Hereditary Cancer Genetics: Know Your Risk

Morgan Tooley, APRN, FNP-C
Genetic Professional
Methodist Breast Care Center

Financial Disclosures

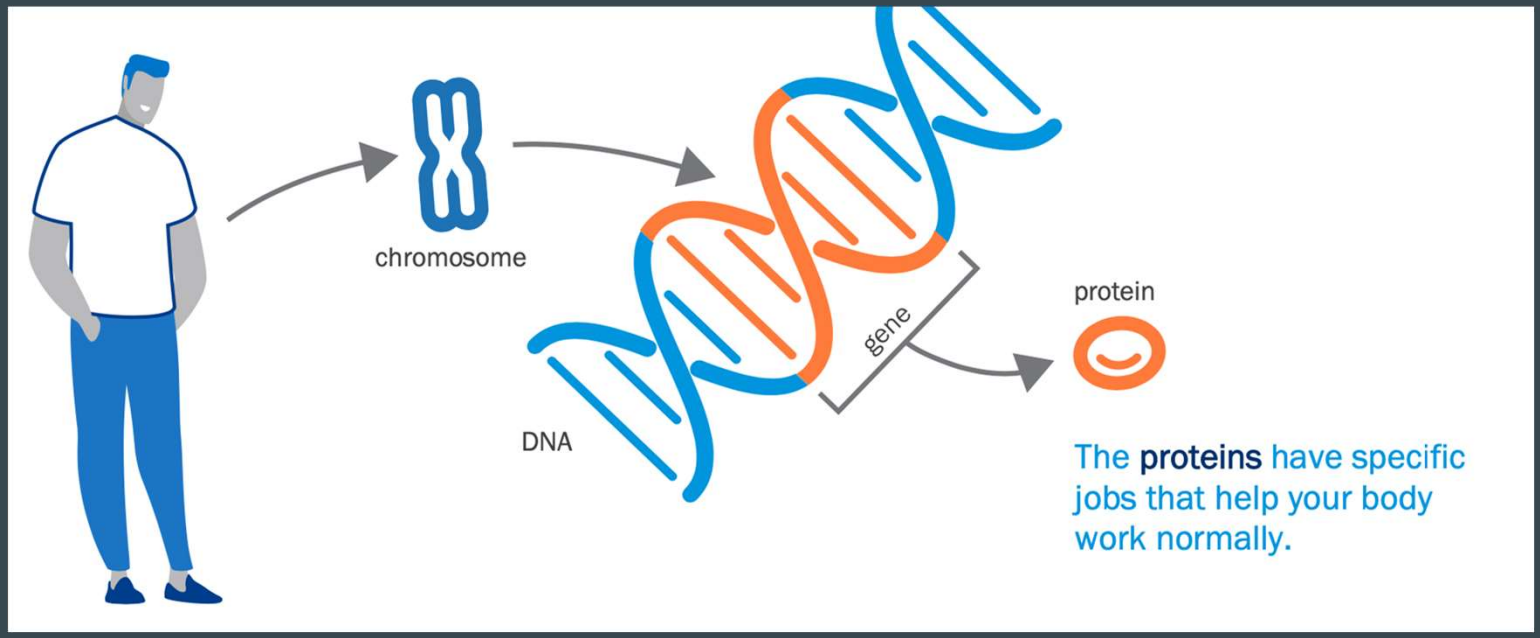
I have no financial disclosures or conflicts of interest

Objectives

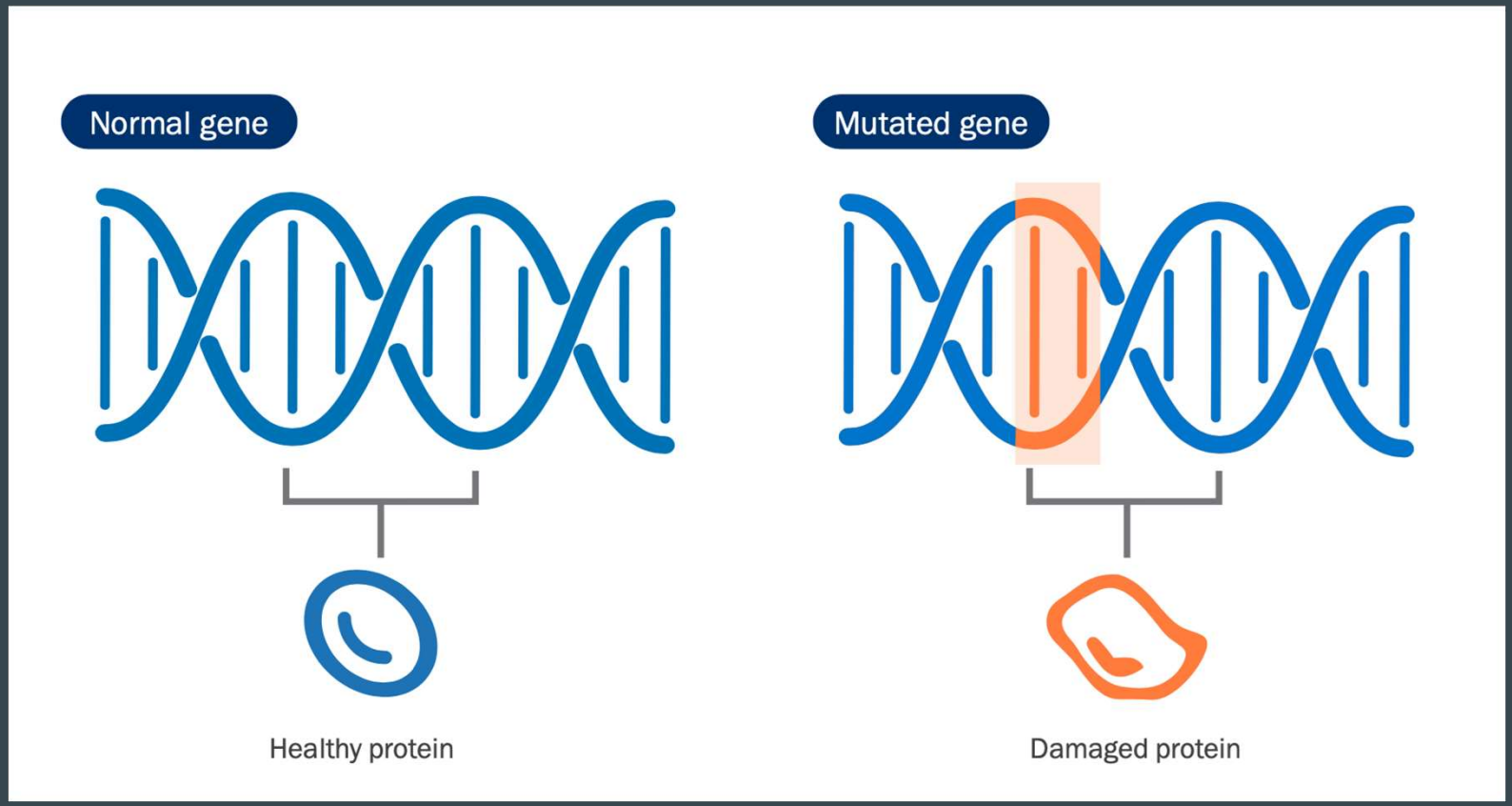
- Understand the role of inherited genetic mutations in cancer risk and the importance of family history in assessing susceptibility
- Learn the process of genetic testing, including its implications for cancer prevention, early detection and personalized treatment options

What is a gene?

- A gene is made of DNA which carries instructions to make proteins

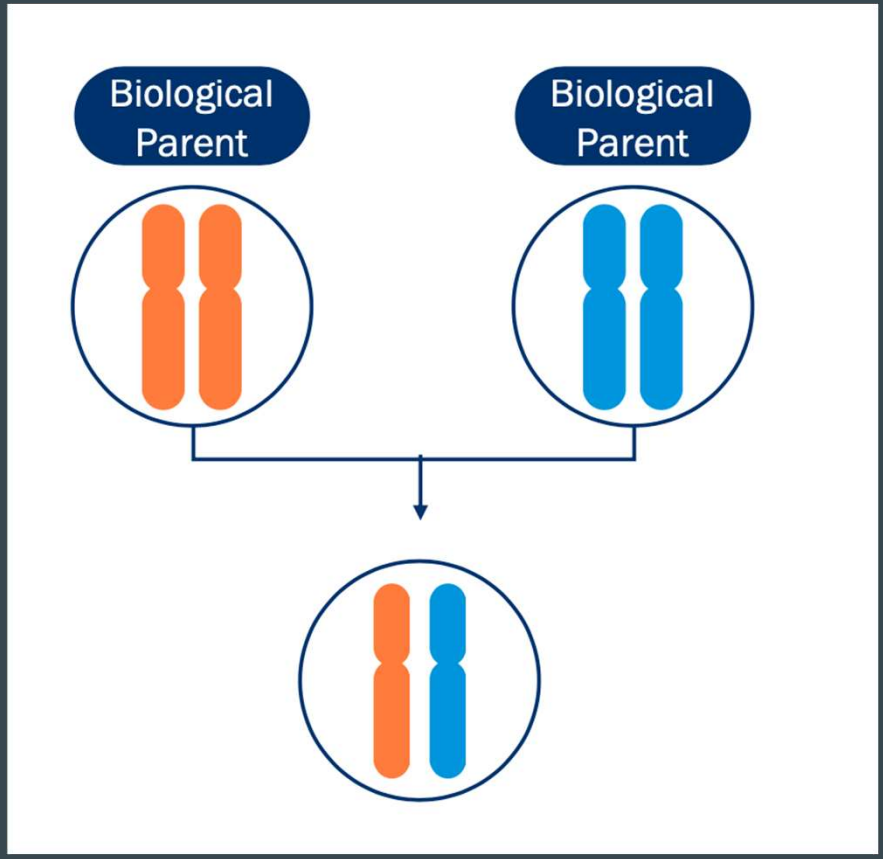


Genetic Mutation

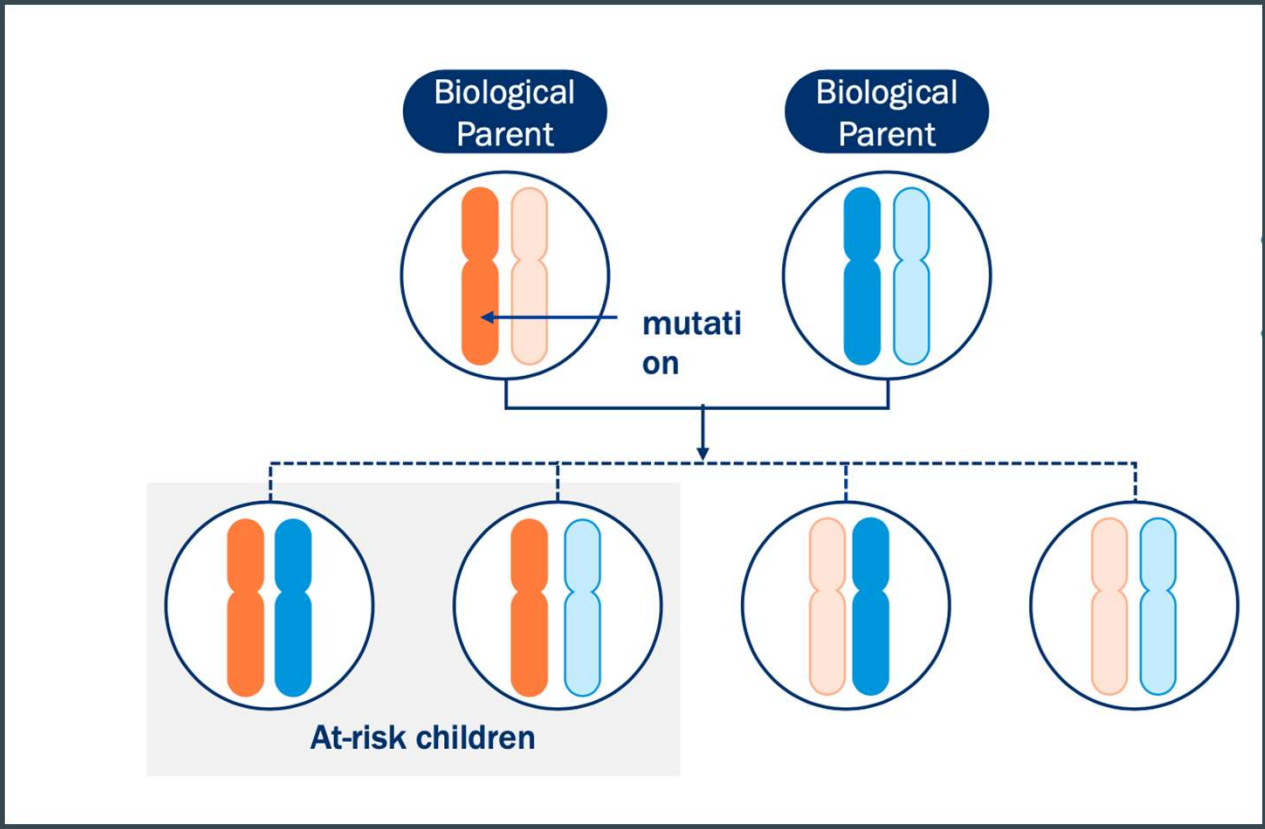


How are genes inherited?

- One gene is inherited from each biological parent



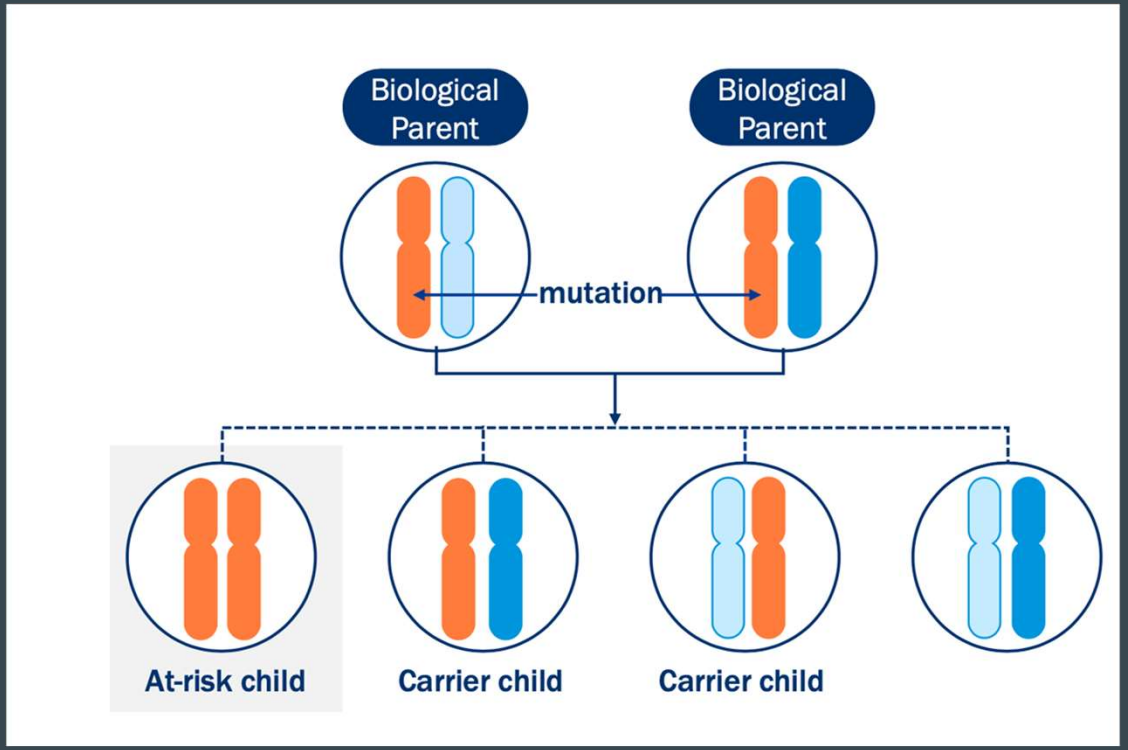
Autosomal Dominant Inheritance



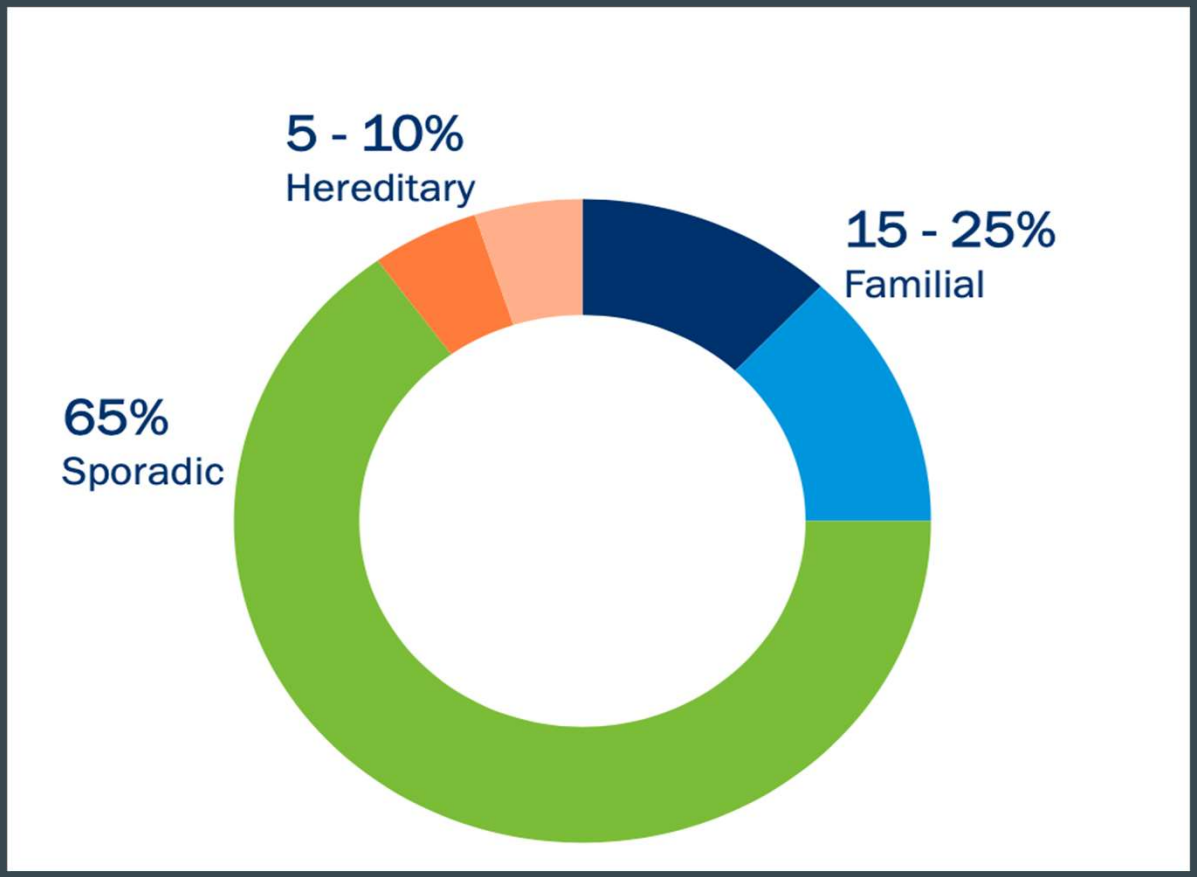
- 50% chance of inheriting mutation from parents
- Same for both males and females

Autosomal Recessive Inheritance

- Both parents have to be carriers of the mutation in order for a child to be “affected”
- 25% chance children would inherit both mutations
- Same for males and females



Cancer: Hereditary, Familial, or Sporadic

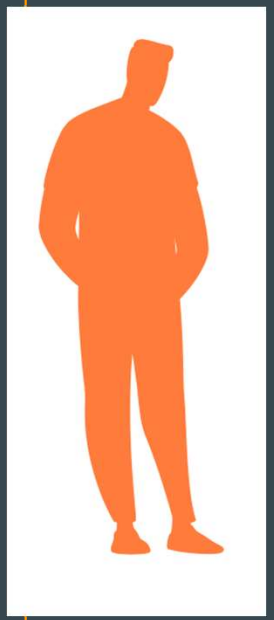


Does having a gene mutation mean that you will end up with cancer at some point in your lifetime?

Germline vs. Somatic mutations

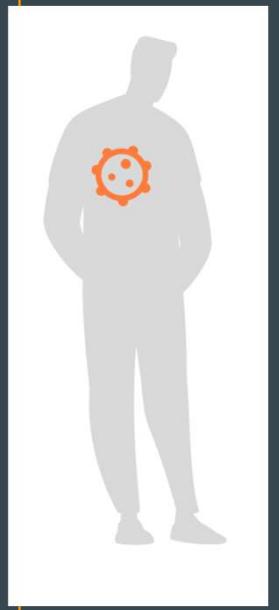
Germline

- A change in the gene that was inherited and caused an increased risk for cancer, known as hereditary cancer
- Only 5-10% of cancer is hereditary

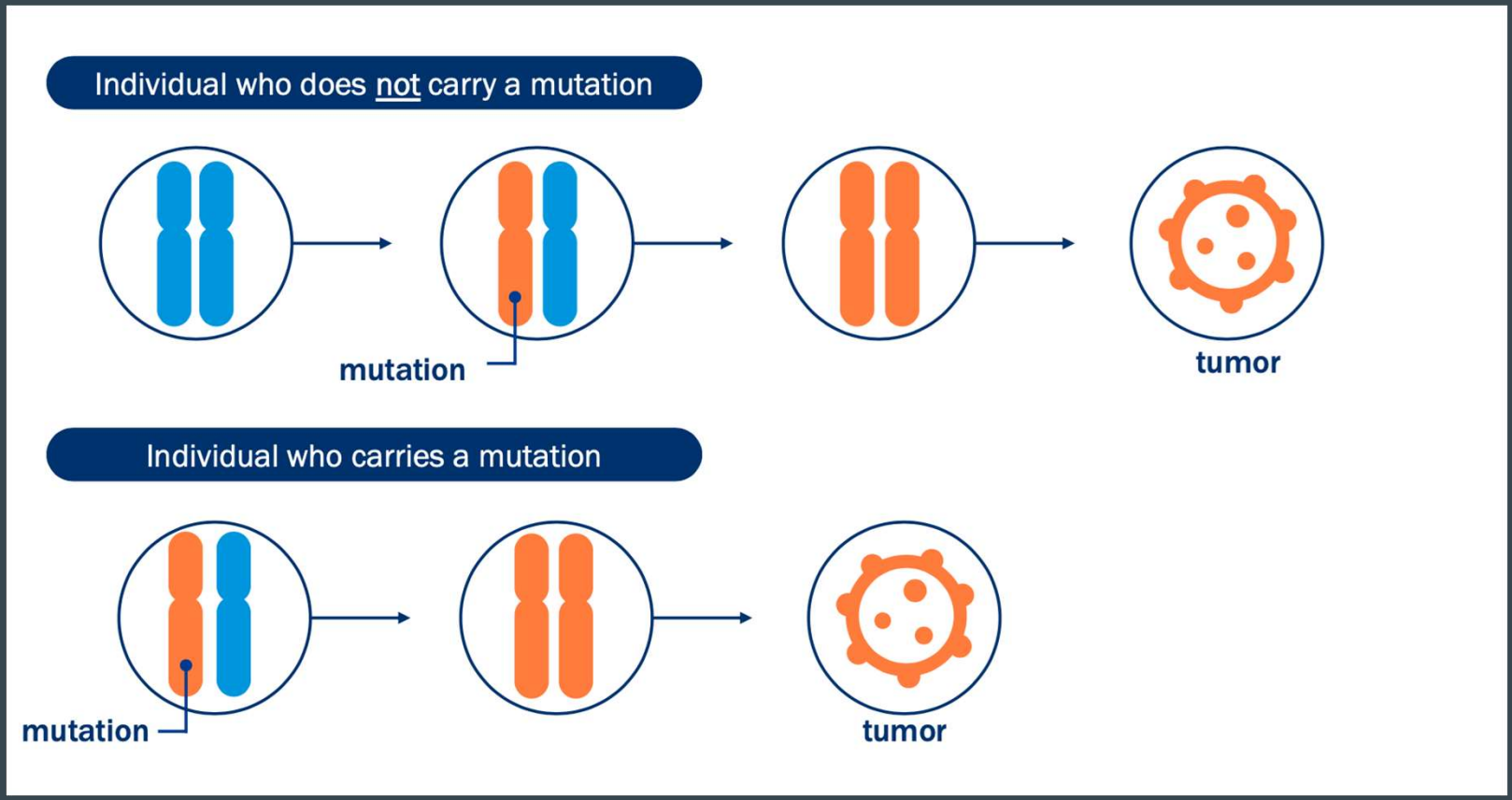


Somatic

- A genomic mutation is a change in the gene that arose in the tumor
- Most cancers are sporadic



Two Hit Hypothesis



Do you qualify for genetic testing?

Personal History:

- Breast cancer at any age
- Ovarian cancer at any age
- Pancreatic cancer at any age
- Colon or rectal cancer at any age
- Metastatic prostate cancer at any age
- Uterine cancer at age 64 or younger

Family History:

- A gene mutation in a family member
- Breast cancer at 49 or younger
- Two breast cancers in relatives at any age
- Three or more breast cancers on the same side of the family at any age
- Ashkenazi Jewish ancestry with breast cancer at any age
- Ovarian or male breast cancer at any age
- Metastatic prostate cancer or pancreatic cancer (1st degree relative)
- Uterine or colorectal cancer at age 49 or younger (1st degree relative)

Genetic Testing Results

Positive: A variant was identified in a gene which increases risk for cancer

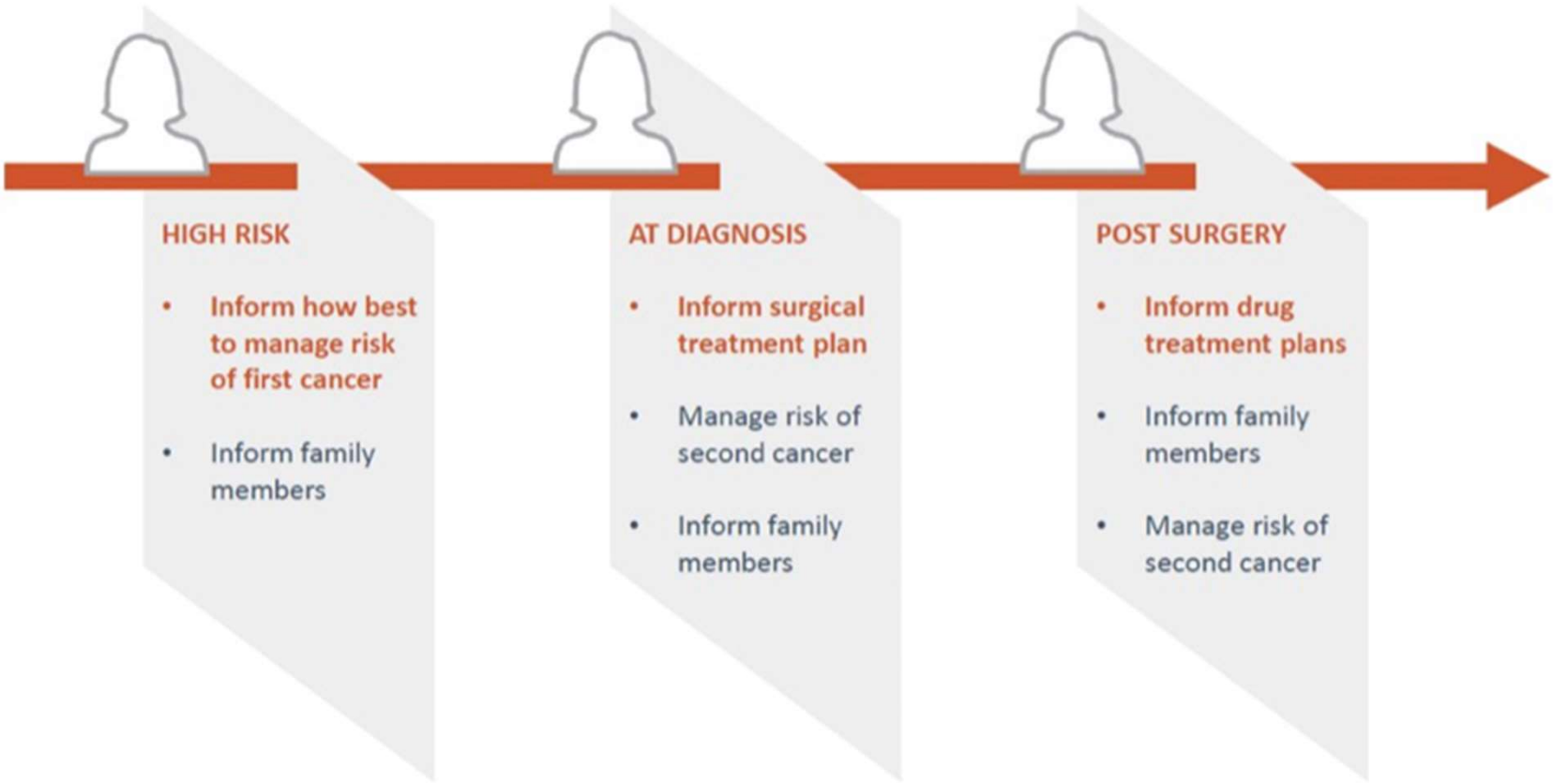
Variant of uncertain significance: Variant found in a gene testing. Unsure if this increases risk for cancer

Negative: No variants found in genes that were testing; important to know if there is a mutation in another family member as this can impact screening recommendations


Polymorphism
Favor polymorphism
Variant of uncertain significance
Suspected deleterious
Deleterious

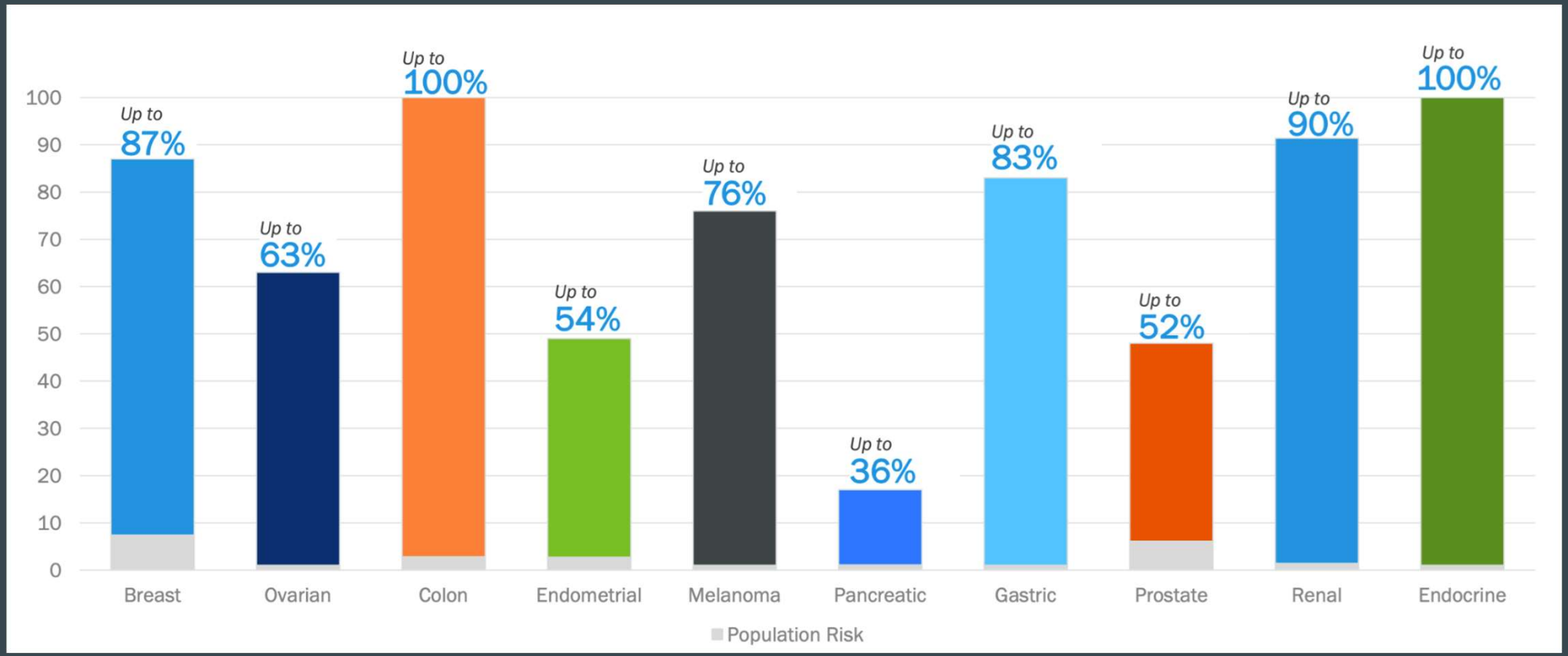
Knowledge is Power

- Increased surveillance
- Risk reducing medications
- Risk reducing surgery
- Treatment options

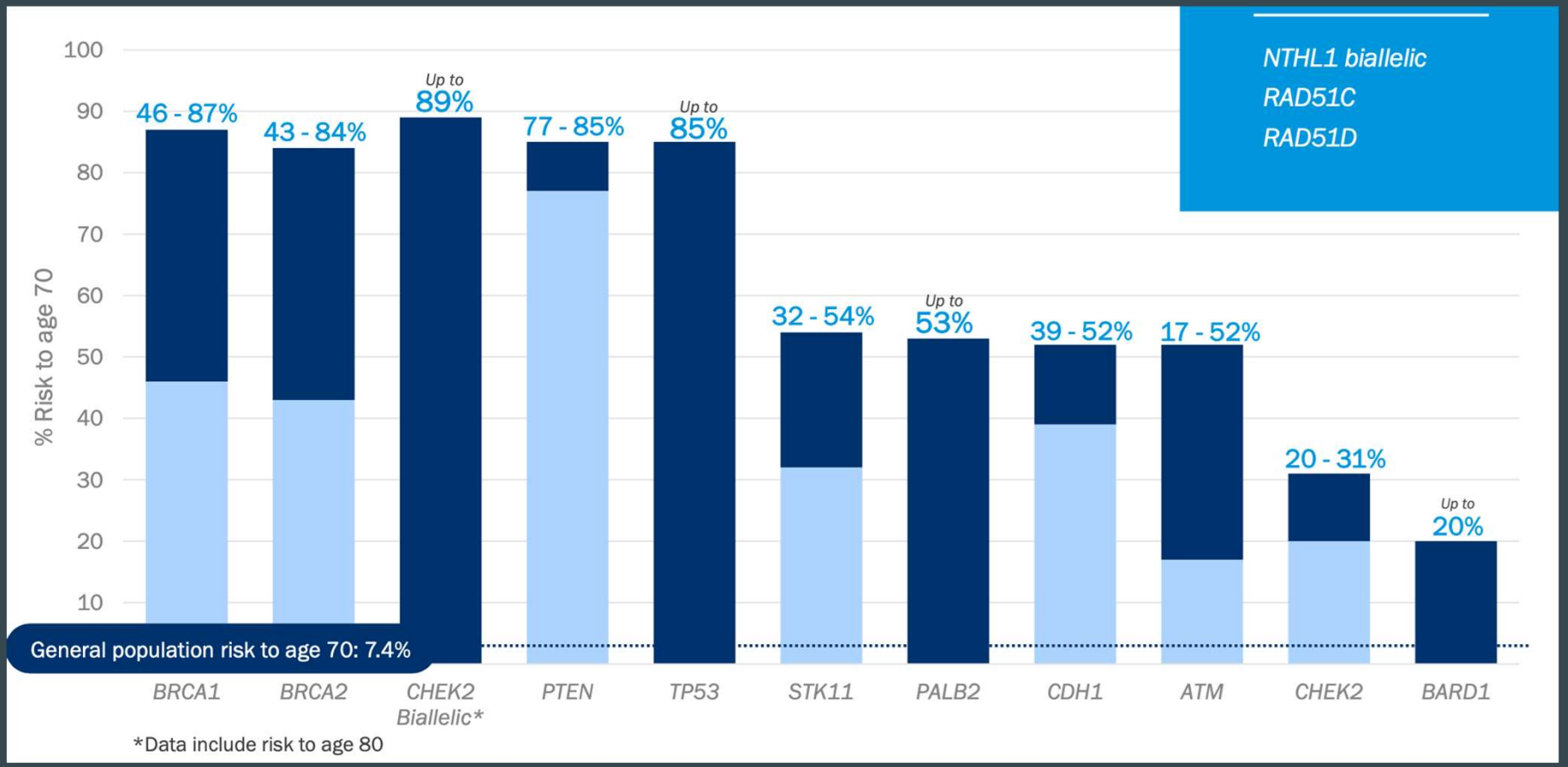

HIGH RISK
• Inform how best to manage risk of first cancer
• Inform family members
AT DIAGNOSIS
• Inform surgical treatment plan
• Manage risk of second cancer
• Inform family members
POST SURGERY
• Inform drug treatment plans
• Inform family members
• Manage risk of second cancer

If your father has a history of pancreatic cancer and is BRCA2 positive and you test negative for this mutation, would you need to do increased pancreatic cancer screening?

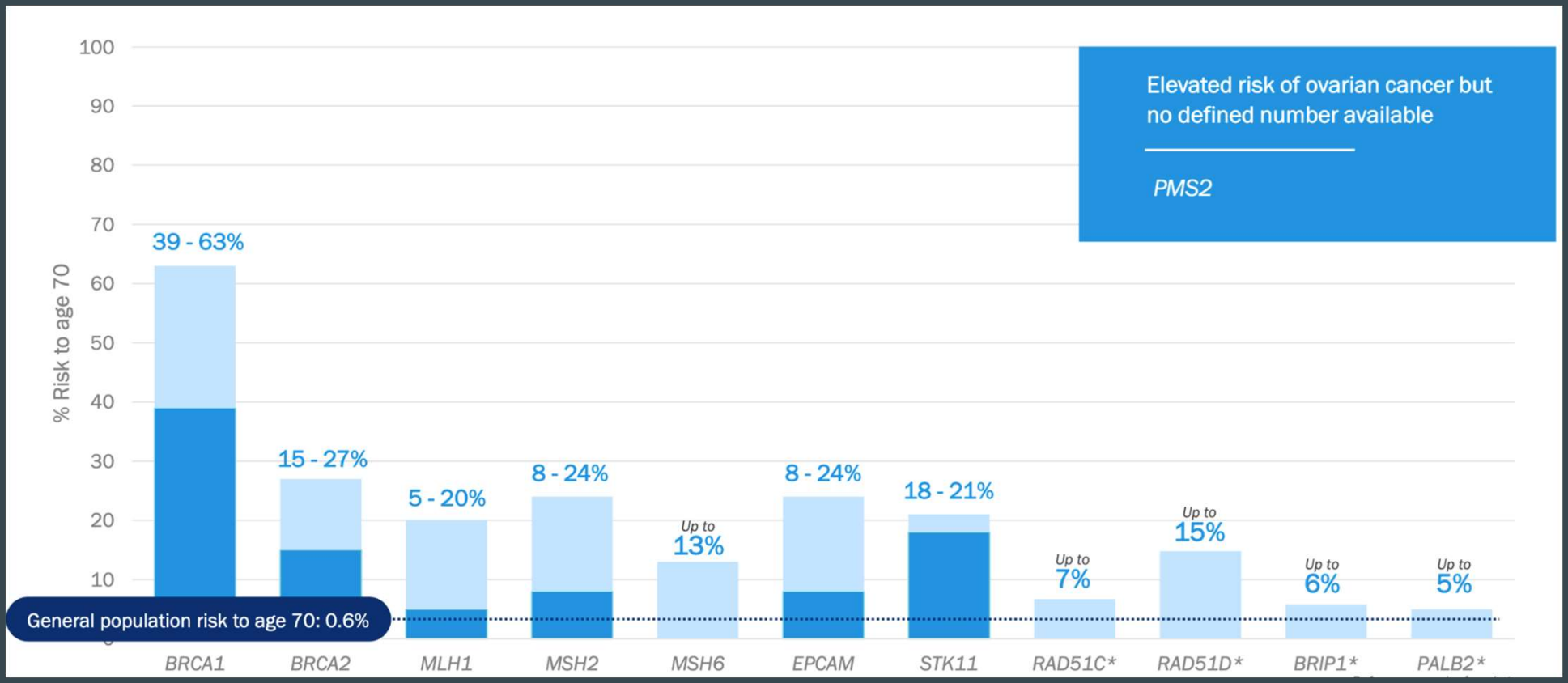
Lifetime Risk of Cancer



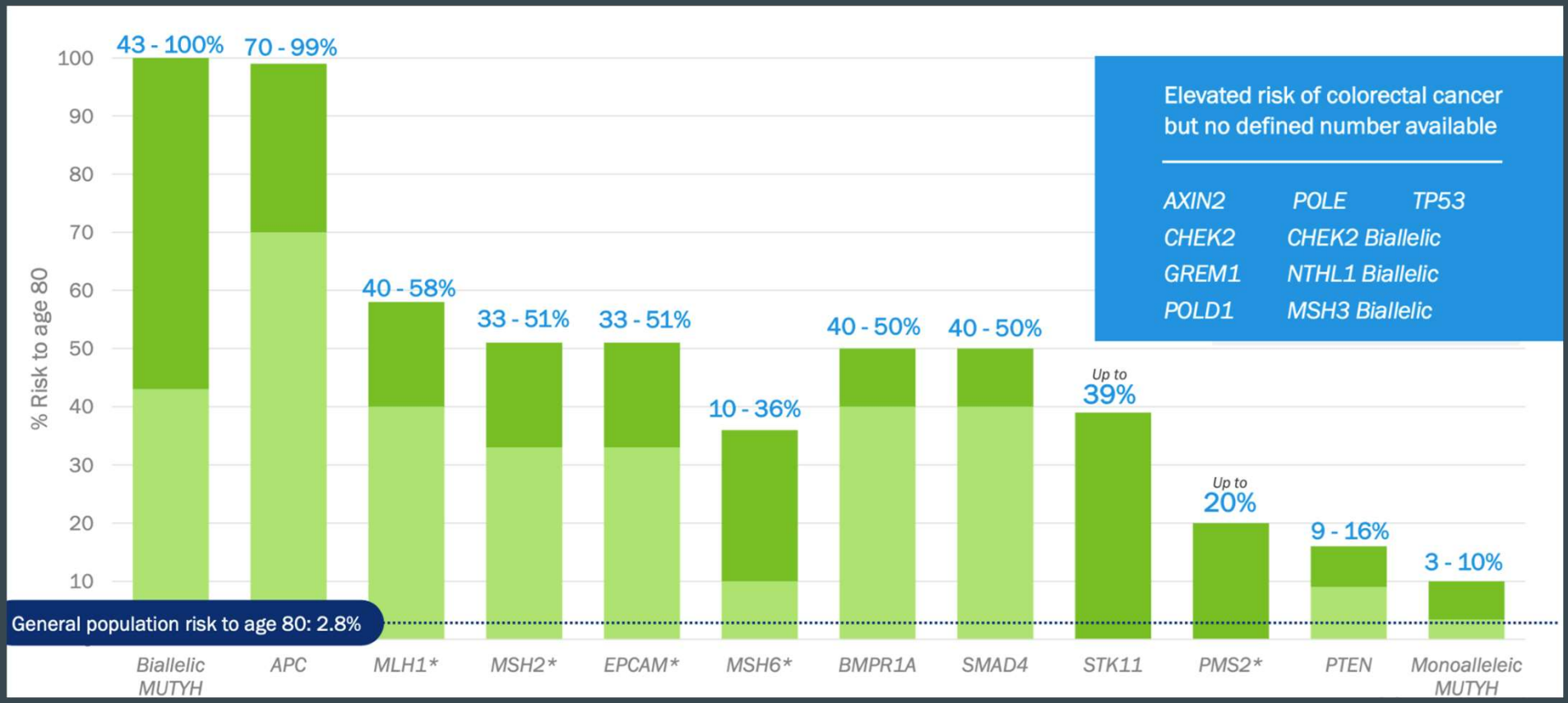
Genes Associated with Breast Cancer Risk



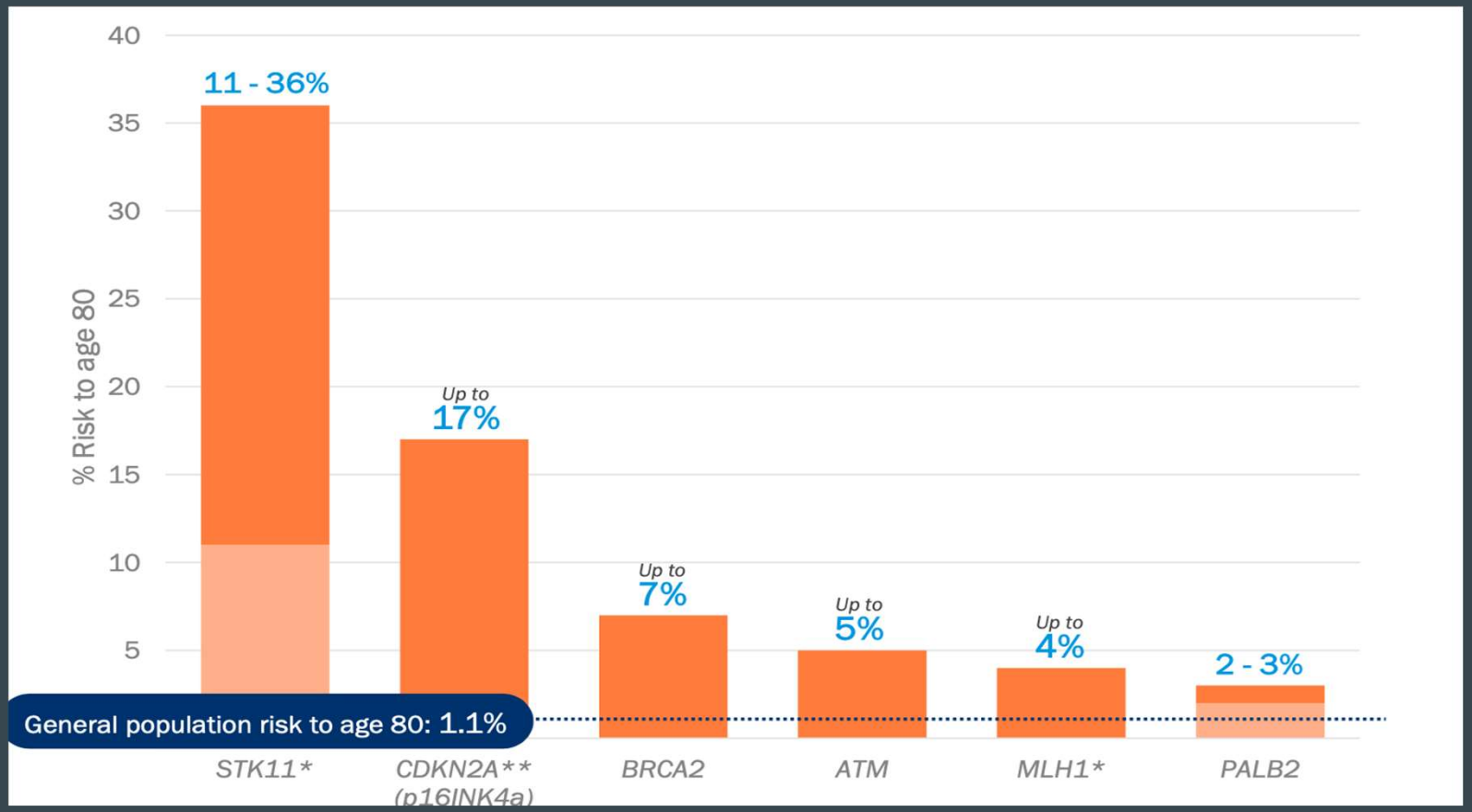
Genes Associated with Ovarian Cancer



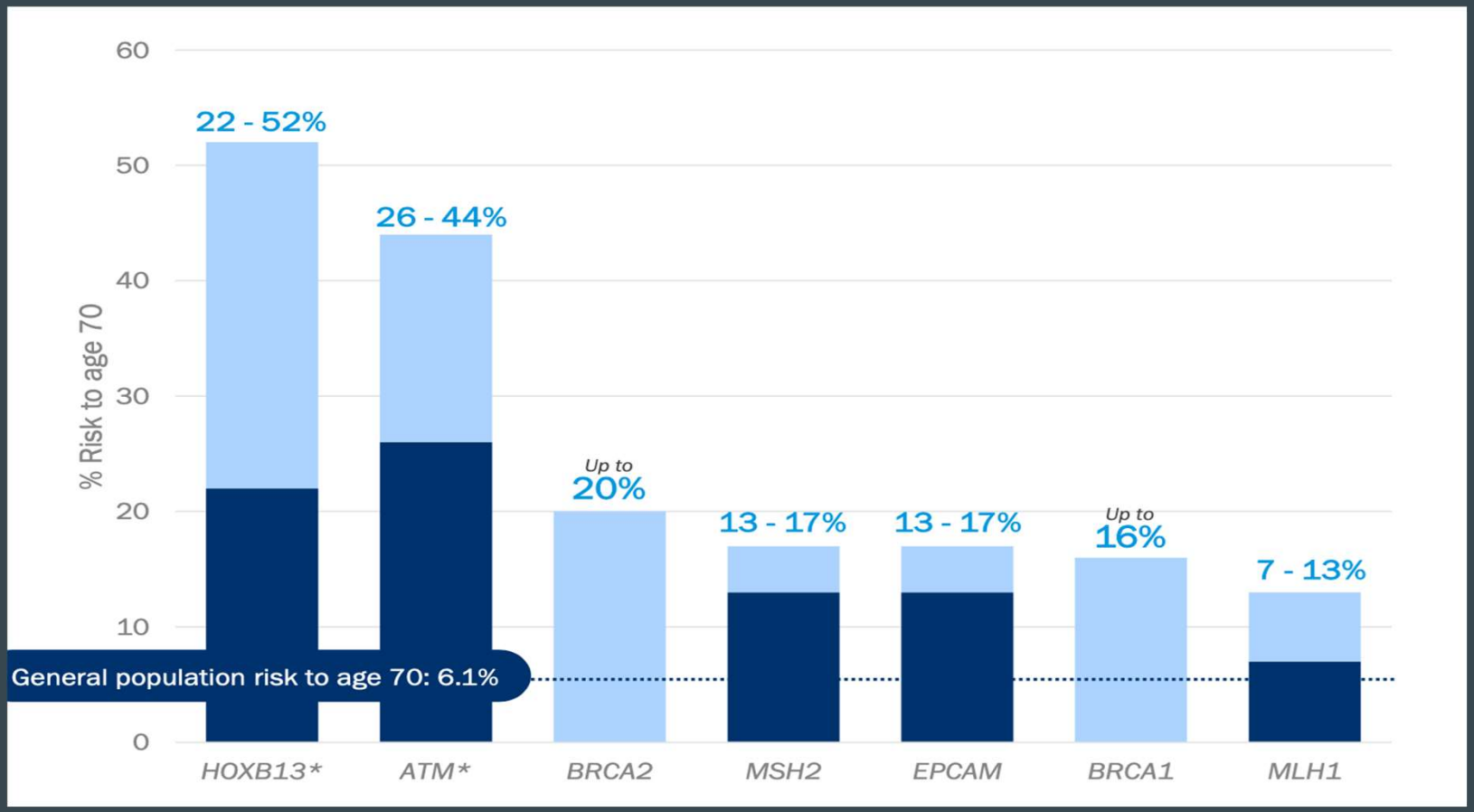
Genes Associated with Colon Cancer



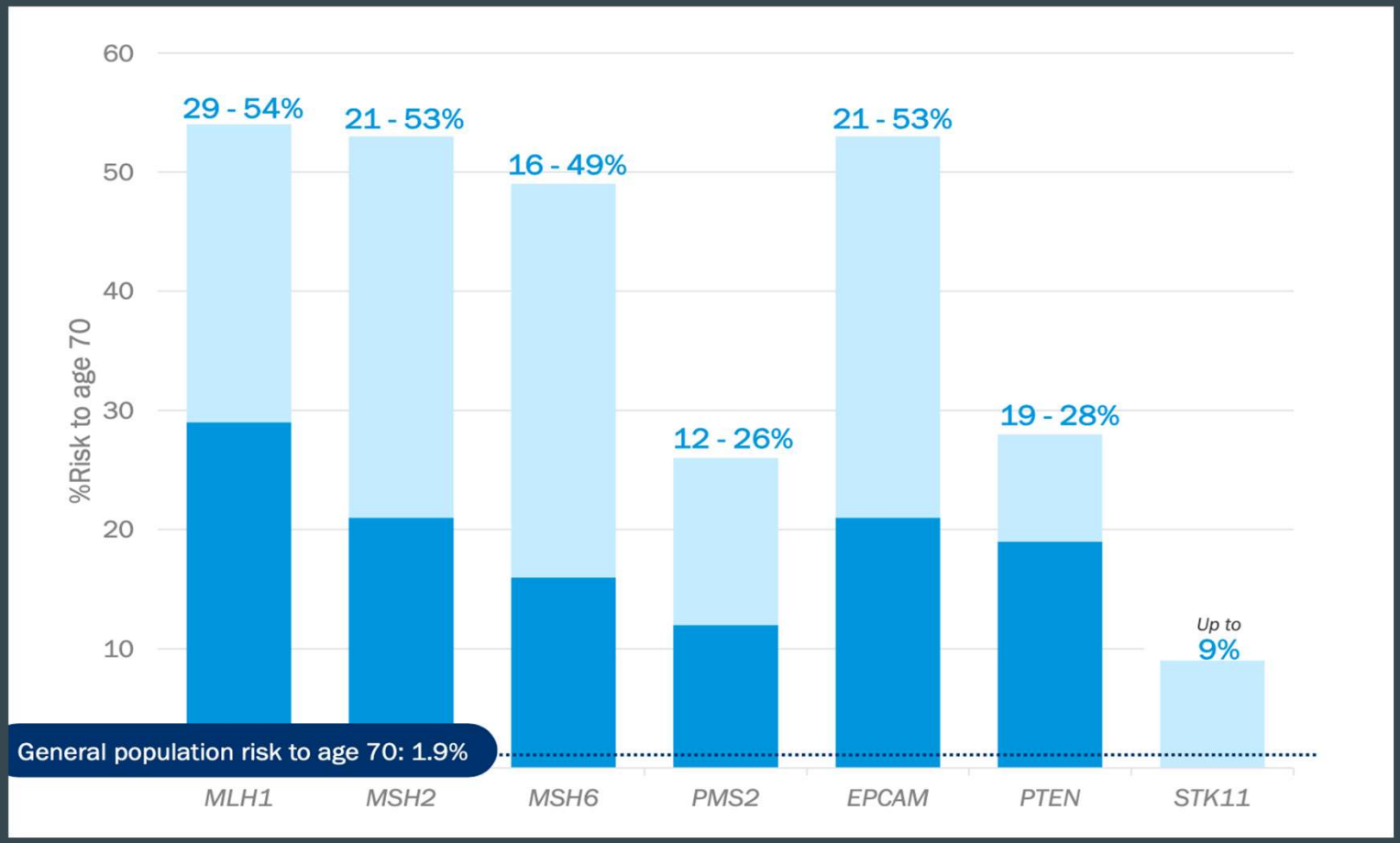
Genes Associated with Pancreatic Cancer



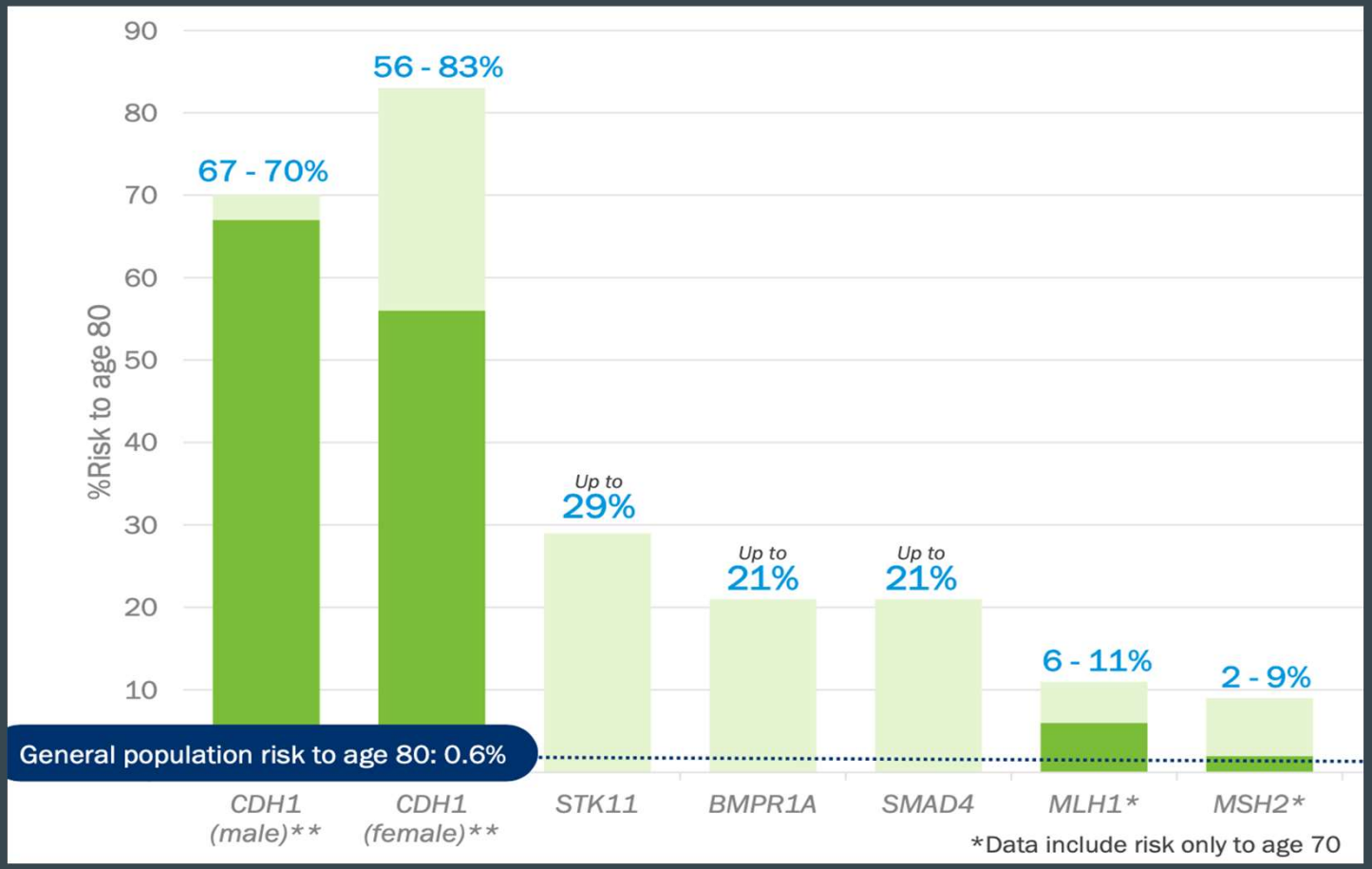
Genes Associated with Prostate Cancer



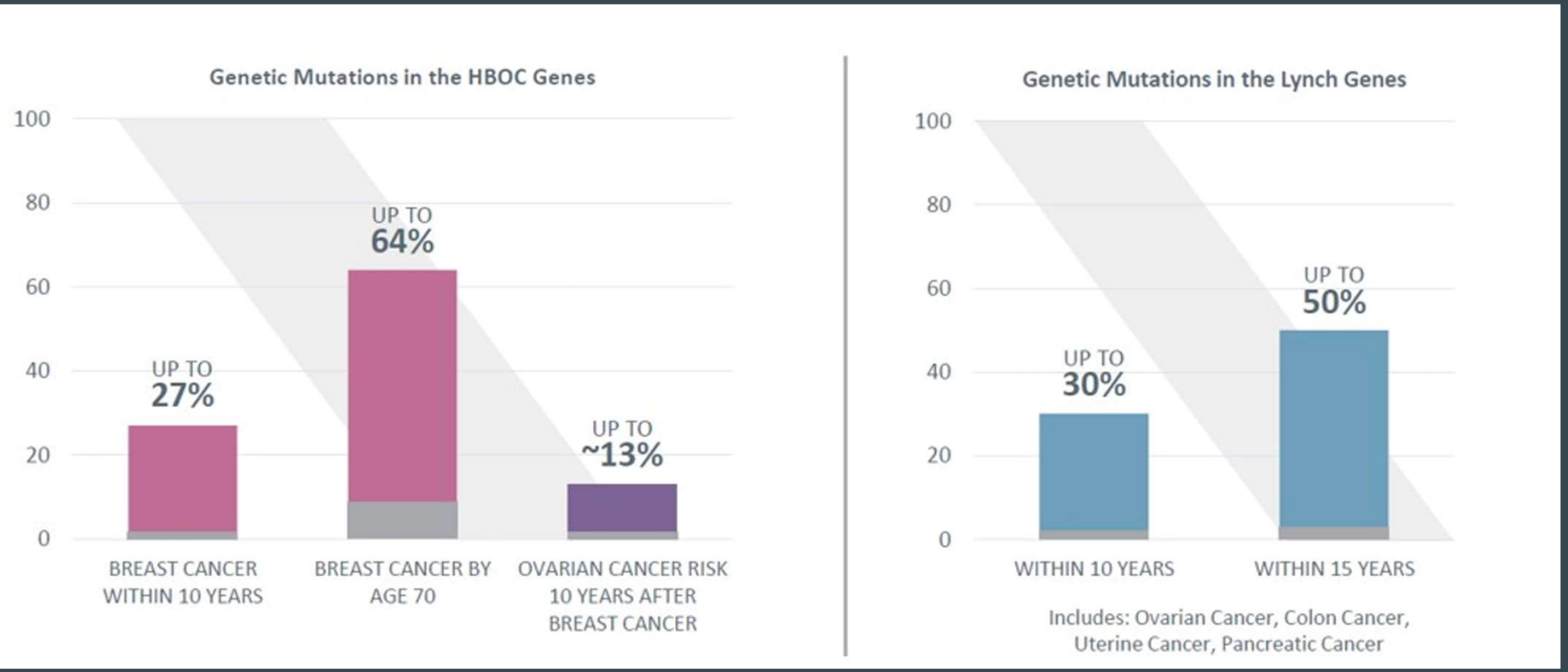
Genes Associated with Endometrial Cancer



Genes Associated with Gastric Cancer



Risk of Second Primary Cancer



Recent NCCN Guideline Changes- September 2024

- CHEK2- no increased risk of colon cancer
  - carriers do not need to do increase colonoscopy screening unless they have a family history of colon cancer
- All individuals with diffuse gastric cancer meet genetic testing criteria, regardless of age and family history

What is the process to complete genetic testing?

- Discuss if you qualify for testing with PCP or OB-GYN
- Pre-test counseling visit with genetic counselor or provider
- Testing completed with saliva kit or blood draw
- Post counseling visit to discuss results and medical management changes

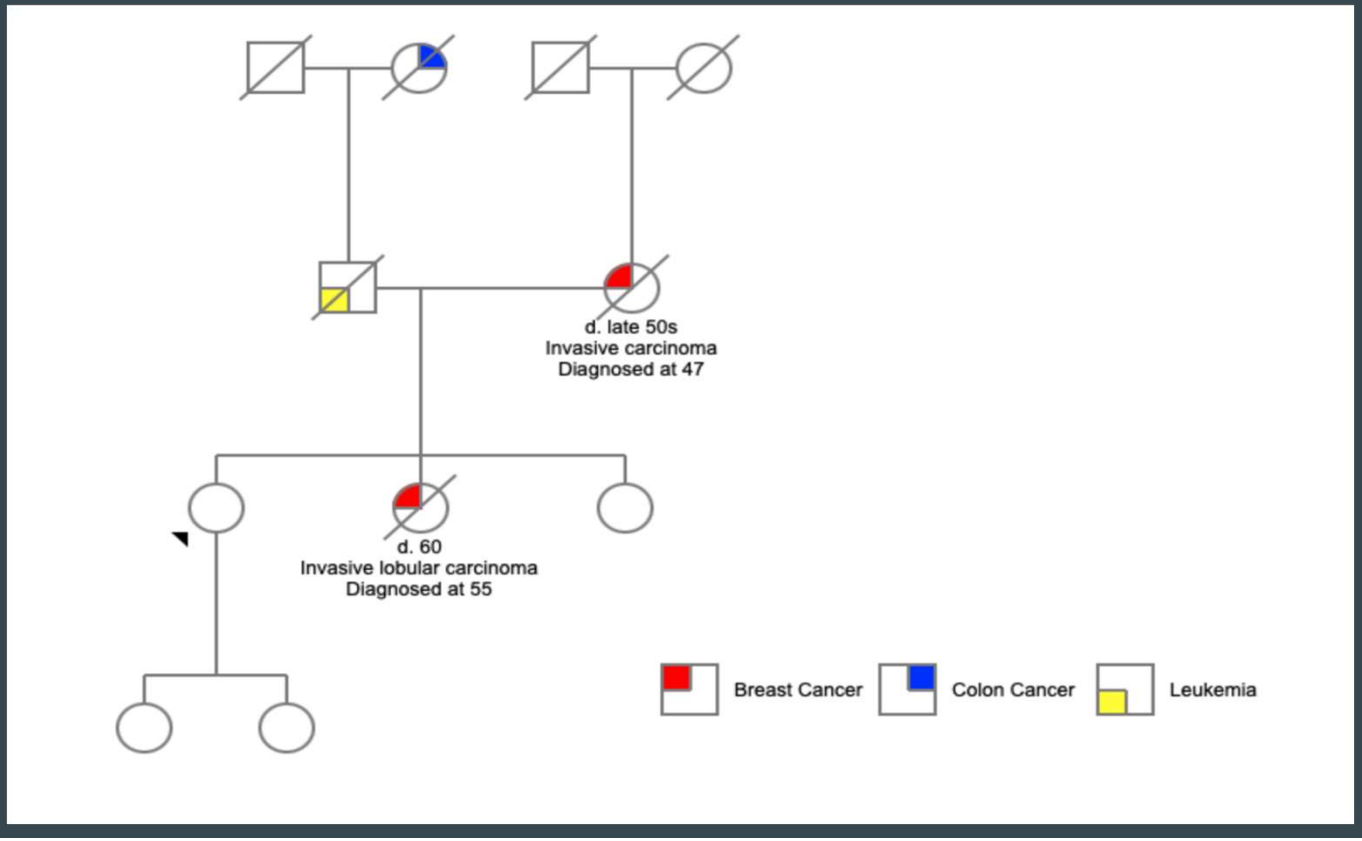
GINA: Genetic Information Non-Discrimination Act

- GINA protects most patients from discrimination with health insurance or an employer. Active-duty military personnel are an exception.

- It does not protect a patient from discrimination with life insurance and disability insurance

Case Study #1

- 56 year old caucasian female, evaluation due to family history of breast cancer



Personal Information: Case #1

- Age of menarche: 12
- Age of first live birth: 22
- Menopausal status: post menopausal, age 53
- Hormone replacement therapy use: Yes, had been using for 3 years
- Breast density: Heterogeneously dense (category C)

Tyrer Cuzick was calculated during clinic visit: **Estimated lifetime risk of developing breast cancer at 28%.**

- Patient at the time was not planning on doing any additional breast screening- going to continue with annual screening mammograms and biannual breast exams

Genetic Results- Case #1

GENETIC RESULT: NEGATIVE - NO 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.

BREAST CANCER RISKSCORE®: REMAINING LIFETIME RISK 53.0%

This level of risk is at or above 20% threshold for consideration of modified medical management.
See RiskScore Interpretation Section for more information.

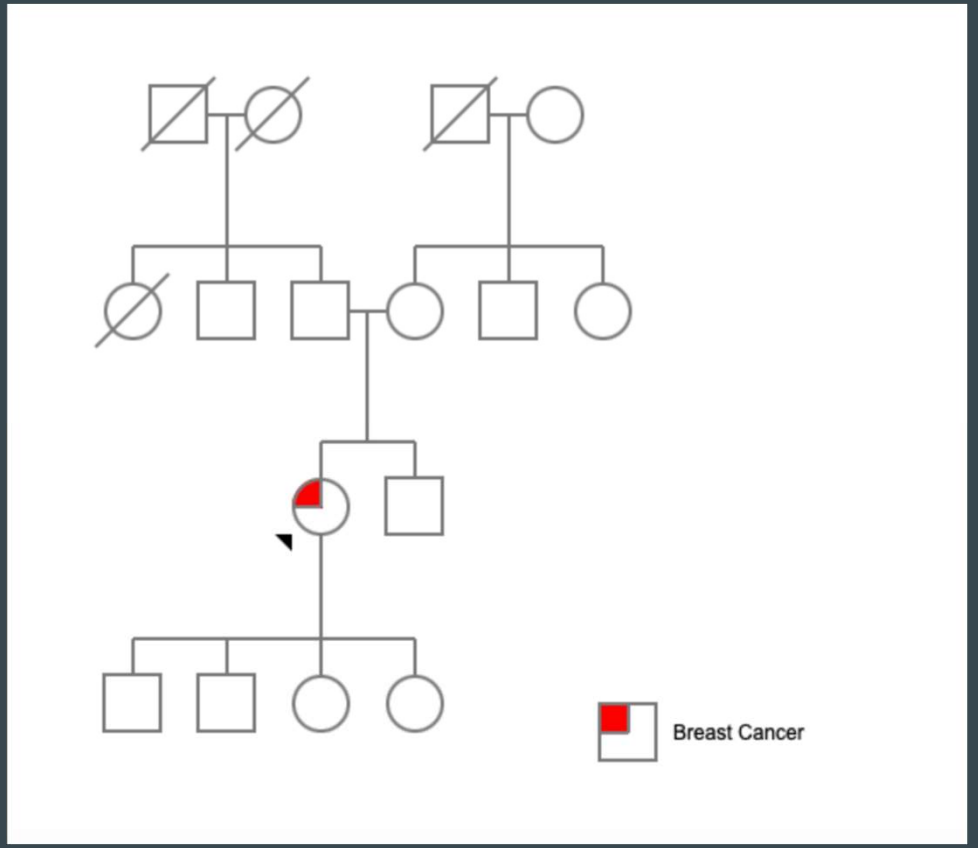
Polygenic Risk Scores (PRS): These are not used alone to make medical management guidelines but can be combined together with family history and other risk models like a Tyrer-Cuzick to evaluate risk

Medical Management Change

- Screening mammogram in June 2023, revealed no abnormalities
- Proceeded with breast MRI in December 2023- 1.7cm area of enhancement was identified in the right breast
- Biopsy revealed Invasive lobular carcinoma- ER positive, PR positive, and HER2 negative
- Proceeded with bilateral mastectomy

Case Study #2

- 49 year old caucasian female, no family history of cancer
- Recently diagnosed with multifocal right breast invasive ductal carcinoma- ER positive, PR positive, and HER2 negative



Genetic Results- Case #2

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: NO ADDITIONAL 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. If this patient also has a clinically significant mutation, the recommendations based on the clinical history analysis should be considered in light of the possibility that this mutation explains all or some of the cancer history in the family.

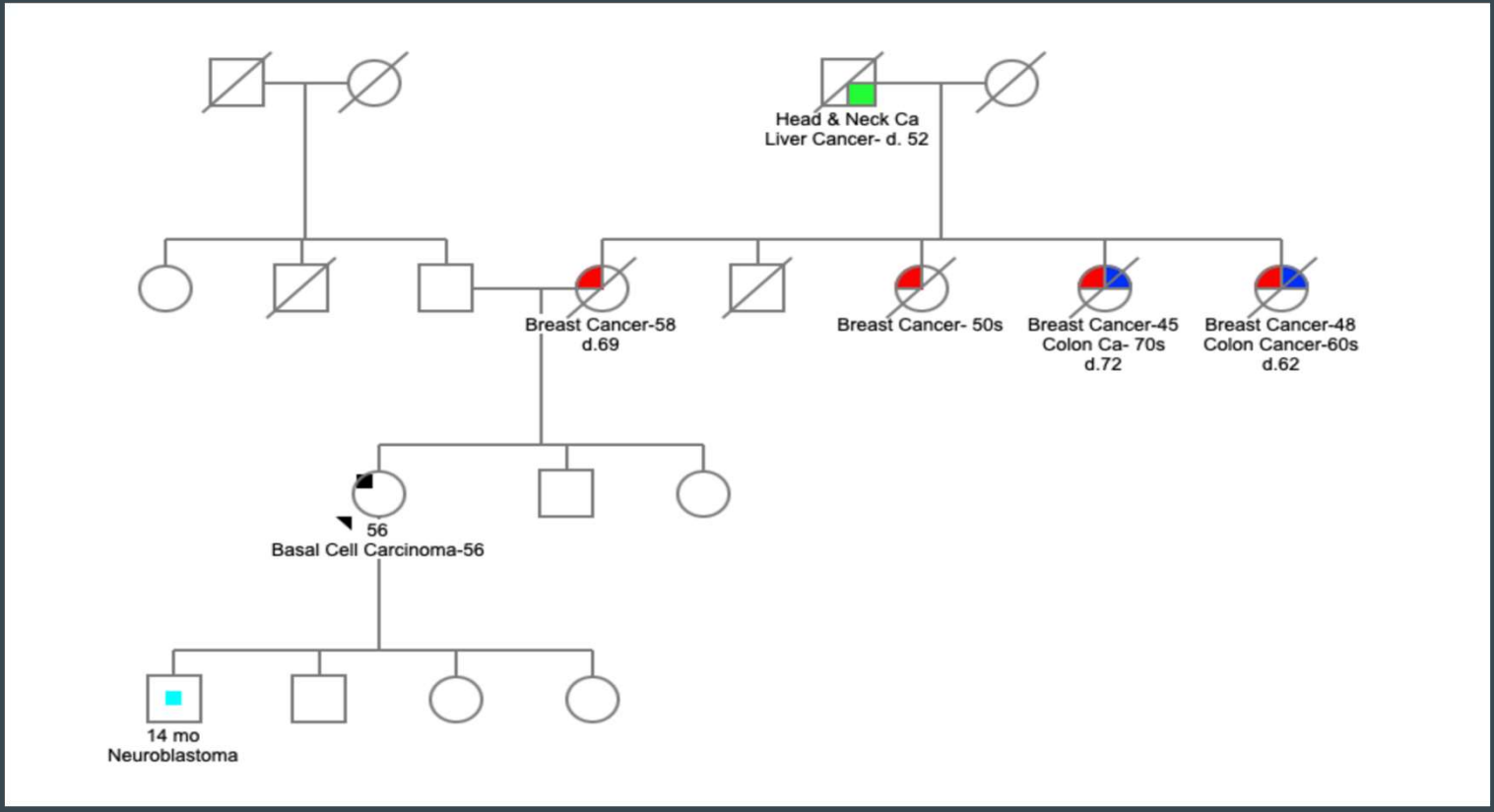
GENE	MUTATION	INTERPRETATION
PMS2	**del exon 13** Heterozygous	**High Risk** This patient has Lynch syndrome/Hereditary non-polyposis colorectal cancer (HNPCC).

Medical Management Change

- Proceeded with breast cancer surgery
- Shortly after, met with Gynecologic Oncology office and scheduled total hysterectomy- no abnormalities identified on pathology
- Colonoscopy was performed and rectosigmoid adenocarcinoma was identified-stage 3

Case Study #3

- 57 year old caucasian female, established care in clinic due to family history of breast cancer



Personal Information: Case #2

- Age of menarche: 12
- Age of first live birth: 20
- Menopausal status: post menopausal, age 38
- Hormone replacement therapy use: Yes, for two years after hysterectomy
- Breast density: Scattered fibroglandular densities (category B)

Tyrer Cuzick was calculated during clinic visit: **Estimated lifetime risk of developing breast cancer at 11%.**

- Patient was just planning on doing annual screening mammograms

Genetic Results: Case #3

GENETIC RESULT: POSITIVE - MULTIPLE CLINICALLY SIGNIFICANT MUTATIONS IDENTIFIED

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

CHEK2 - MODIFIED BREAST CANCER RISKSCORE®: REMAINING LIFETIME RISK 18.0%

Individualized breast cancer risk estimate for this patient, based on the presence of a clinically significant mutation in *CHEK2* and additional genetic and clinical factors. See RiskScore interpretation section for more information.

CLINICAL HISTORY ANALYSIS: NO ADDITIONAL 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. If this patient also has a clinically significant mutation, the recommendations based on the clinical history analysis should be considered in light of the possibility that this mutation explains all or some of the cancer history in the family.

GENE	MUTATION	INTERPRETATION
CHEK2	c.433C>T (p.Arg145Trp) Heterozygous	High Risk This patient has *CHEK2*-associated Cancer Risk.
BRIP1	c.1126_1127del (p.Gln376Asnfs*18) Heterozygous	High Risk This patient has *BRIP1*-associated Cancer Risk (Women only).

Medical Management Change

- Was alternating mammogram and breast MRI every 6 months
- Recently elected to proceed with prophylactic mastectomies as new calcifications were identified on her mammogram
- Previously had a total hysterectomy at 38
- With two maternal aunts that had colon cancer- recommend colonoscopy screening every 5 years

References

Genetic Alliance; The New York-Mid-Atlantic Consortium for Genetics. Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; 2009 Jul 8. CHAPTER 1, GENETICS 101.Available from: https://www.ncbi.nlm.nih.gov/books/NBK115568/

Iniesta, M. D., Chien, J., Wicha, M., & Merajver, S. D. (2010). One-hit effects and cancer. *Cancer Prevention Research*, *3*(1), 12–15. https://doi.org/10.1158/1940-6207.CAPR-09-0249

Mavaddat, N., Pharoah, P. D. P., & Michailidou, K. (2023). Polygenic risk scores and breast cancer risk prediction. *Journal of Personalized Medicine, 13*(1), 115. https://doi.org/10.3390/jpm13010115

Myriad Genetics. *MyRisk® hereditary cancer test*. https://myriad.com/myrisk-hereditary-cancer/

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2025. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2025. Available at: https://www.nccn.org/guidelines/category_1.

Tung N, Ricker C, Messersmith H, et al. Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. J Clin Oncol. 2

QUESTIONS?

Email: morgan.tooley@nmhs.org