]<br>• Management: Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A.<br>• Strength of evidence of association with cancer: Strong<br>Prostate cancer<br>• Absolute risk: 7%–26%[30]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management |
| | Comment: See GENE-B for reproductive implications/recessive disease. The risk for breast cancer appears to be lower for the *BRCA1* R1699Q variant (24% by age 70 y) (Spurdle AB, et al. J Med Genet 2012;49:525-532). Screening should be individualized based on personal and family history. | | |
| *BRCA2* | Primary breast cancer<br>• Absolute risk: 55%–69%[23,24]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong<br>Contralateral breast cancer[i,j]<br>• 20-year cumulative risk: 25%[5,25]<br>• 15-year cumulative risk in premenopausal women: >20%[5,25]<br>• Strength of evidence of association with cancer: Strong<br>Male breast cancer<br>• Absolute risk: 1.8%–7.1% by age 70 y[26-28]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Strong | • Absolute risk: 13%–29%[29]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>• Strength of evidence of association with cancer: Very strong | Pancreatic cancer<br>• Absolute risk: 5%–10%[27]<br>• Management: Screening, see PANC-A.<br>• Strength of evidence of association with cancer: Very strong<br>Prostate cancer<br>• Absolute risk: 19%–61%[30,31]<br>• Management: See *BRCA* Pathogenic Variant-Positive Management<br>Melanoma<br>• See *BRCA* Pathogenic Variant-Positive Management |
| | Comment: See GENE-B for reproductive implications/ recessive disease. | | |

# CANCER COMMITTEE REPORT – GENETICS
## Jan-Dec 2024

| 2024<br>INVITAE GENETIC TESTING | Q1-Q4 Total |
|---|---|
| Referred/Evaluated for Testing | 699 |
| Met criteria for testing | 544 |
| Family Studies (Unaffected) | 34 |
| Contacted & Pending Scheduling/Results | --- |
| Scheduled & Pending OV | --- |
| Declined Education/Testing (Not Insurance related) | --- |
| Not covered/denied by insurance (criteria not met) | 0 |
| Educated: Pre/Post Test | --- |
| Variants (Pathogenic) | 16.4% |
| Variants (Uncertain) | --- |
| Negatives | 83.5% |

**MyRisk**

183
22+ (12%)

**Natera (Empower)**

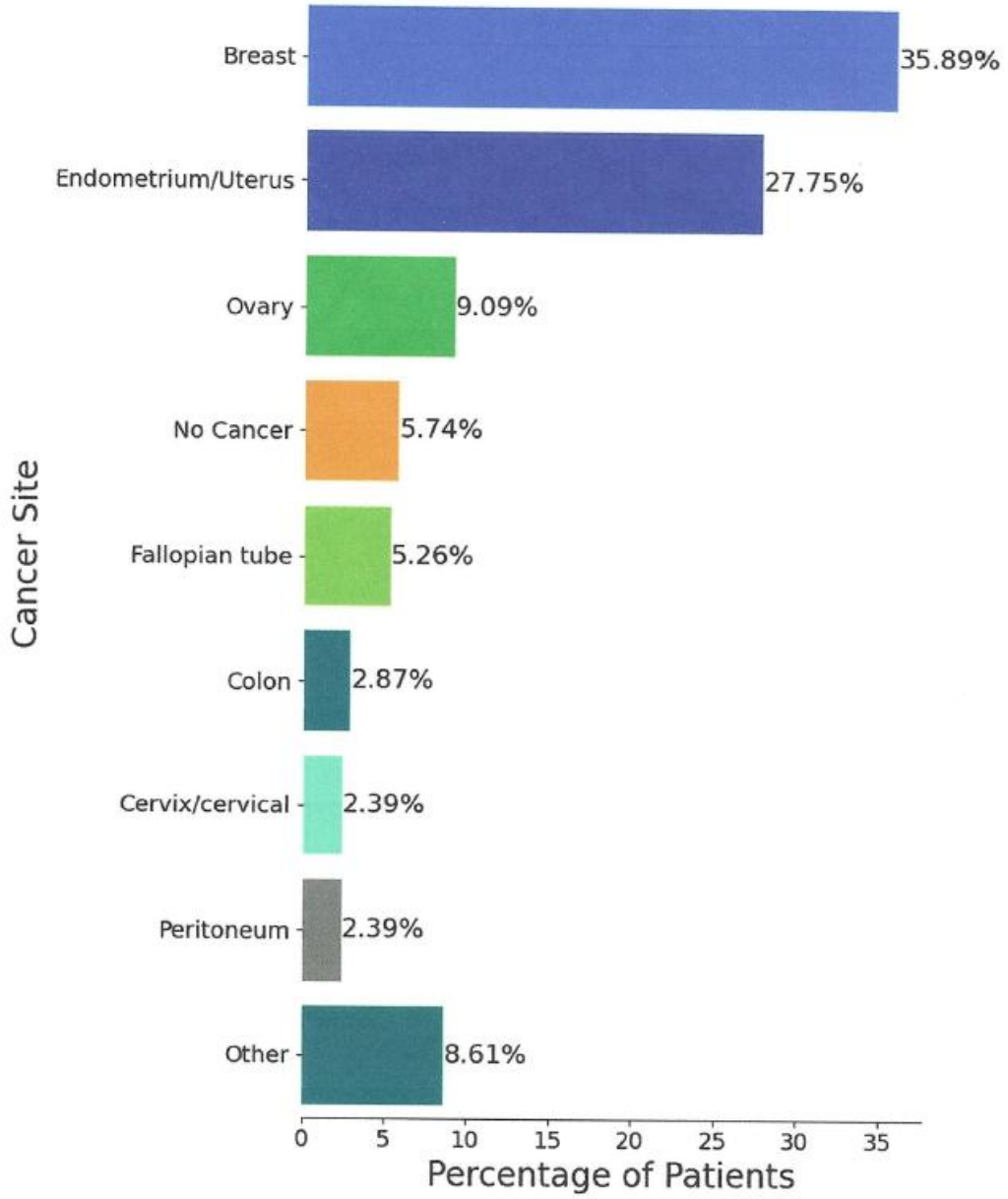
92

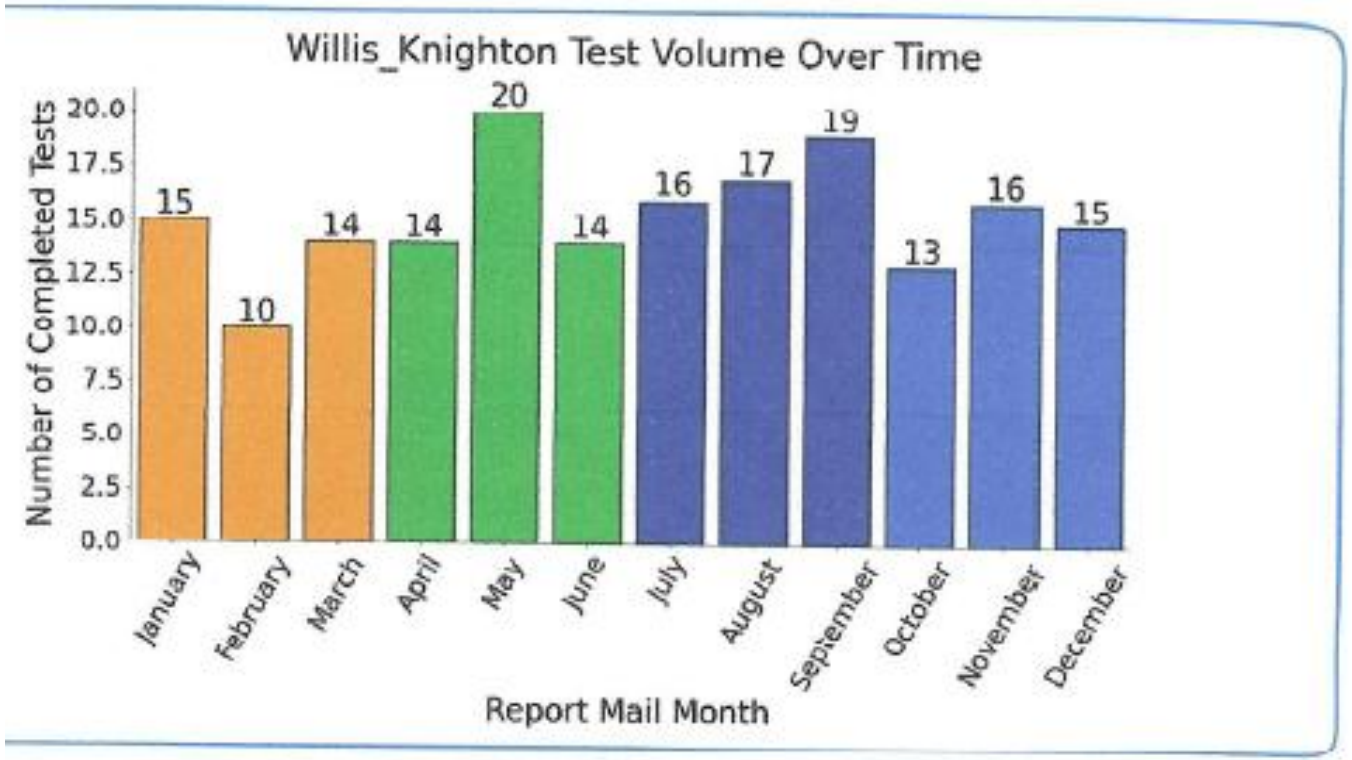
**Ambry**

18 (11% +)

**Total Tested for 2024:**

**819**




**Myriad MyRisk**

Patients tested and reported: 183

Affected patients tested: 92.9%

Unaffected patients tested: 7.1%

Gene positive results: 22

**High-risk negative results: 39**

**% results indicated for medical management changes: 33.3%**

CANCER GENETICS

original reports abstract

# Development and Validation of a Breast Cancer Polygenic Risk Score on the Basis of Genetic Ancestry Composition

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**PURPOSE** Polygenic risk scores (PRSs) for breast cancer (BC) risk stratification have been developed primarily in women of European ancestry. Their application to women of non-European ancestry has lagged because of the lack of a formal approach to incorporate genetic ancestry and ancestry-dependent variant frequencies and effect sizes. Here, we propose a multiple-ancestry PRS (MA-PRS) that addresses these issues and may be useful in the development of equitable PRSs across other cancers and common diseases.

JCO Precis Oncol 6:e2200084. 

FORCE
Facing Hereditary Cancer EMPOWERED
25 years


- 2024-
- 82 Virtual Meetings
- ~25 people per group
- YOUNG PREVIVORS
- BEYOND BRCA & LYNCH
- LGBTQI1+
- MENS GROUP
- ATM, PALB2, BRCA1/2
- Lynch Syndrome

# Key Take-aways

- Germline genetic testing is vital to patient care and outcomes
- Collecting/assessing cancer history helps assess hereditary cancer risk for your patient and identifies potential family members at risk
- Identifying hereditary cancer risks leads to better patient management and overall patient outcomes (maybe avoidance of cancer)