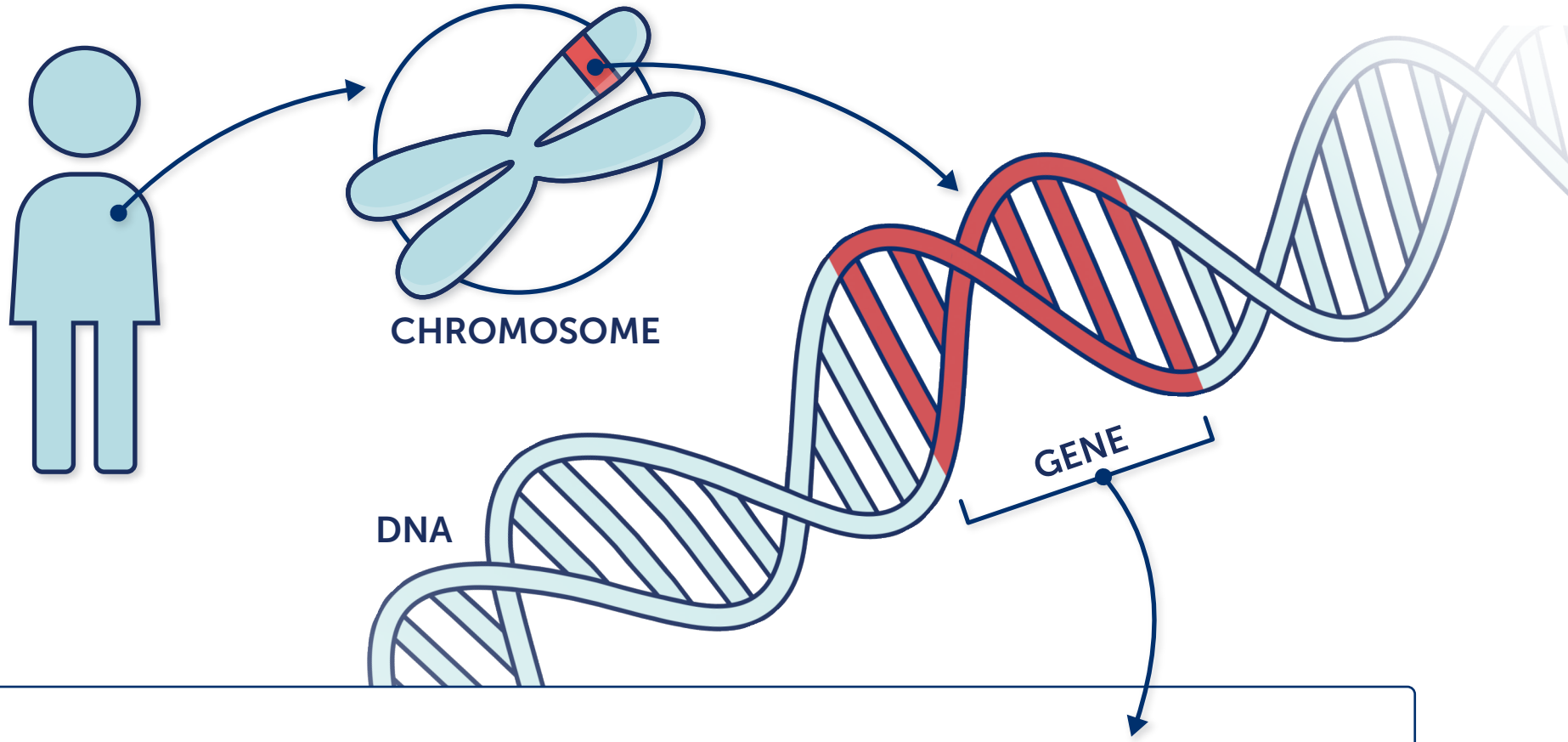
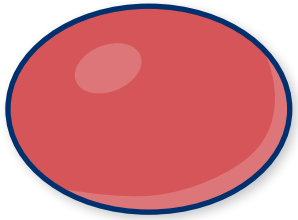
WHAT IS A GENE?



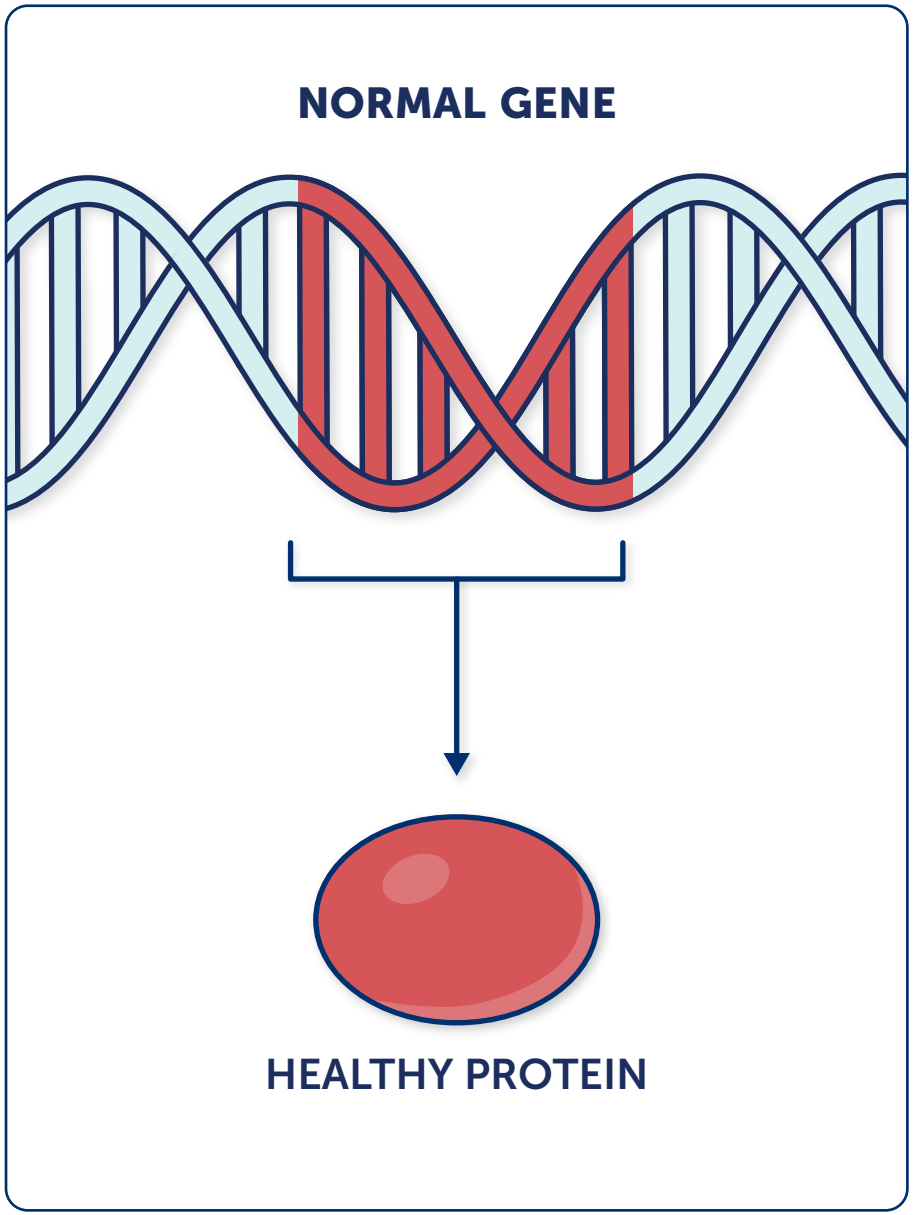
A **gene** is made up of **DNA**. It carries instructions to make proteins.

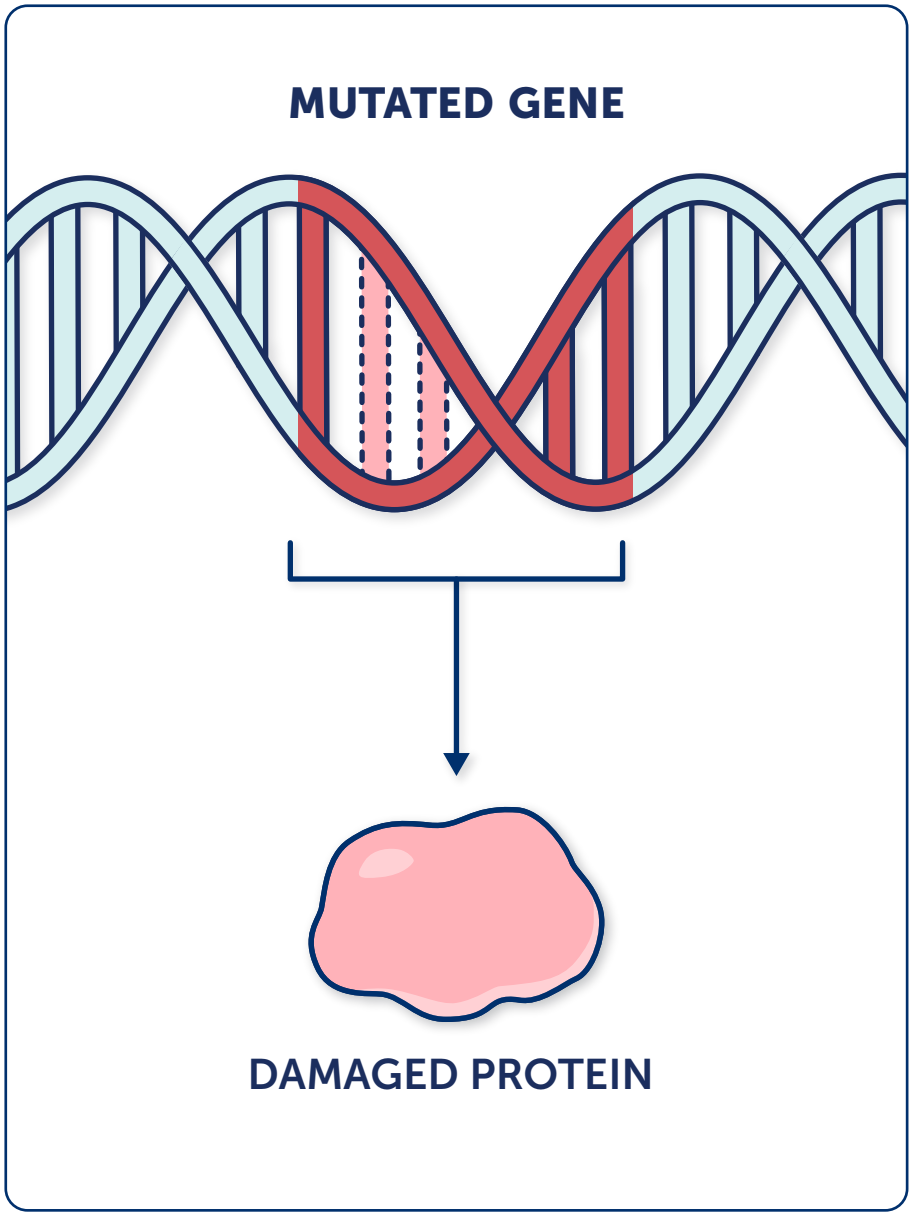
The **proteins** have specific jobs that help your body work normally.



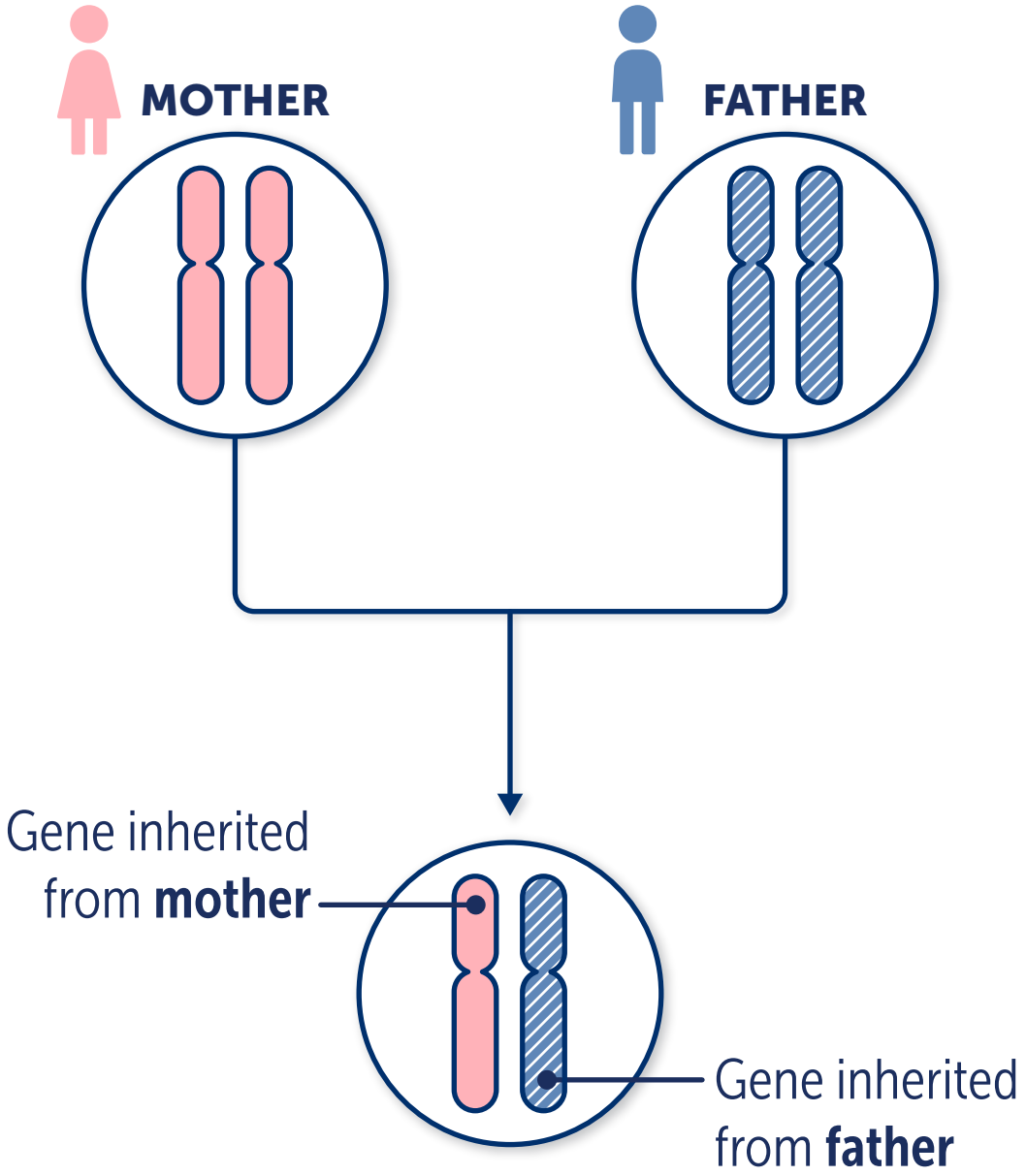
PROTEIN

WHAT HAPPENS WHEN THERE IS A GENETIC MUTATION?

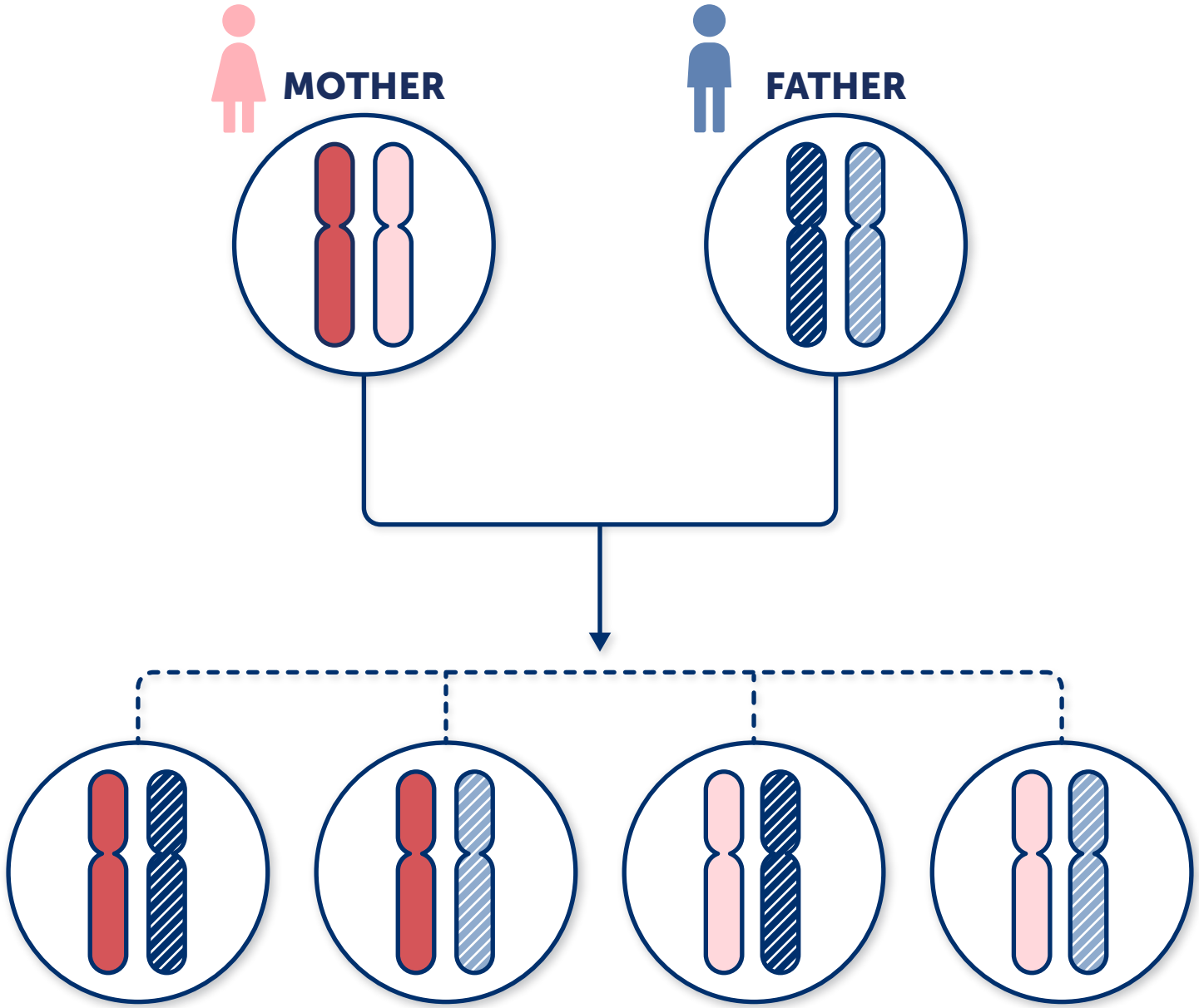




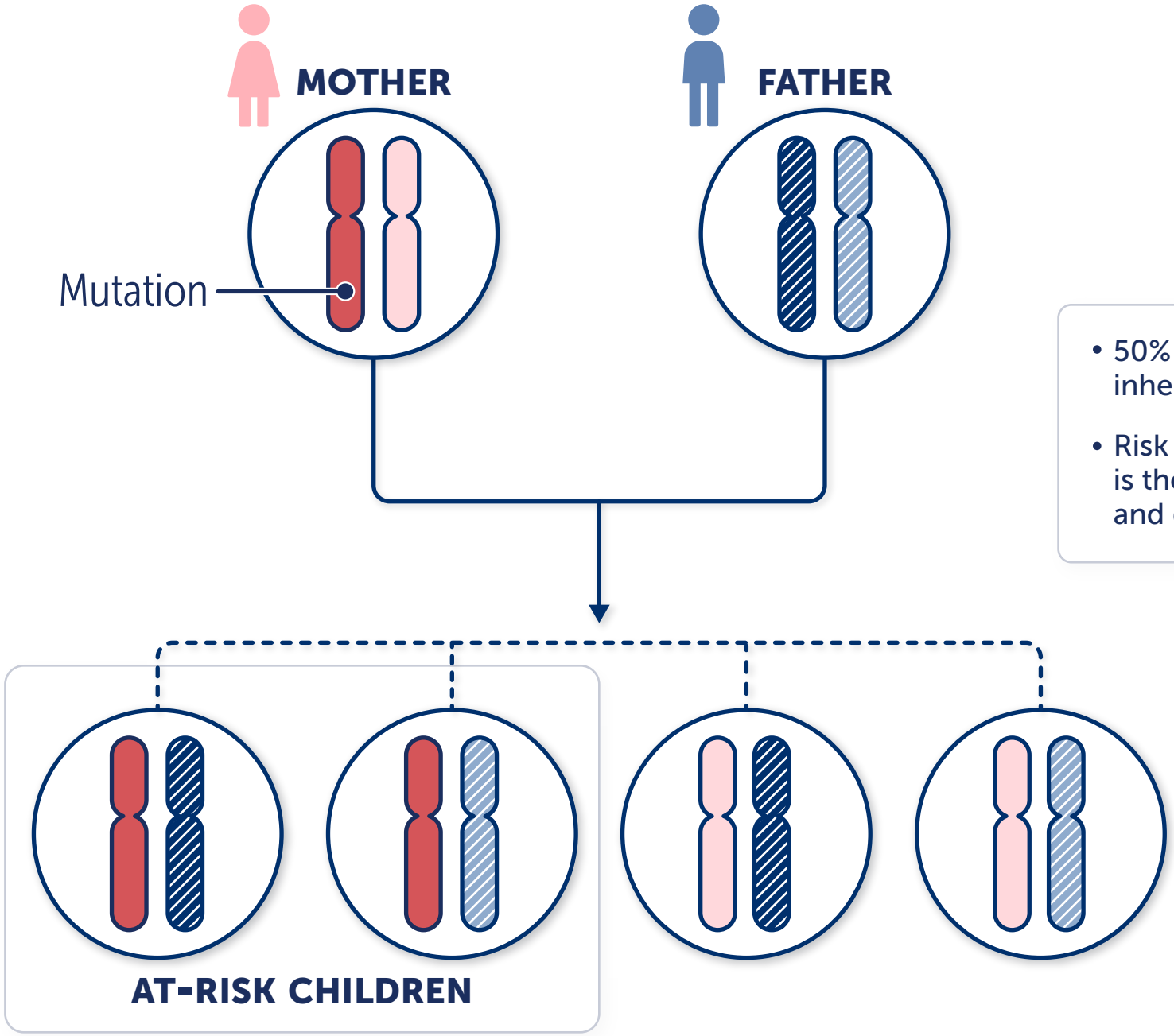
HOW ARE GENES INHERITED?



HOW ARE GENES INHERITED?

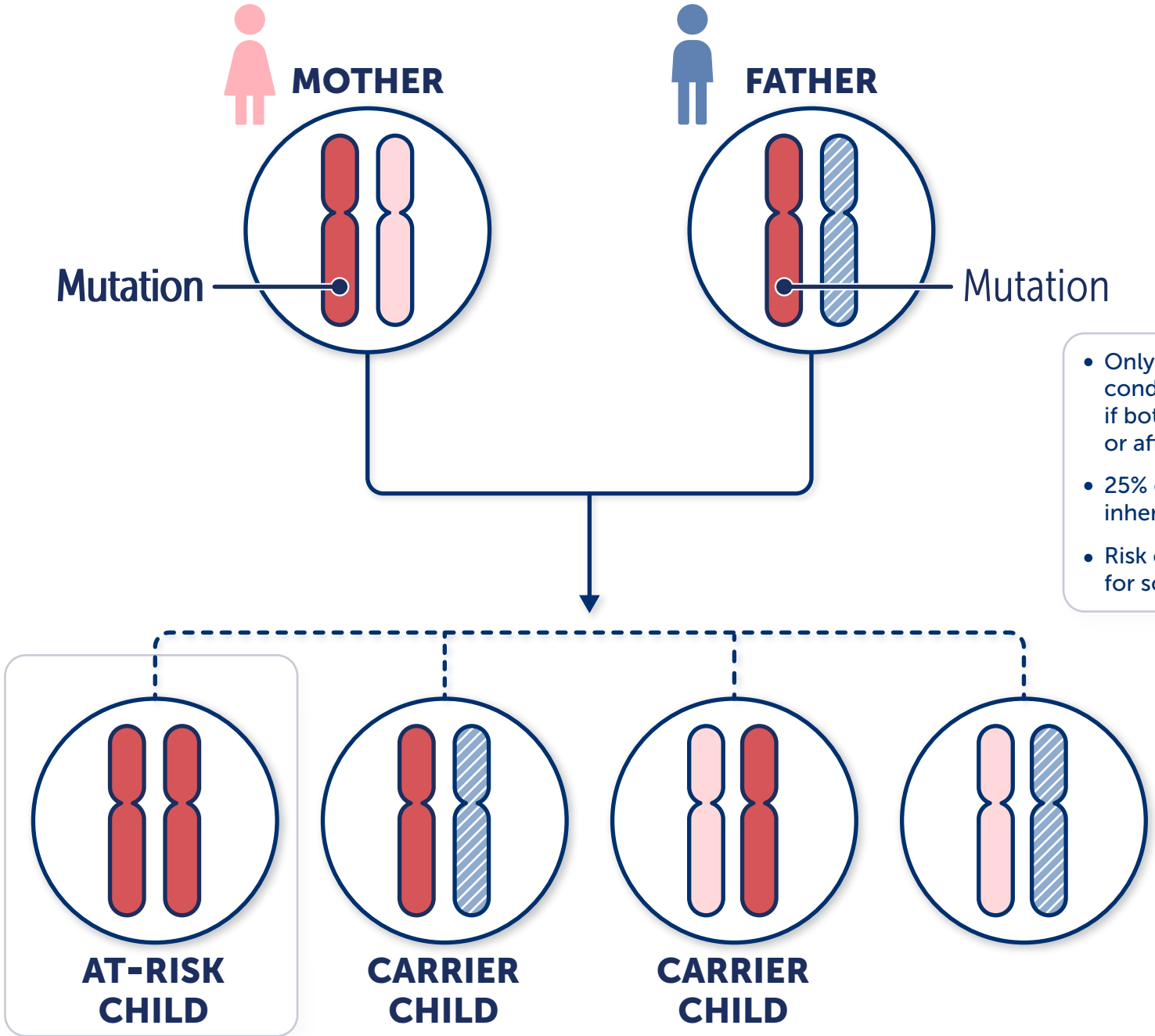


AUTOSOMAL DOMINANT INHERITANCE



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

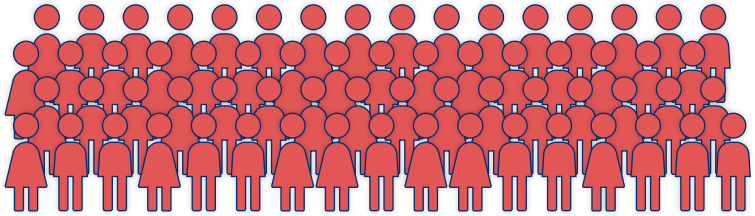
AUTOSOMAL RECESSIVE INHERITANCE



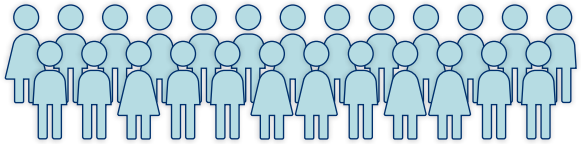
- Only at risk of inheriting the condition ("being affected") if both parents are carriers or affected.
- 25% chance of child inheriting both mutations
- Risk of inheritance is same for sons and daughters

CANCER CAN BE HEREDITARY, FAMILIAL, OR SPORADIC

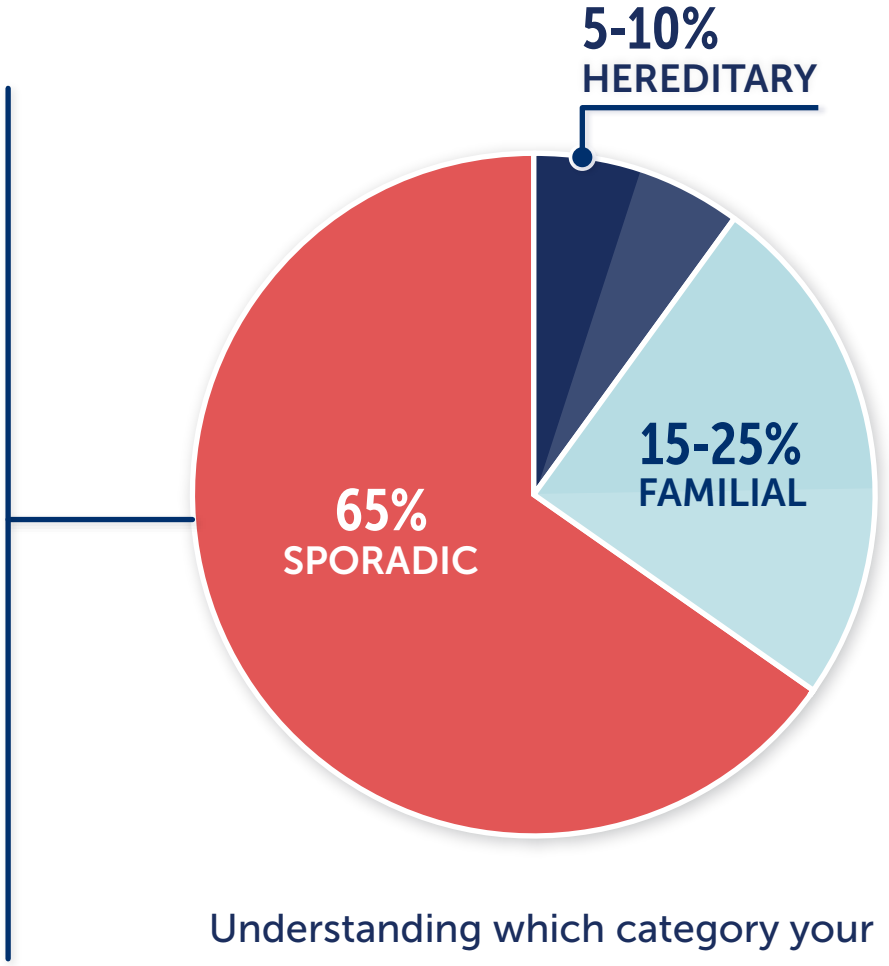
SPORADIC CANCER



FAMILIAL CANCER

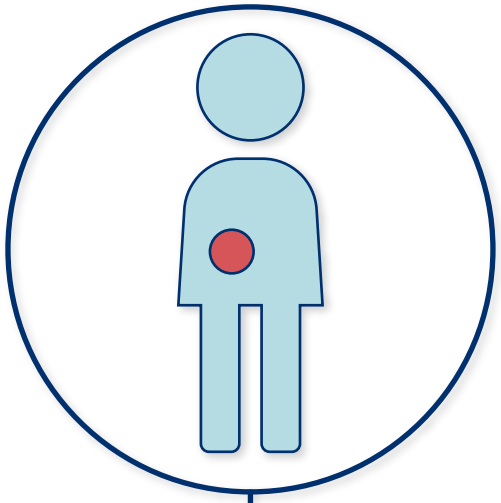


HEREDITARY CANCER



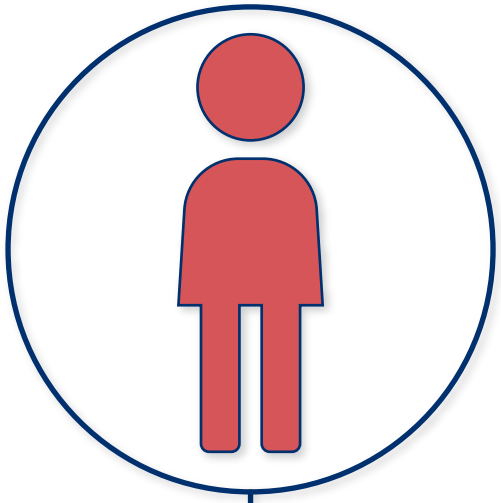
Understanding which category your cancer falls into will help guide the management of your risk better.

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)

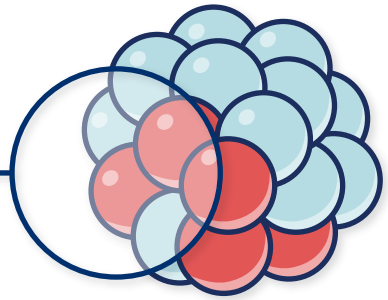


GERMLINE MUTATION

- 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.

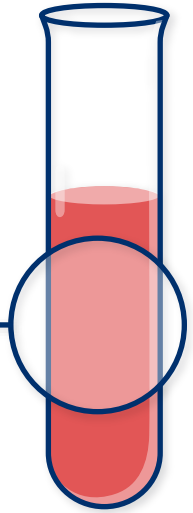
TUMOR TESTING VS GERMLINE TESTING

Tumor testing can help guide treatment options (e.g., chemotherapy)



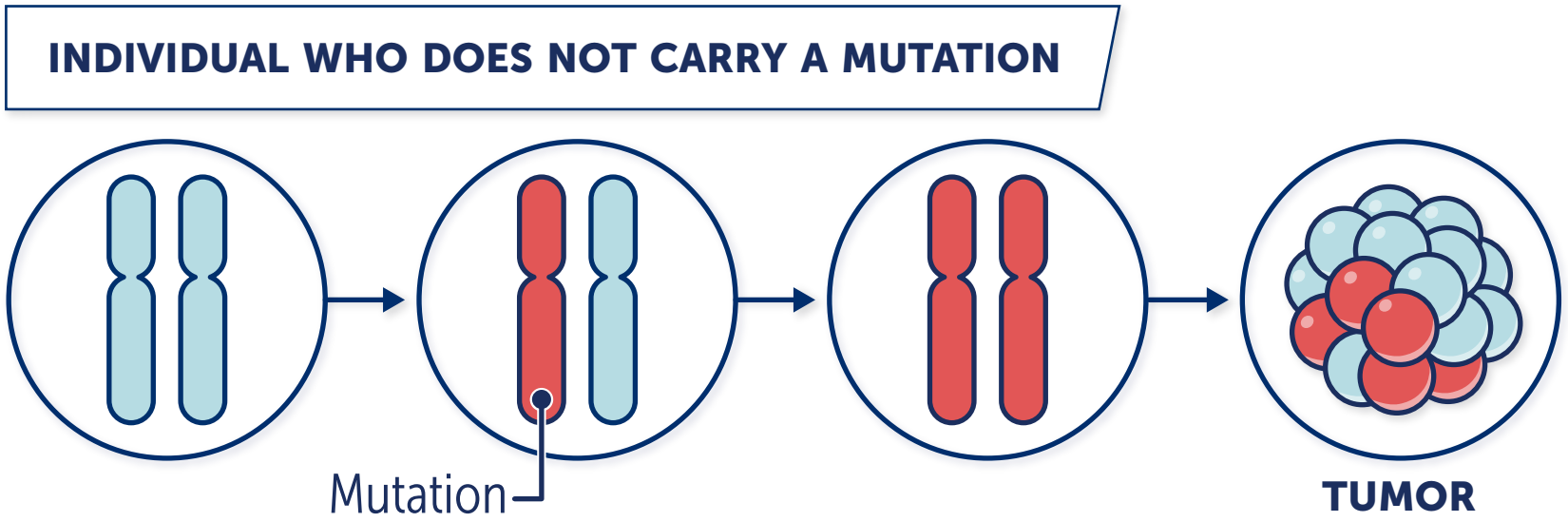
TUMOR BIOPSY

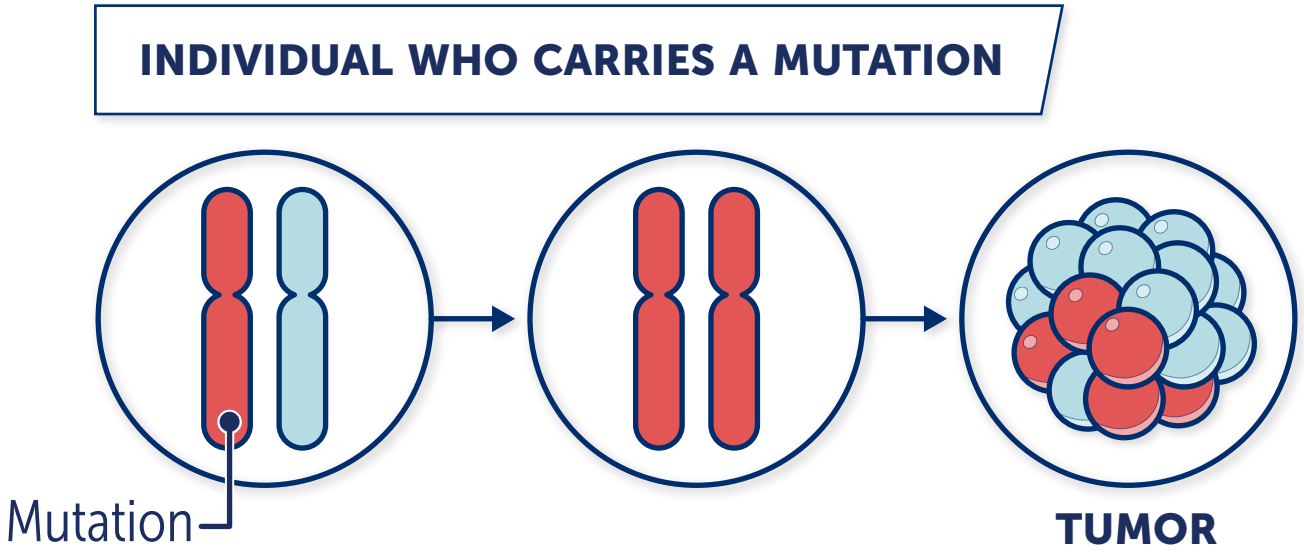
Germline testing can help determine if a mutation was inherited and help guide treatment and risk management options



BLOOD TEST

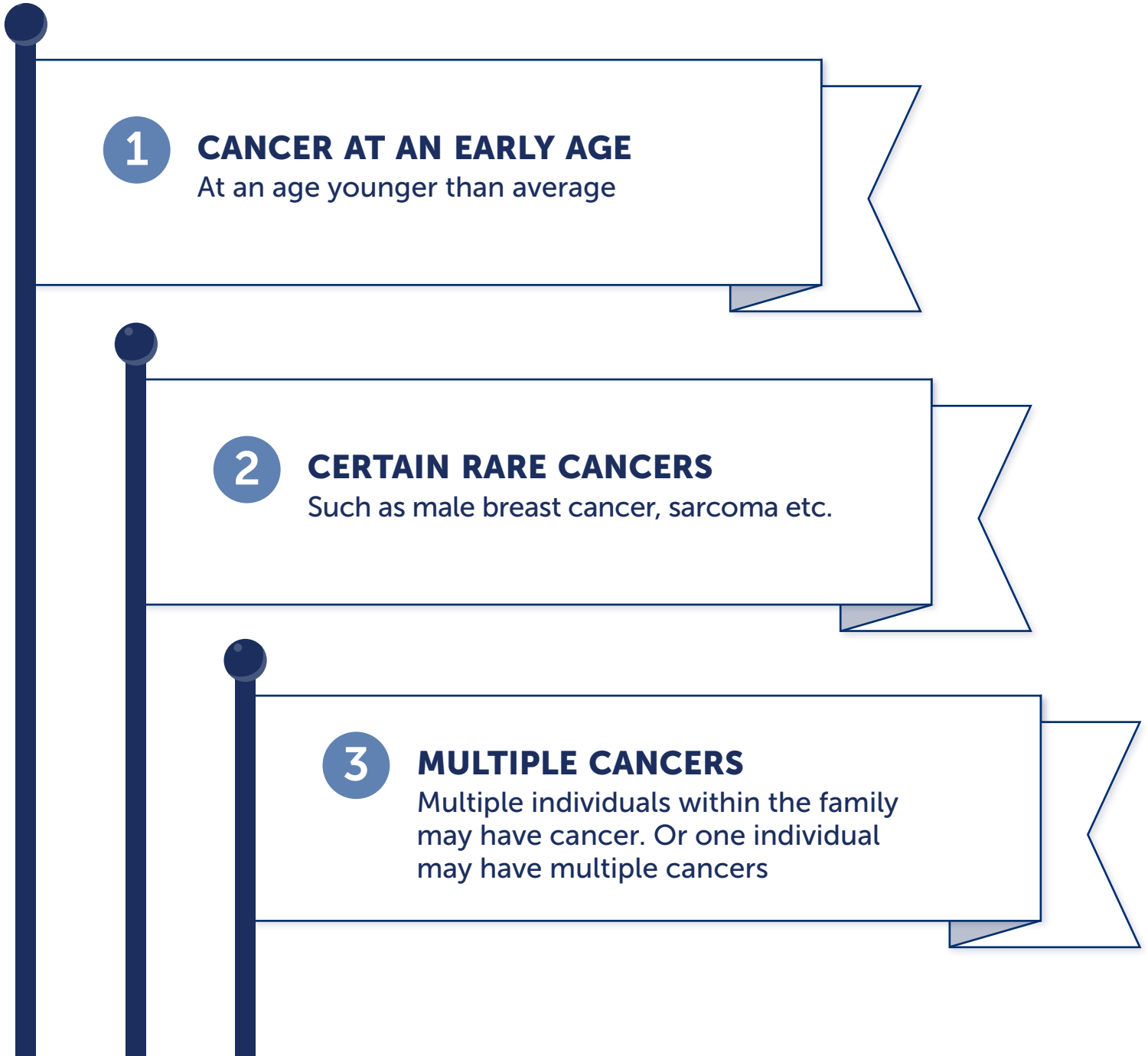
THE TWO-HIT HYPOTHESIS



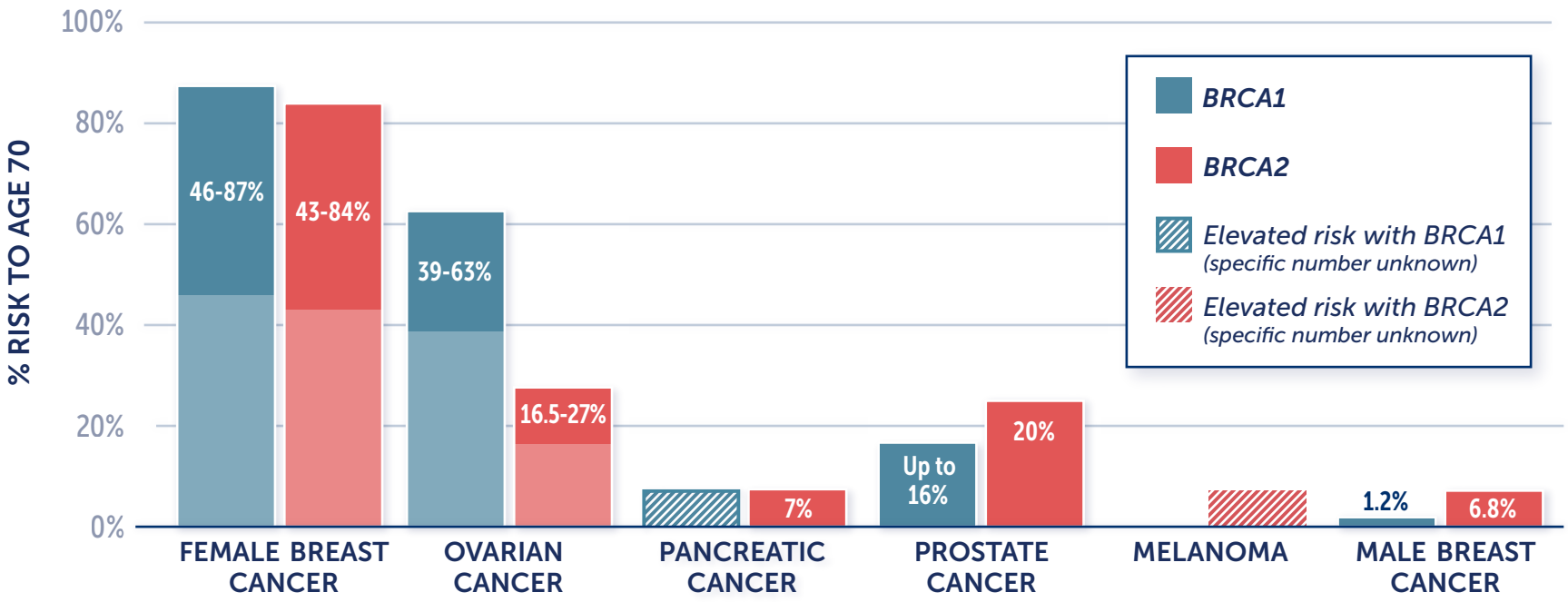


FLAGS FOR GENETIC TESTING

What are the common traits associated with hereditary cancer?

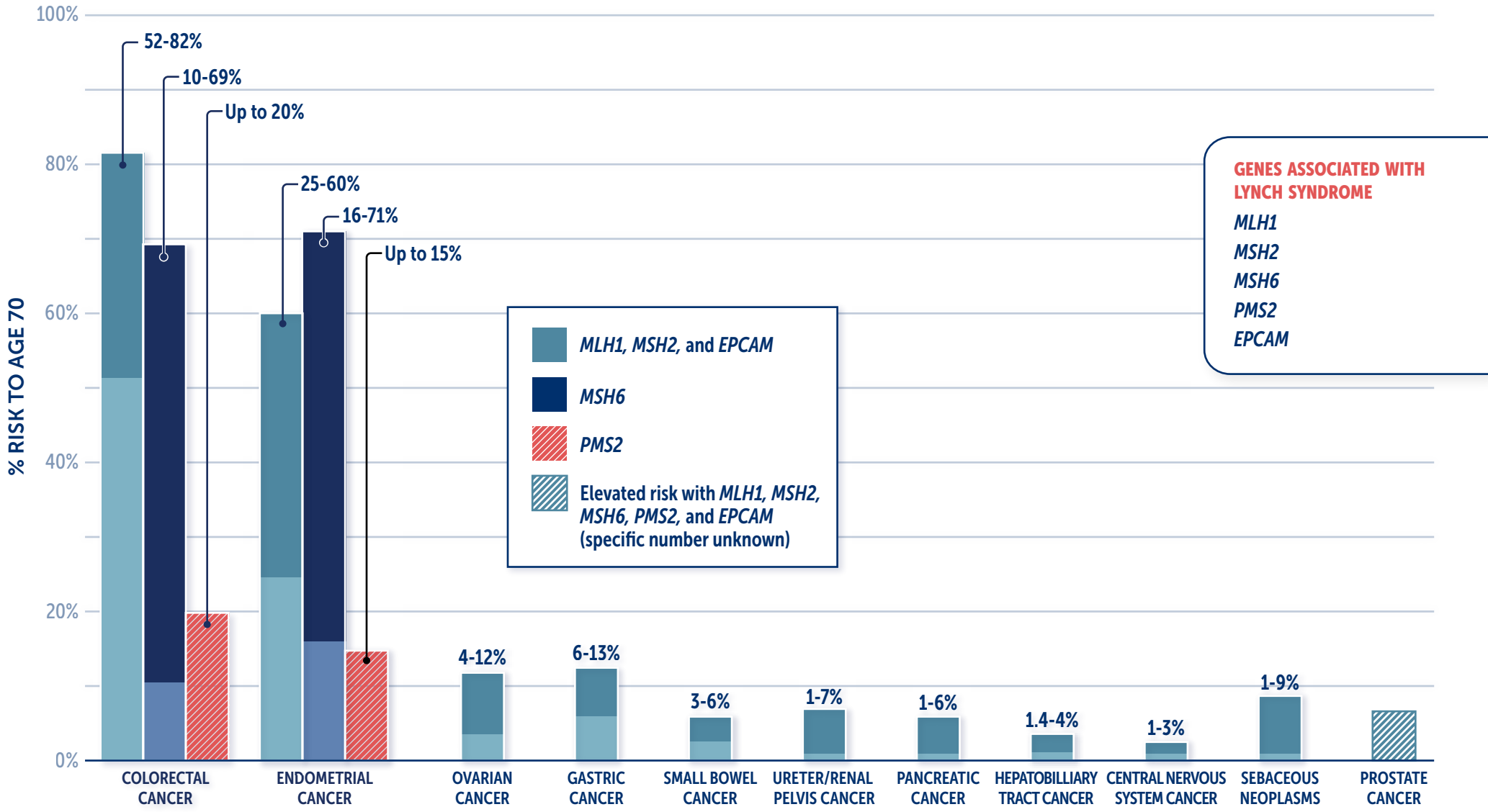


CANCER RISKS ASSOCIATED WITH *BRCA1* & *BRCA2*



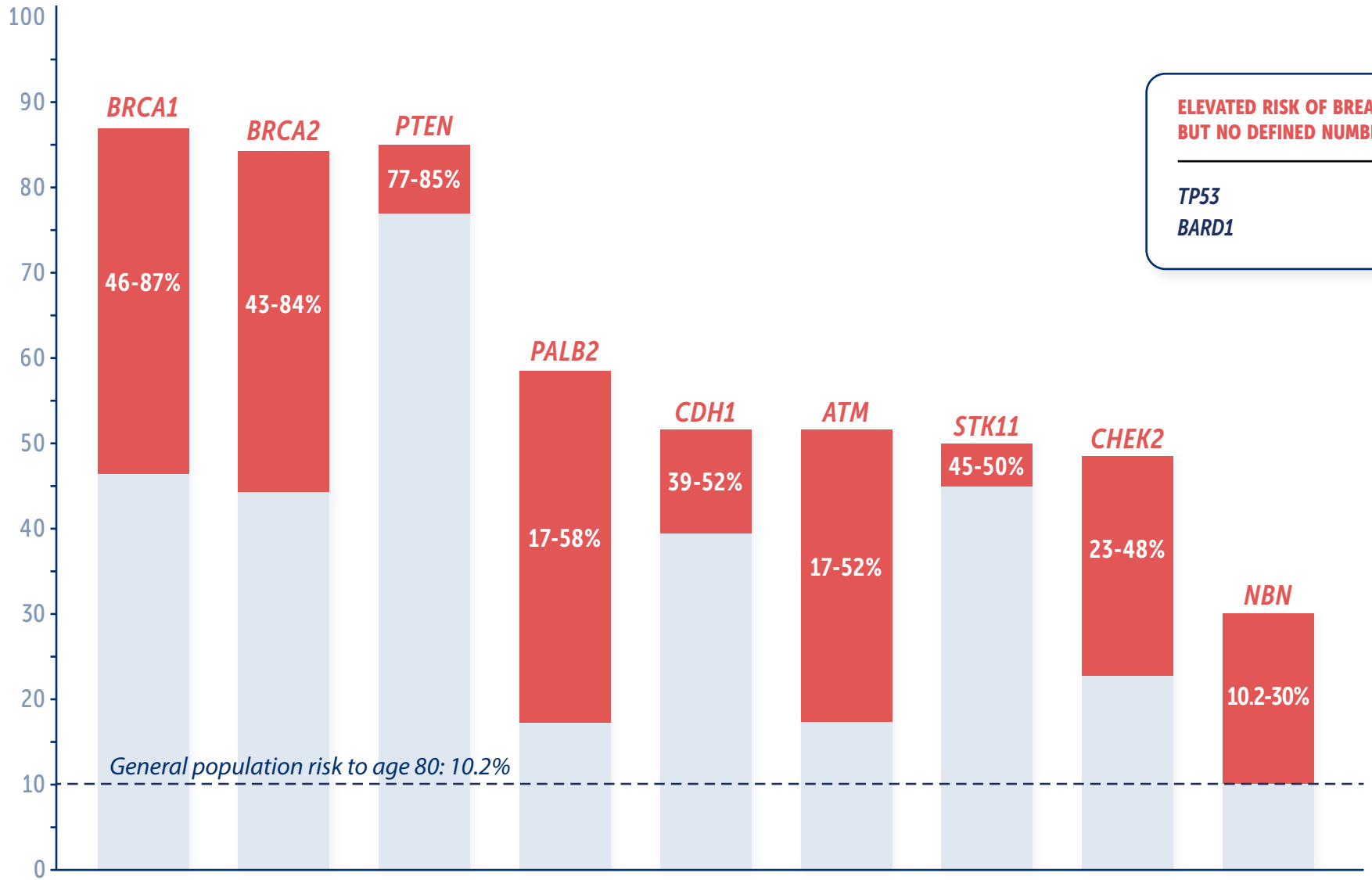
	BRCA1	*BRCA2*
Female breast cancer risk to age 50	28-51%	23-28%
Second breast cancer within 5 years of first diagnosis	20%	12%
Ovarian cancer risk to age 50	13-23%	0.4-4%
Ovarian cancer risk within 10 years of breast cancer diagnosis	12.7%	6.8%

CANCER RISKS ASSOCIATED WITH LYNCH SYNDROME



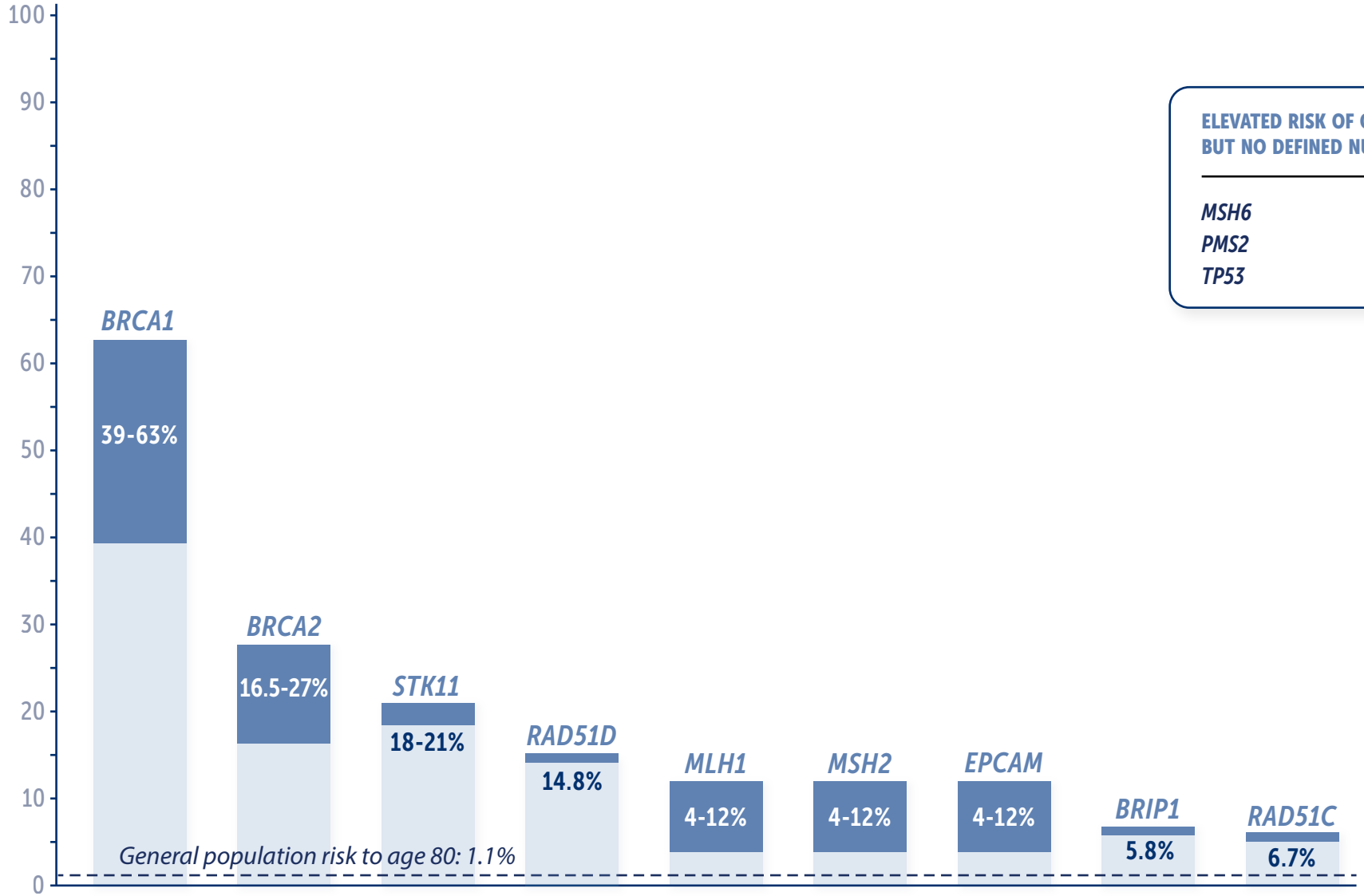
GENES ASSOCIATED WITH BREAST CANCER

and their associated risk ranges



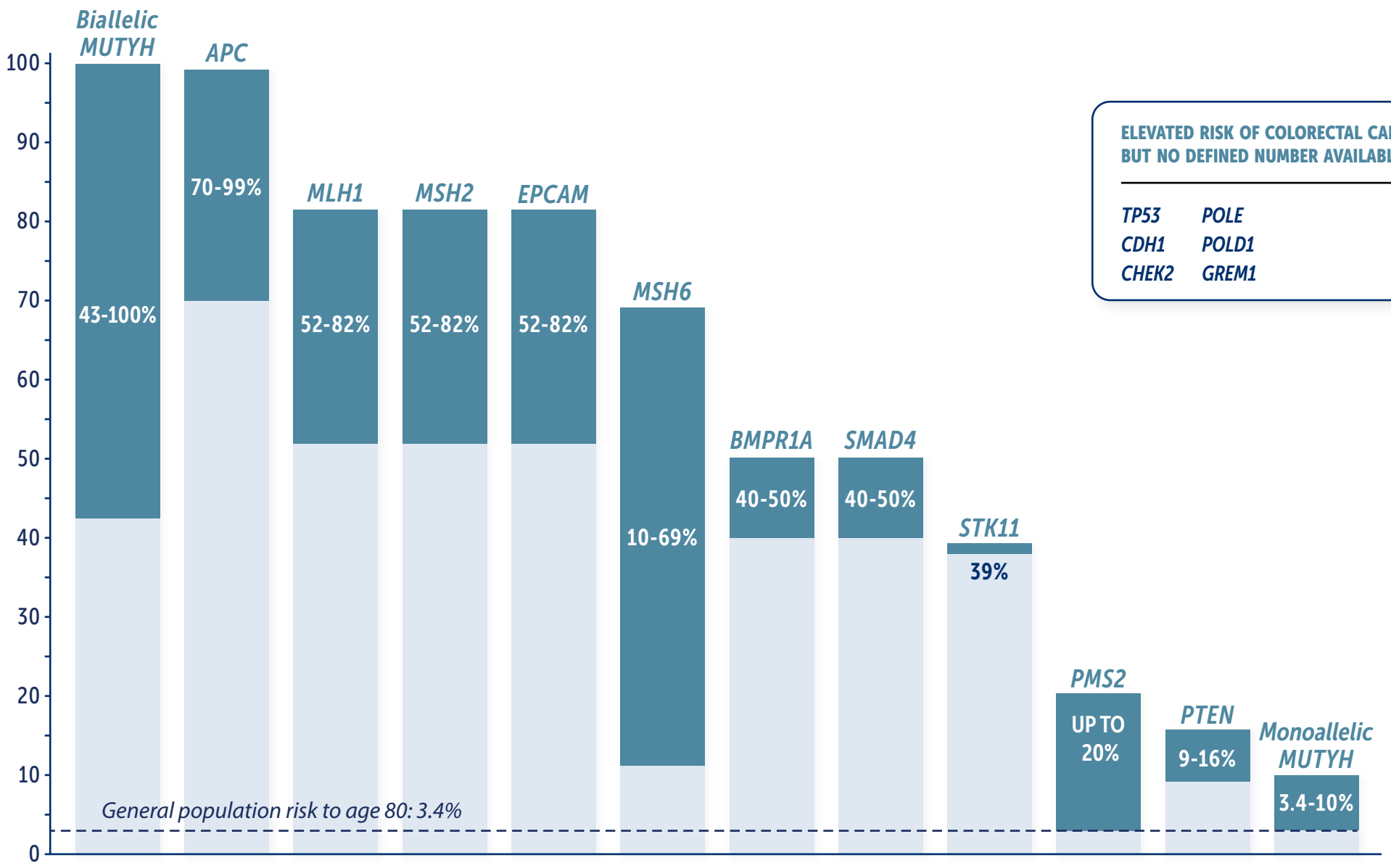
GENES ASSOCIATED WITH OVARIAN CANCER

and their associated risk ranges



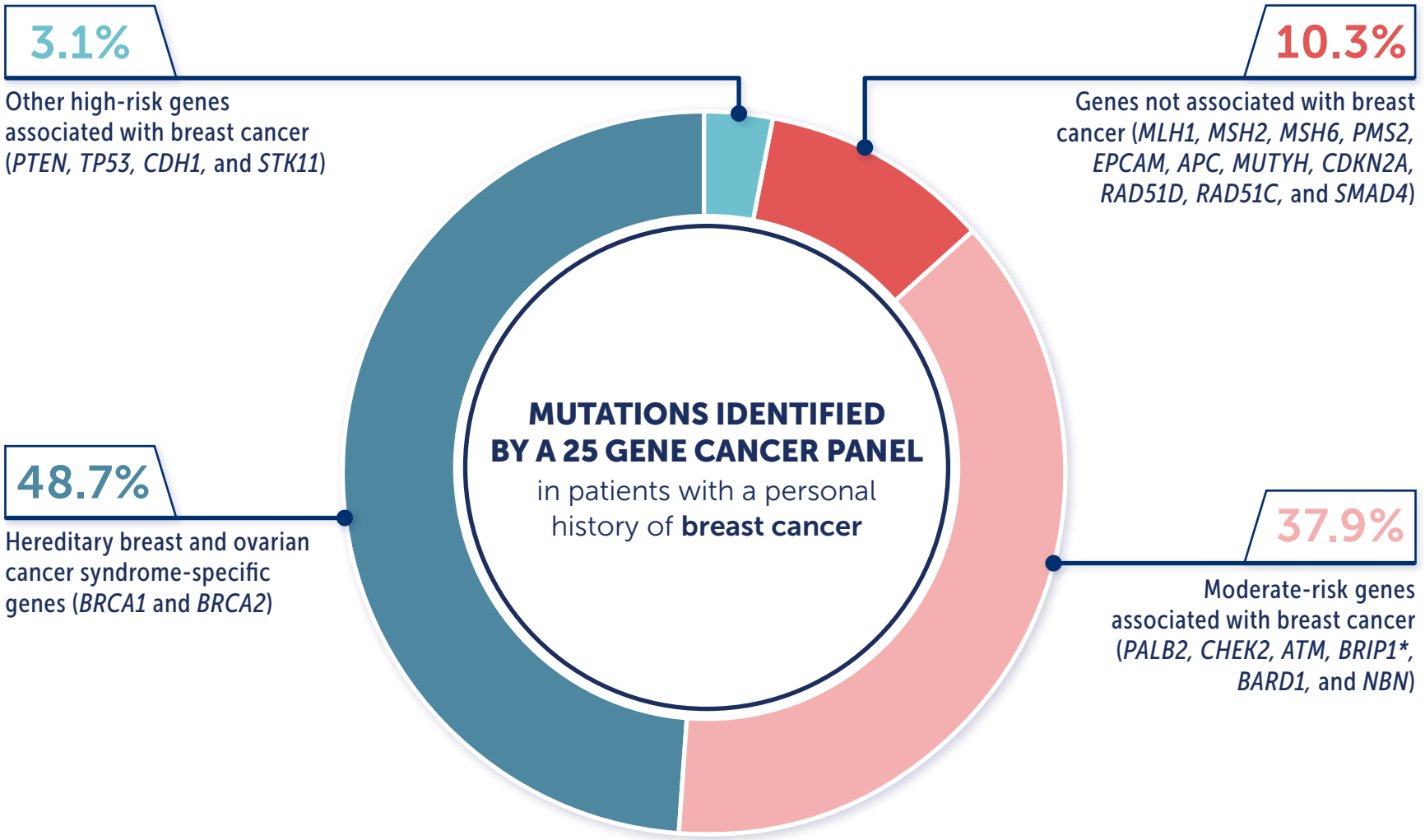
GENES ASSOCIATED WITH COLORECTAL CANCER

and their associated risk ranges



A PANEL APPROACH MAY CHANGE MEDICAL MANAGEMENT

*even if it includes genes not associated with **breast cancer***

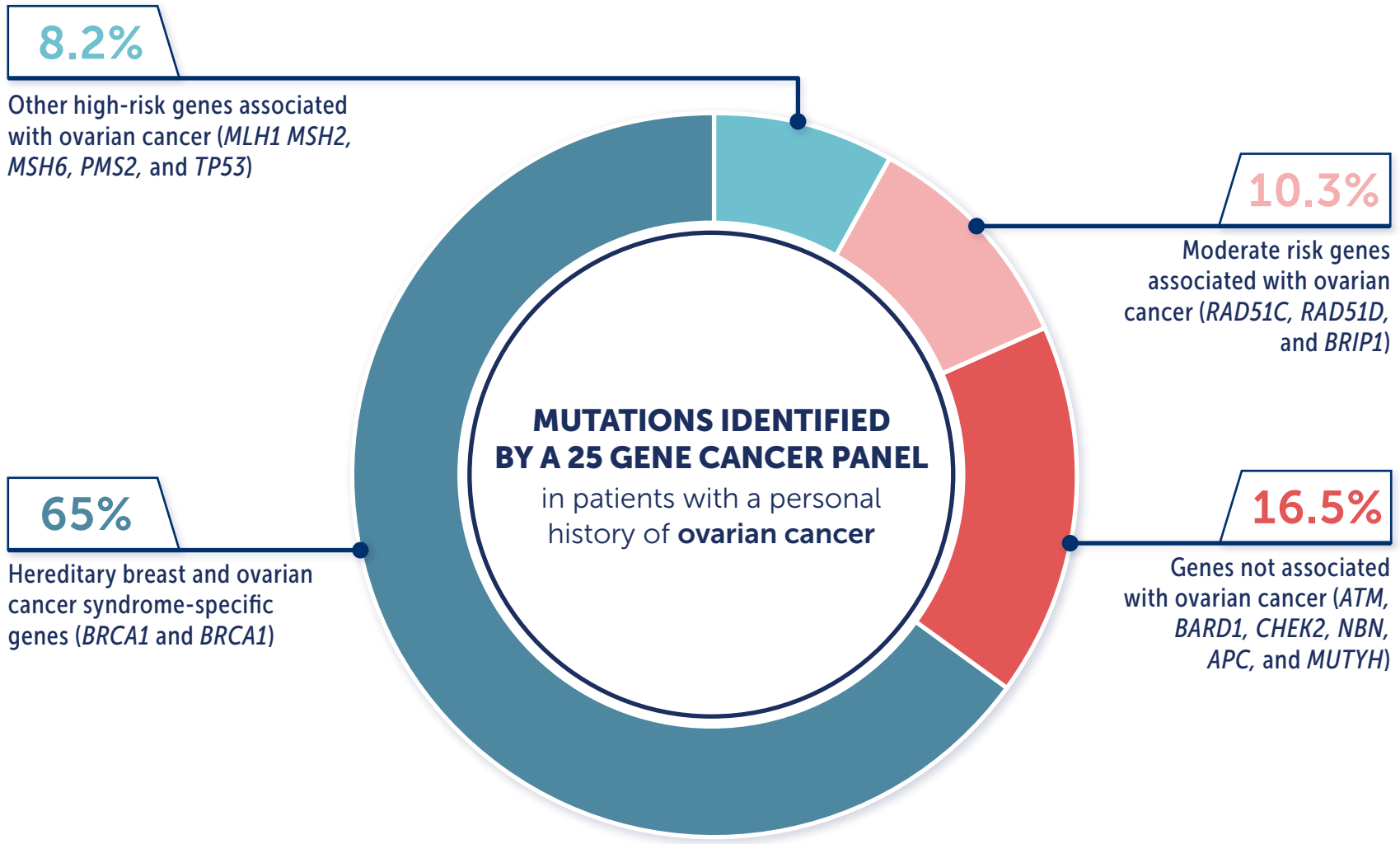


Sharma et al. Spectrum of Mutations Identified in a 25-gene Hereditary Cancer Panel for Patients with Breast Cancer. Presented at ESHG 2015

*Evolving data suggests that BRIP1 may not be associated with significantly increased breast cancer risk.

A PANEL APPROACH MAY CHANGE MEDICAL MANAGEMENT

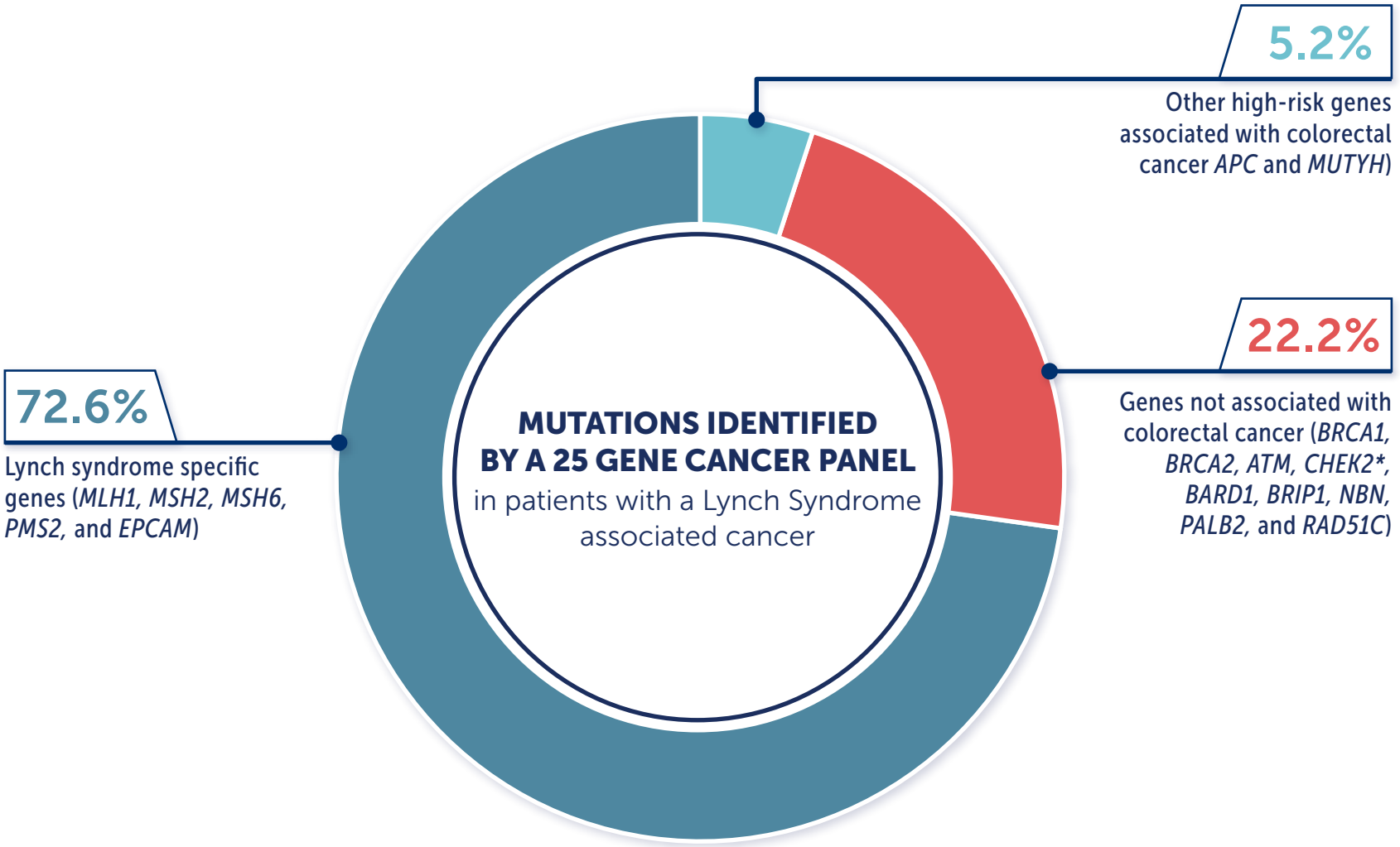
*even if it includes genes not associated with **ovarian cancer***



Langer et al. The Genetic Basis of Ovarian Cancer: Identifying Hereditary Ovarian Cancer Using a 25-gene Panel. Presented at SGO 2015

A PANEL APPROACH MAY CHANGE MEDICAL MANAGEMENT

*even if it includes genes not associated with **colorectal cancer***



Yurgelun, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients with Suspected Lynch Syndrome. Gastroenterology May 2015

*Evolving data suggests that CHEK2 may be associated with increased colorectal cancer risk.

TYPES OF RESULTS A PATIENT MAY RECEIVE AFTER GENETIC TESTING

NEGATIVE

Negative for the genes tested. Important to consider if there is a known mutation in your family

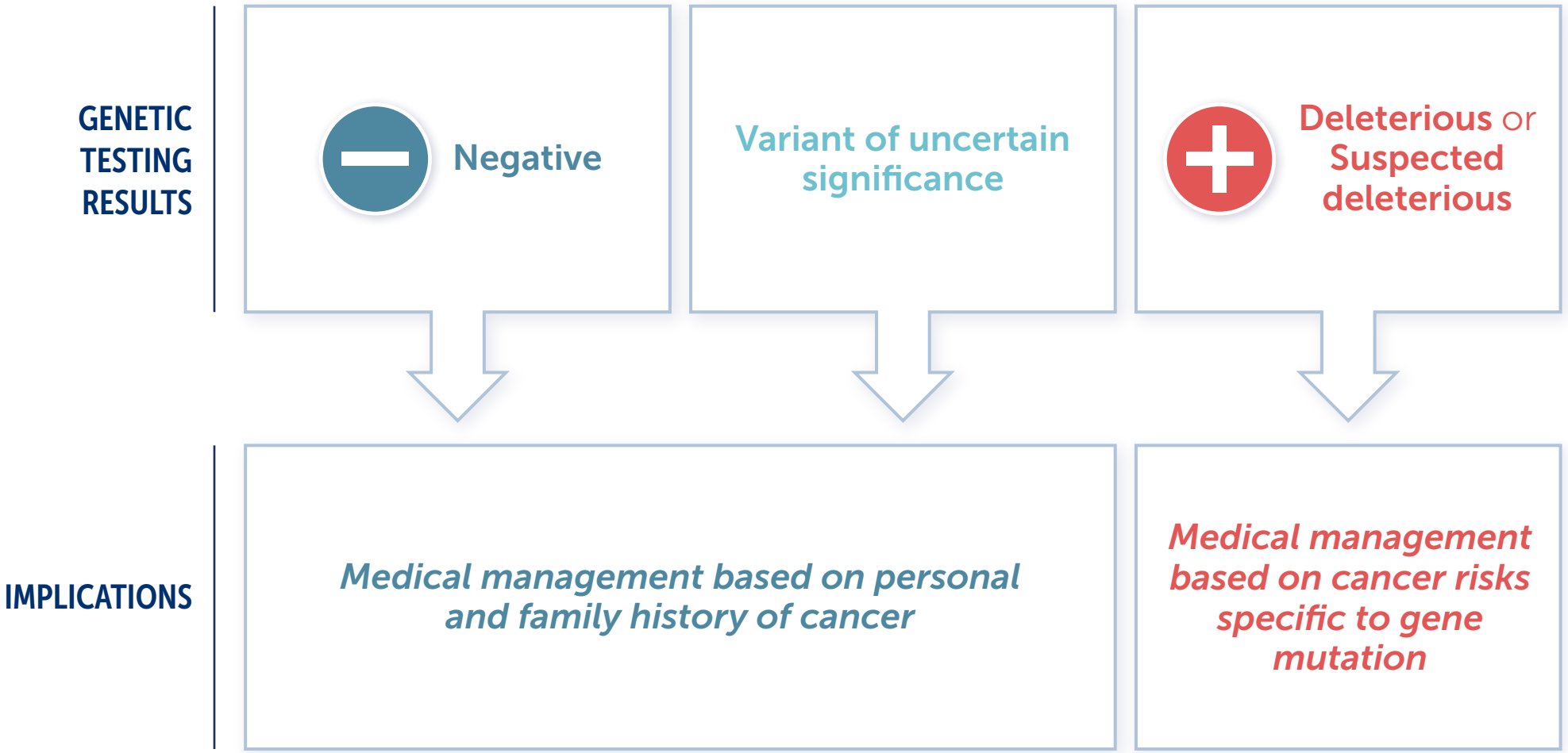
VUS *Variant of Uncertain Significance*

Unknown at this time if change identified is harmful

POSITIVE

Positive for a gene that increases the risk of cancer

WHAT DO THESE TEST RESULTS MEAN?



WHICH GENES HAVE MANAGEMENT GUIDELINES?

GENES WITH MANAGEMENT GUIDELINES

BRCA1	*MSH6*	*MUTYH*	*PTEN*	*SMAD4*	*BRIP1*	*POLD1*
BRCA2	*PMS2*	*CDKN2A*	*STK11*	*PALB2*	*RAD51C*	*GREM1*
MLH1	*EPCAM*	*CDK4*	*CDH1*	*CHEK2*	*RAD51D*	
MSH2	*APC*	*MLH1*	*BMPR1A*	*ATM*	*POLE*	

IMPORTANT OTHER GENES

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

NBN *BARD1*

Management guidelines are put forth by professional societies such as the National Comprehensive Cancer Network (NCCN)

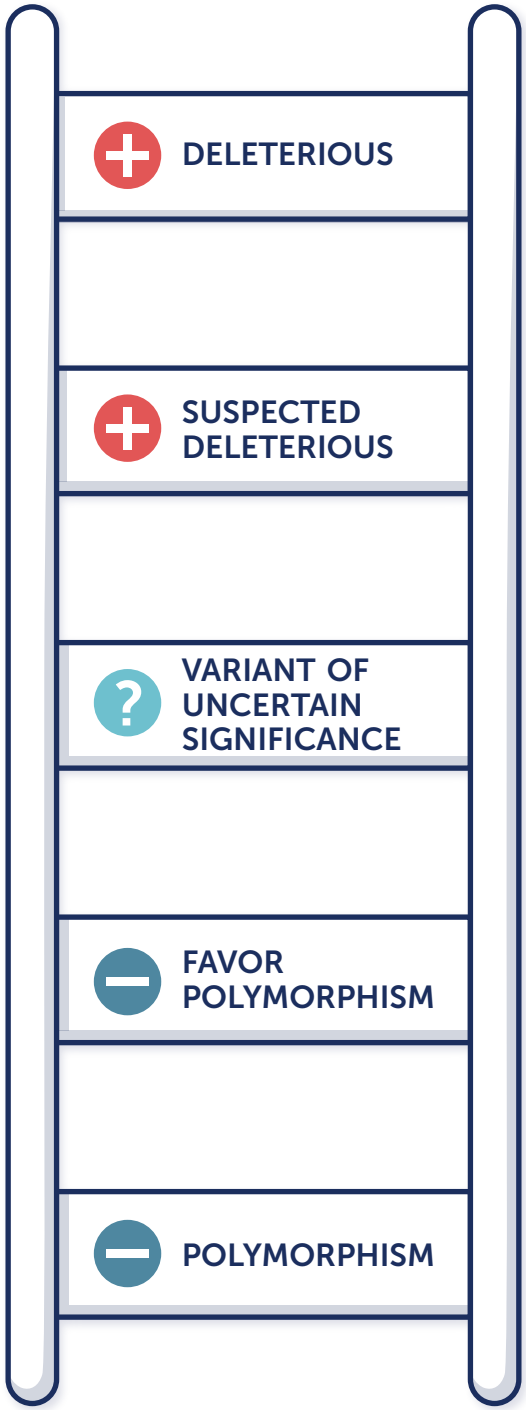
MANAGEMENT OPTIONS AVAILABLE FOR PATIENTS WHO TEST POSITIVE

HEREDITARY CANCER RISK

FAMILIAL CANCER RISK

GENERAL POPULATION CANCER RISK

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



VUS

Variant of Uncertain Significance

A VUS is a change in a gene for which there is insufficient data at this time to know if it is:

a benign change - also known as a **polymorphism**

or

a mutation that causes an increased risk of developing cancer - also known as **deleterious**

VUS: DATA NEEDED TO CONFIRM IF BENIGN OR HARMFUL

HARMFUL

griy

EXPECTED

gray

BENIGN

grey

GINA

Genetic Infomation Non-Discrimination Act

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

However, it **does not protect** a patient from **discrimination with life insurance or disability**.

WHAT THIS MEANS FOR FAMILY MEMBERS

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

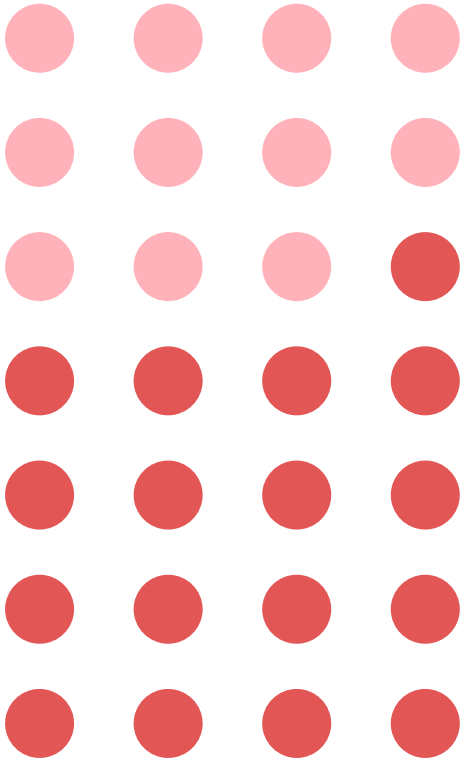
POSITIVE

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.

DISRUPTIVE GENE CHANGES



28 genes

Risk based on testing positive for one of these genes

MULTIPLE COMPLEX FACTORS

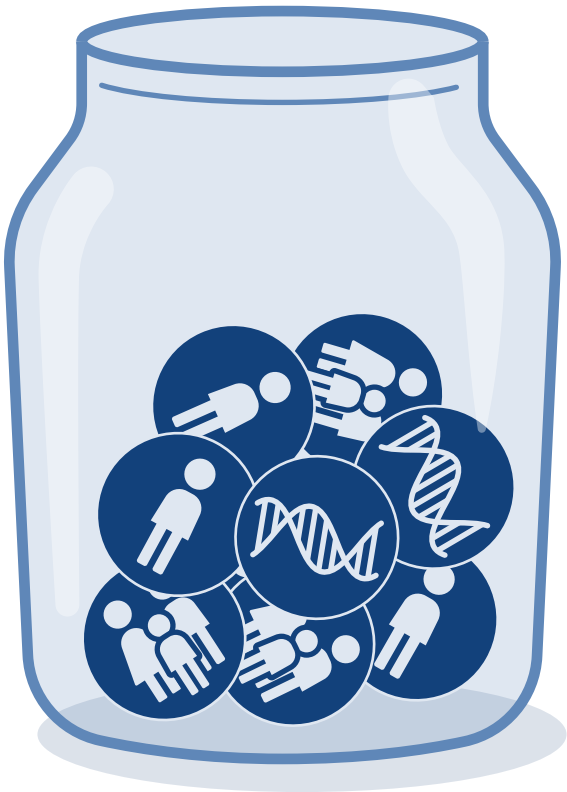
Genetic factors across genome

Family history of cancer

Personal clinical factors

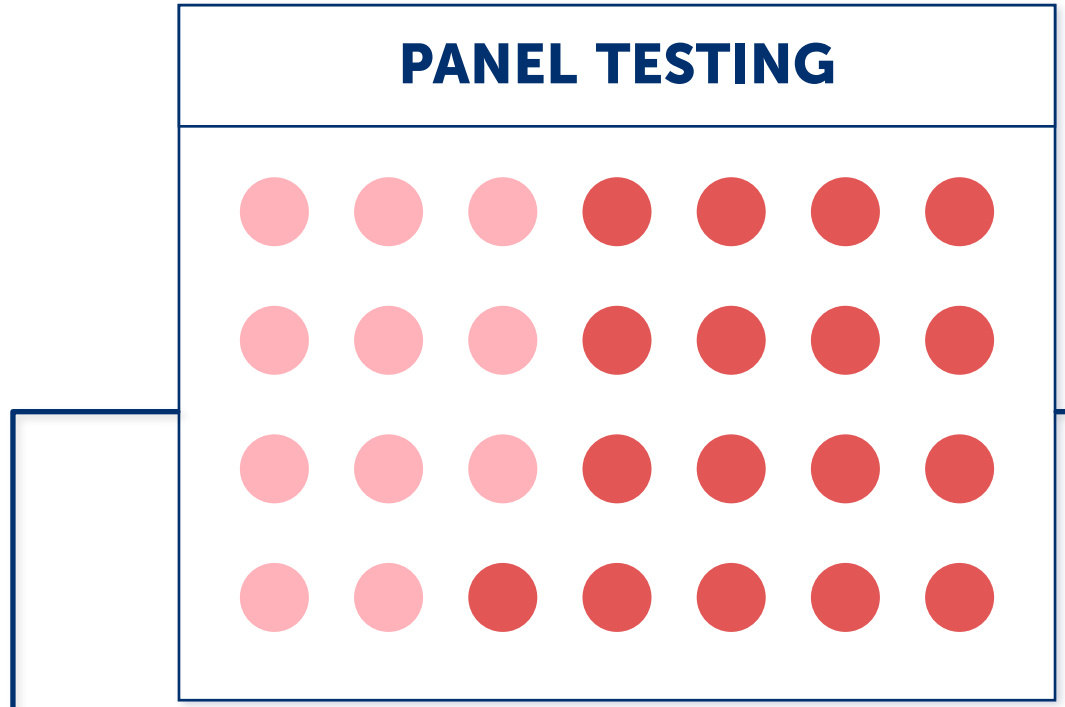
Risk based on complex calculation

RISK FACTORS:



Risk calculation

Risk calculation



POSITIVE

- *Discuss management options*
- *Discuss family members*

NEGATIVE

Risk model to help determine breast cancer risk

- *Discuss management options*
- *Discuss family members*