Identifying Your Risk for Hereditary Breast and Ovarian Cancer

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Boulder Community Health

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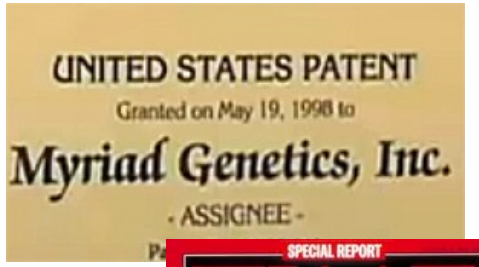
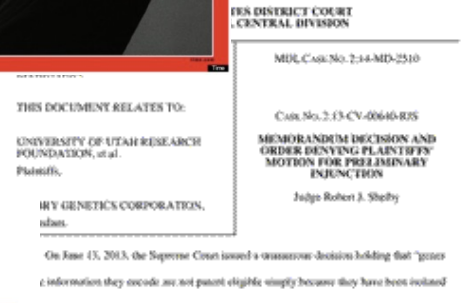
You may have seen….



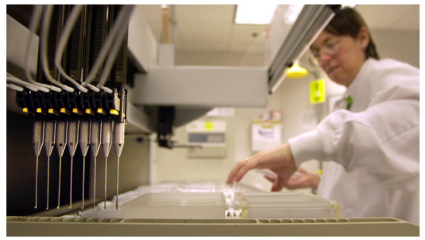


TREATMENTS

Women With Breast Cancer Miss Out On Recommended Genetic Testing

February 7, 2017 · 12:03 PM ET

JESSICA BODDY



Tests for mutations in BRCA genes that increase the risk of ovarian and breast cancer can help guide treatment and prevention.
Douglas C. Pizac/AP

Women with breast cancer who are at high risk for having a BRCA mutation that raises cancer risk often don't get genetic testing, or even a chance to speak with a genetic counselor who'd help them weigh the necessity of such a test, a study finds.

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…or have even been curious…

…but what does hereditary cancer really mean?

Genetics of Cancer

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- All cancer is genetic, but not all cancer is hereditary.
- Cancer is caused by the abnormal growth of cells.
  - Abnormal growth can start when naturally occurring DNA damage builds up.

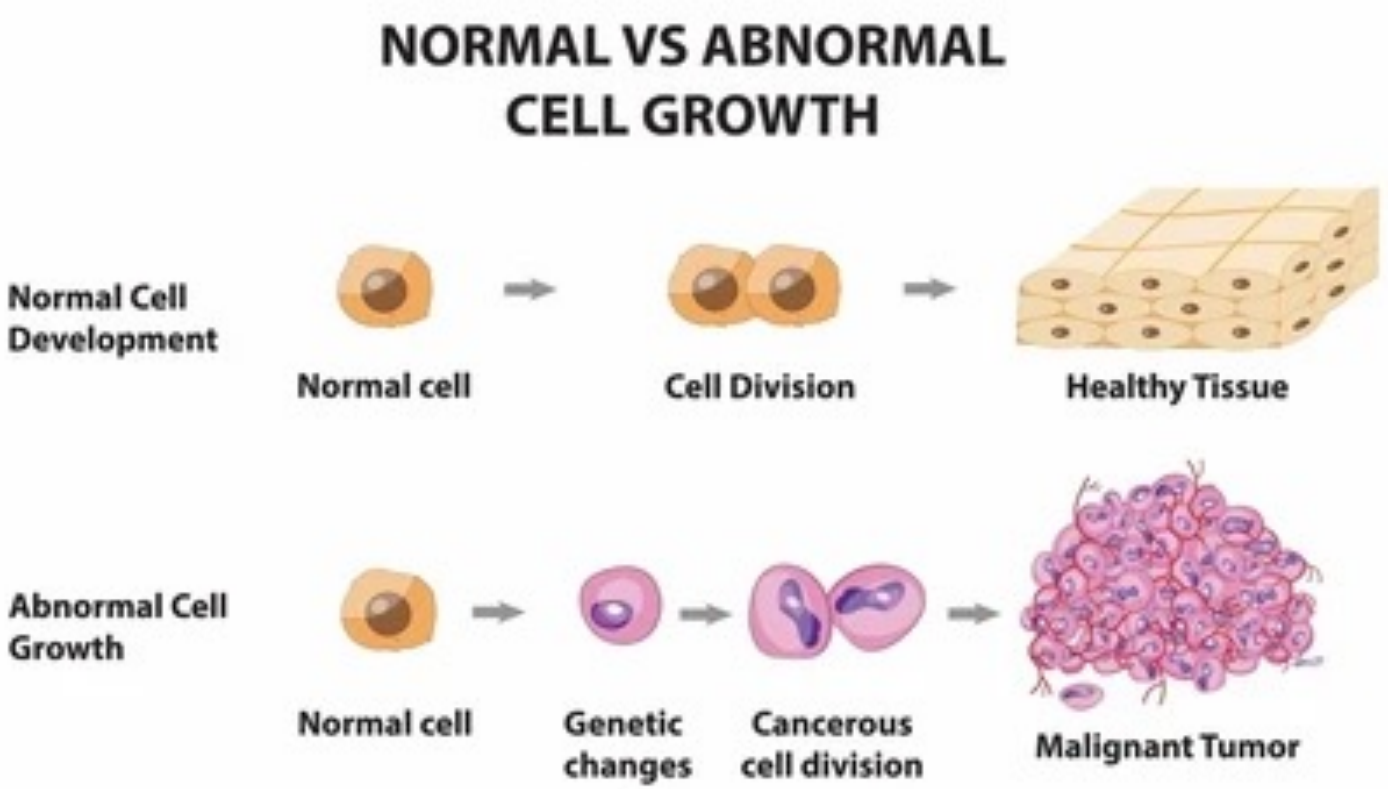

Image: https://www.shutterstock.com/image-vector/normal-vs-abnormal-cell-growth-development-2207801345

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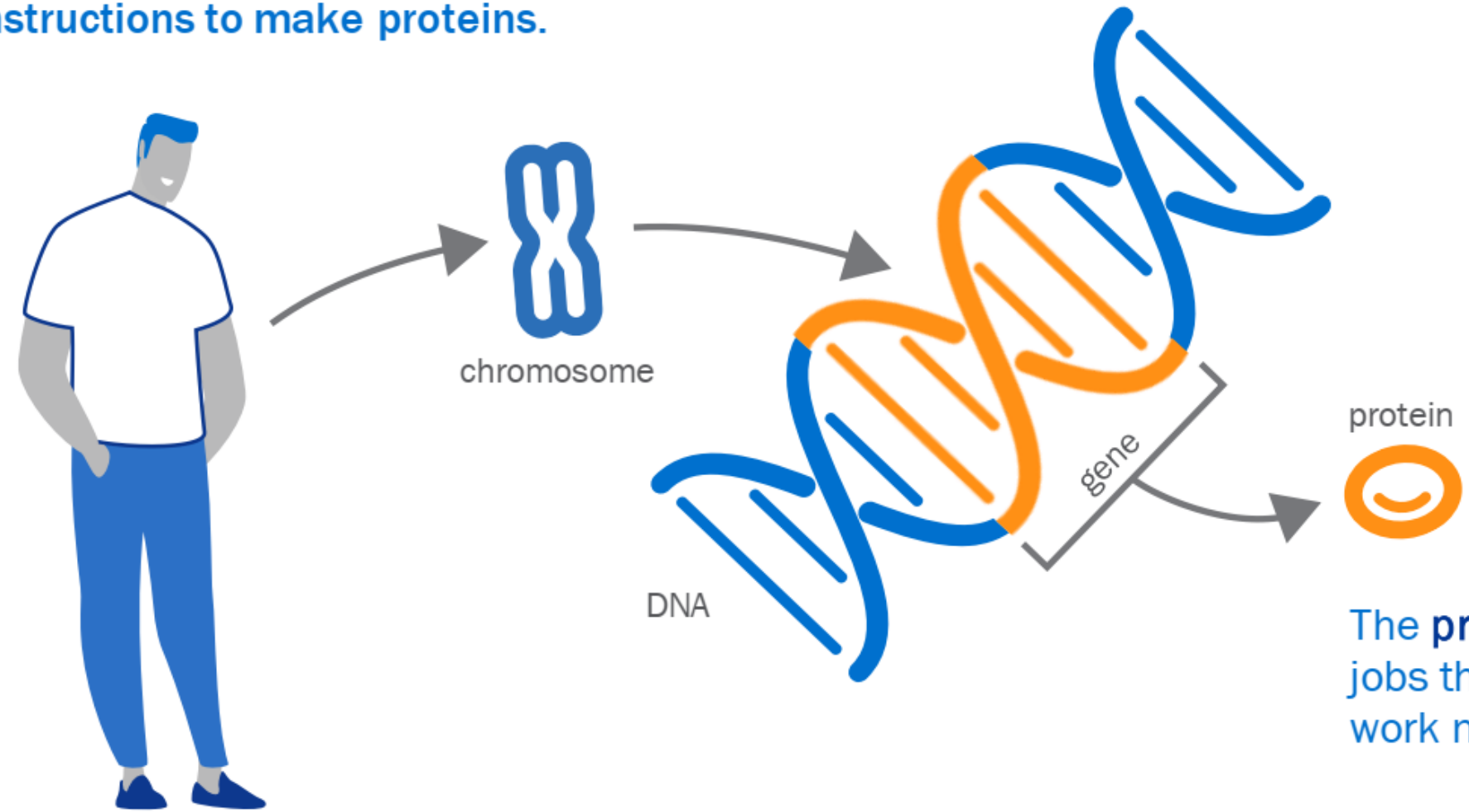
A gene is made up of DNA.

It carries instructions to make proteins.



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

Image credit: Myriad Genetics

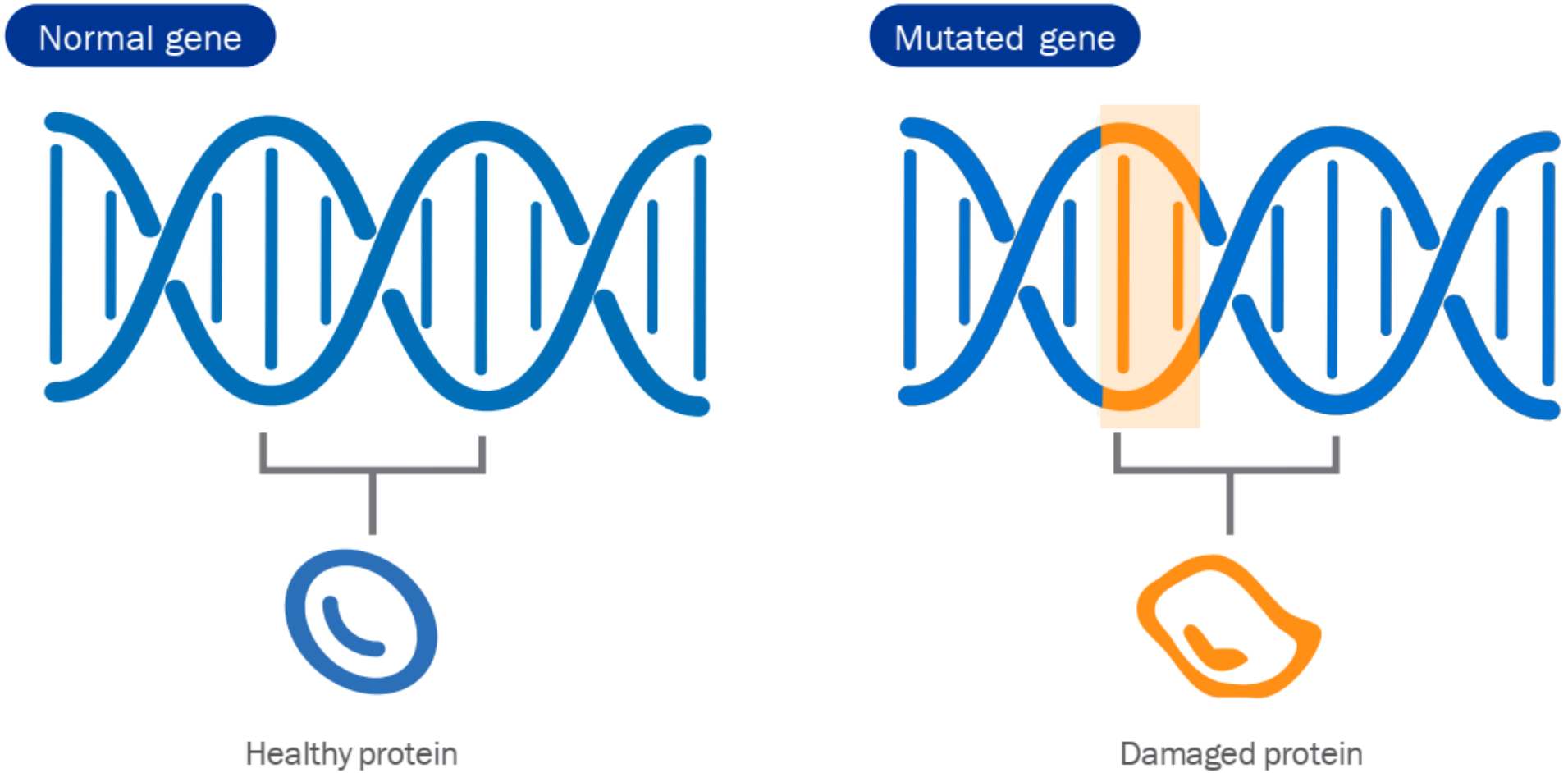


Image credit: Myriad Genetics

Variants vs. Mutations

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- Genetic variation is normal
  - Everyone is unique and no two people are the same.
  - Slight differences in the DNA code from person to person is what causes the variation we see in the human population.
- Mutations are typically harmful
  - Genetic changes that inhibit normal cell function.
  - Can be responsible for causing a disease.

Genetics of Cancer

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- Hereditary cancer is caused when a gene mutation is passed down through a family.
  - Can be inherited from either mother or father
- Only 5-10% of diagnosed cancers are considered hereditary.
- Familial cancer is when we see more cancer than we expect, but no gene mutation can be found on testing.

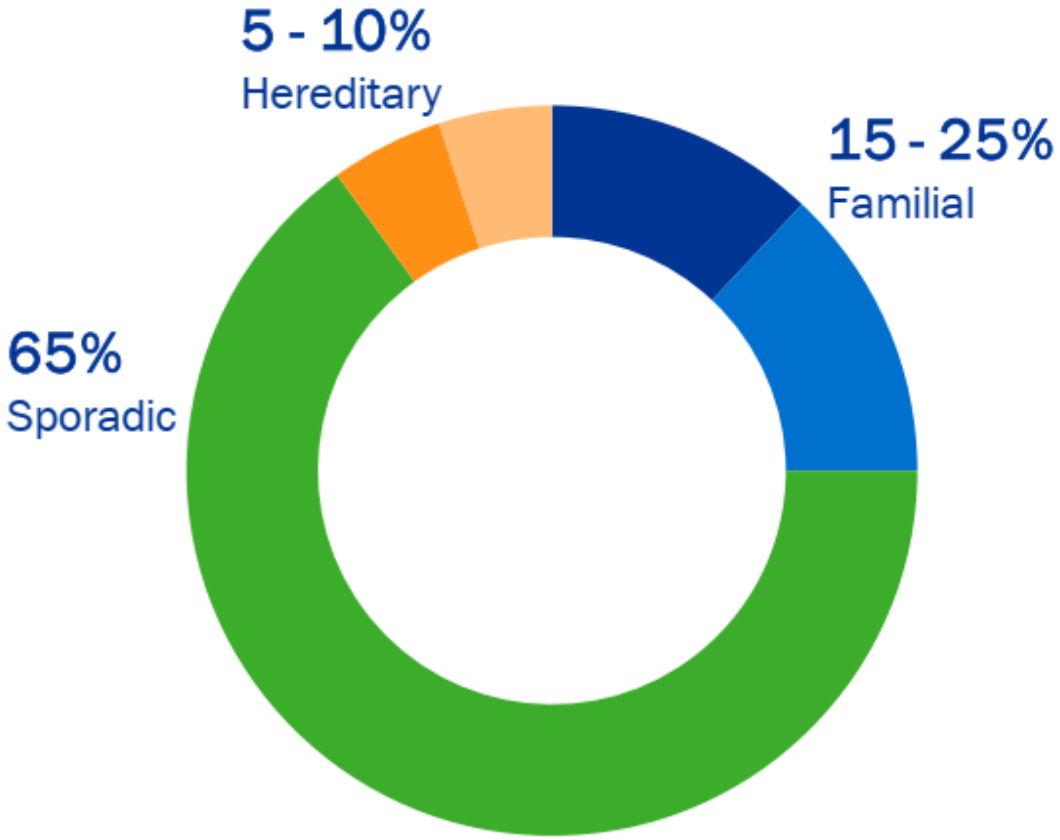

Image credit: Myriad Genetics

Identifying Hereditary Cancer

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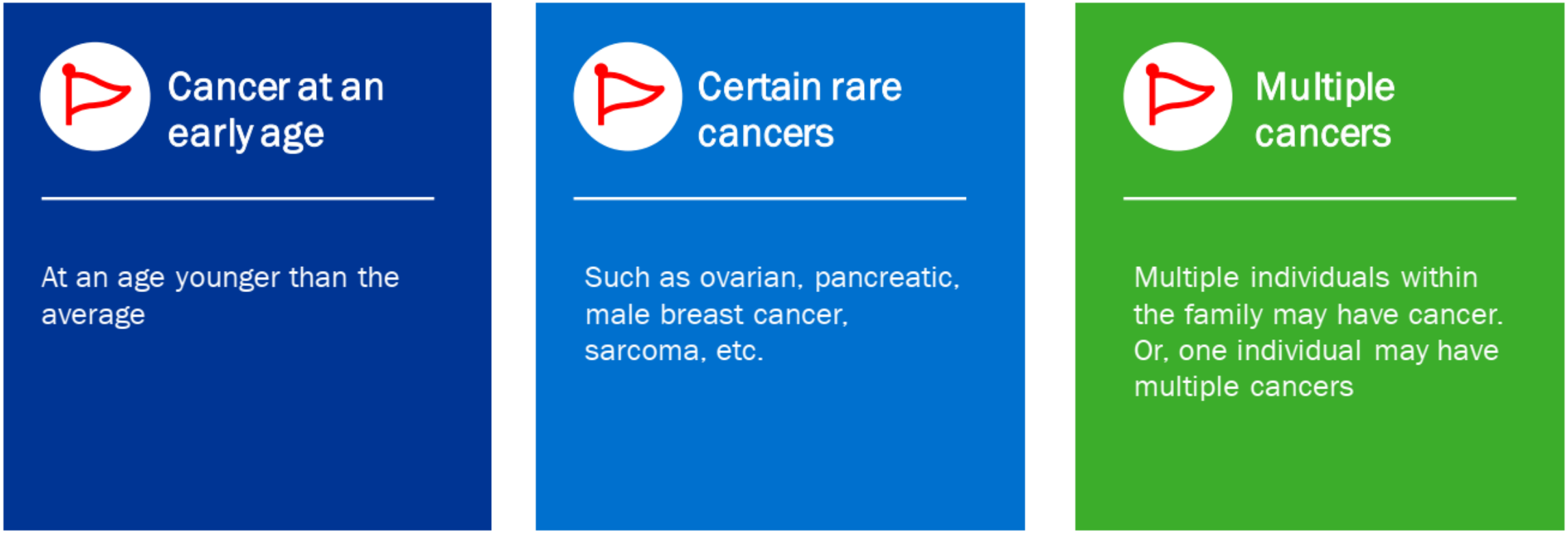
- Collect a family history
- Look for "red flags"
- Undergo genetic testing for genes known to cause hereditary cancer



Identifying Hereditary Cancer

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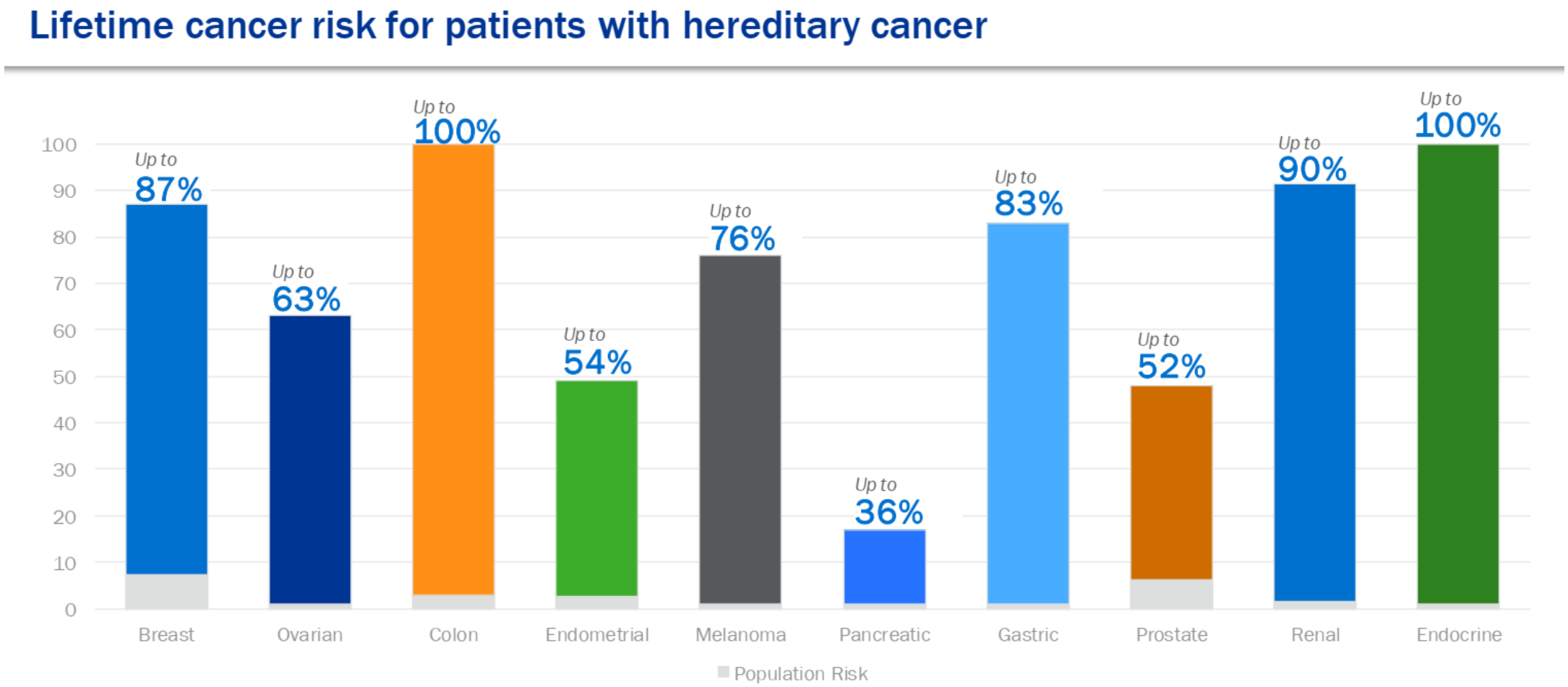
Why is it important to identify individuals with hereditary cancer?



Medical Management Options

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Hereditary cancer risk

Familial cancer risk

General population cancer risk

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

Genetic Testing for Hereditary Cancer

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- Can be for 1 gene or multiple genes at a time.
- Typically uses either a blood or saliva sample to collect DNA.
- Laboratories perform the sequencing and classify any variants found into different categories.

DTC Genetic Testing

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- Direct to Consumer (DTC) genetic testing has become more and more popular.
- DTC is testing not ordered by a health care provider.
- The sensitivity of DTC genetic testing is much lower than diagnostic testing.
  - Mutations can be missed!
  - Not all genes may be analyzed!
- FDA has issued a warning about DTC genetic tests:
  - "the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. **Results should be confirmed in a clinical setting before taking any medical action**."

Genetic Testing Results

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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

Genetic Testing Results

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Genetic testing results:

Implications:

Medical management based on personal and family history of cancer	Medical management based on cancer risks specific to gene mutation

Genetic Testing Costs / Legal Protections

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- Testing guidelines are based on personal and/or family history of cancer.
- Testing is typically covered by insurance for those who meet guidelines.
- Cost of testing has decreased tremendously.
- GINA is a federal law that prohibits discrimination based on genetic testing.
- Some states have additional protections.
  - CO has protections for long- and short-term disability insurance

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 insurance.**

Breast Cancer Overview

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- US General population risk 12.4% (1 in 8 women)
- Approximately 264,000 women and 2,400 men are diagnosed each year
- Over 3.8 million breast cancer survivors living in the US in 2020
- Average 5-year survival is 90.8%, black women have the highest death rate from breast cancer
- Average age of diagnosis is 63 for White women & age 60 for Black women
- Approximately 12-14% of all breast cancers diagnosed are due to a hereditary cause

Diagnosing Breast Cancer

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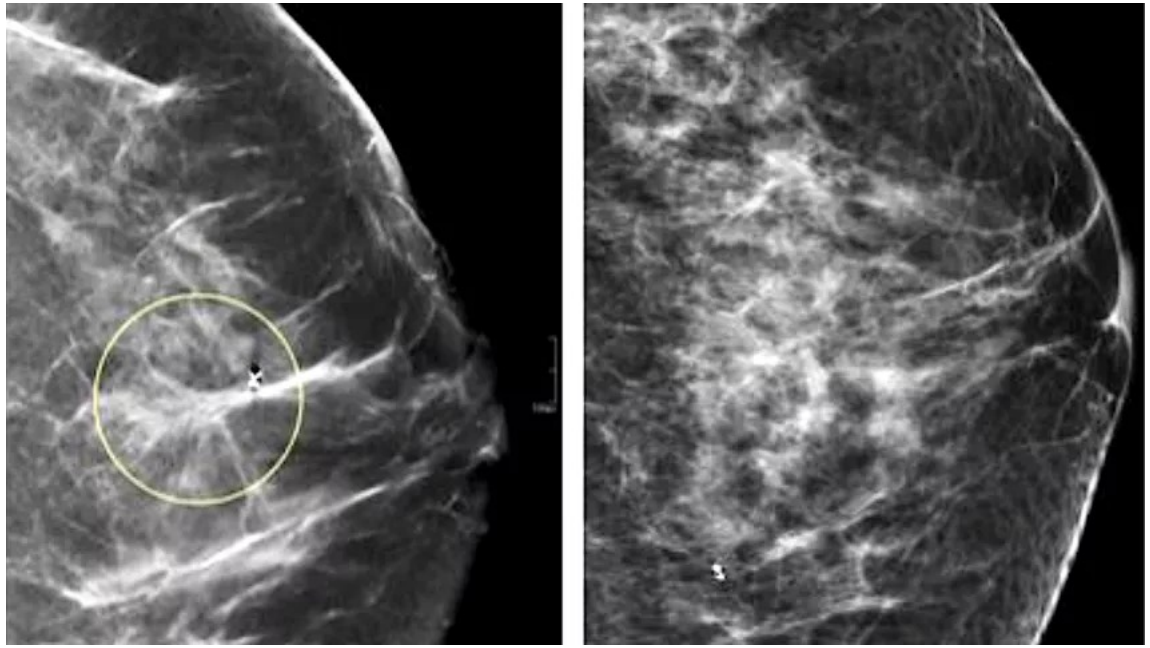
- Physical Exam:
  - Self-exam or clinical exam
    - Lump/mass or pain/swelling in breast or axilla
    - Asymmetry, skin or nipple changes
- Imaging:
  - Mammogram
  - Ultrasound
  - Breast MRI
- Biopsy:
  - Tissue is sent to pathology to confirm diagnosis
    - Ductal carcinoma in-situ
    - Invasive ductal/lobular



Spectrum of Breast Cancer Risk

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Average	Intermediate	High	Hereditary
• Lifetime risk <15% • Annual mammogram starting age 40 • No evidence to suggest breast MRI necessary	• Lifetime risk 15-20% • Annual mammogram starting age 40 • Not enough evidence to make a recommendation for or against annual breast MRI	• Lifetime risk ~20-25% or greater • Annual breast MRI and mammograms generally recommended	• High risk for breast cancer, risk dependent on gene • Bilateral mastectomy or increased screening • Possible elevated risks for other cancers associated with the gene

(Saslow, et al., 2007)

Genes Linked to Hereditary Breast Cancer

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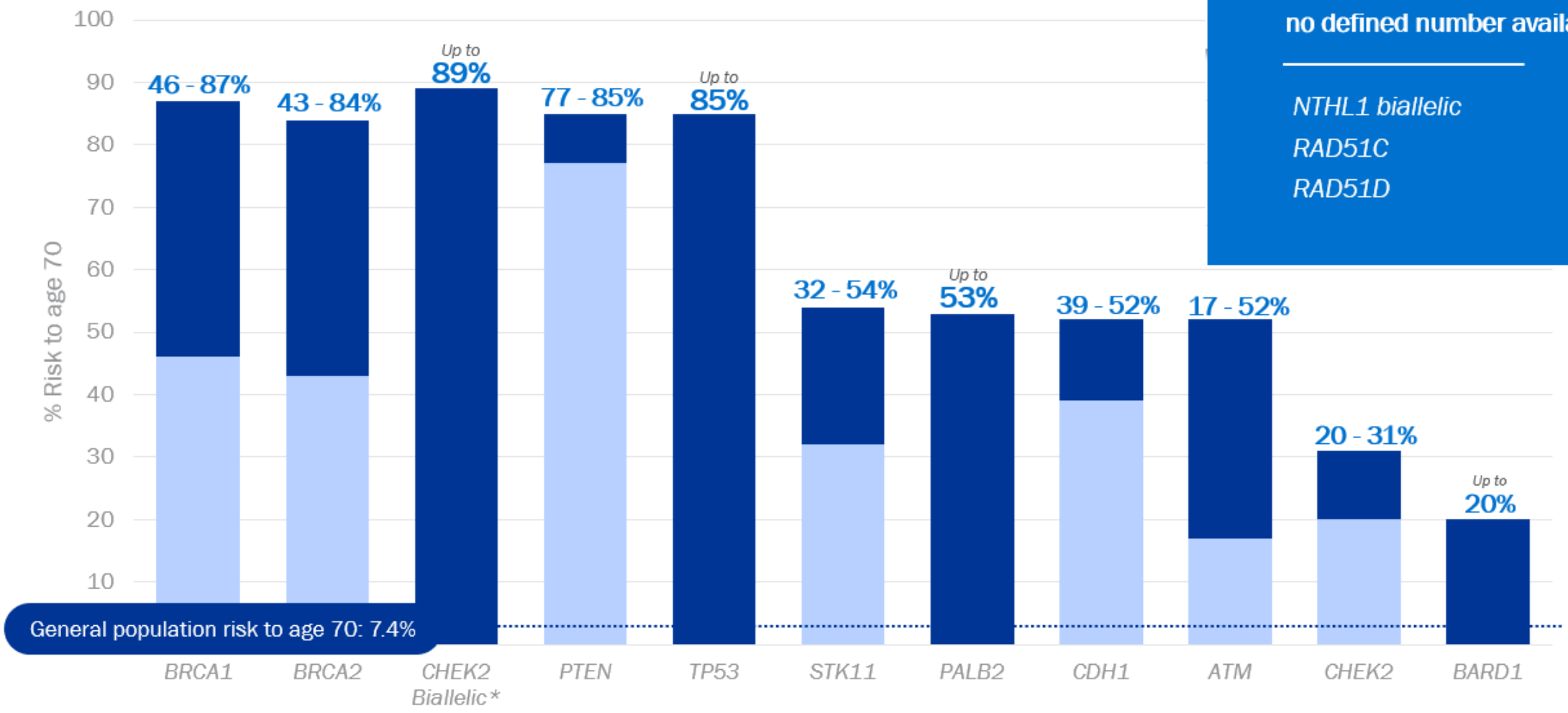

Elevated risk of breast cancer but no defined number available

NTHL1 biallelic

RAD51C

RAD51D

*Data include risk to age 80

Overlapping Cancer Risks

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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	●		●									

Ovarian Cancer Overview

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- Female US general population risk 1.1%
- 236,511 ovarian cancer survivors living in the US in 2020
- Average 5-year survival is 50.8%, lower for Black women
- Average age of diagnosis is 63
- Approximately 1 out of 4 (24%) of all ovarian cancers diagnosed are due to a hereditary cause

Ovarian Cancer Diagnosis

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- Symptoms:
  - Bloating
  - Trouble eating or feeling full quickly
  - Fatigue
  - Bleeding or discharge from the vagina that is not normal for you
  - Pain or pressure in the pelvic area
  - Abdominal or back pain
  - A change in bathroom habits, such as more frequent or urgent need to urinate
- Symptoms may be difficult to distinguish from normal menstrual symptoms, and some women may not experience any symptoms at all.
- Difficult to detect early because there may not be symptoms unless the disease has spread.
- If diagnosed early, about 94% of patients live longer than 5 years after diagnosis.

Genes Linked to Hereditary Ovarian Cancer

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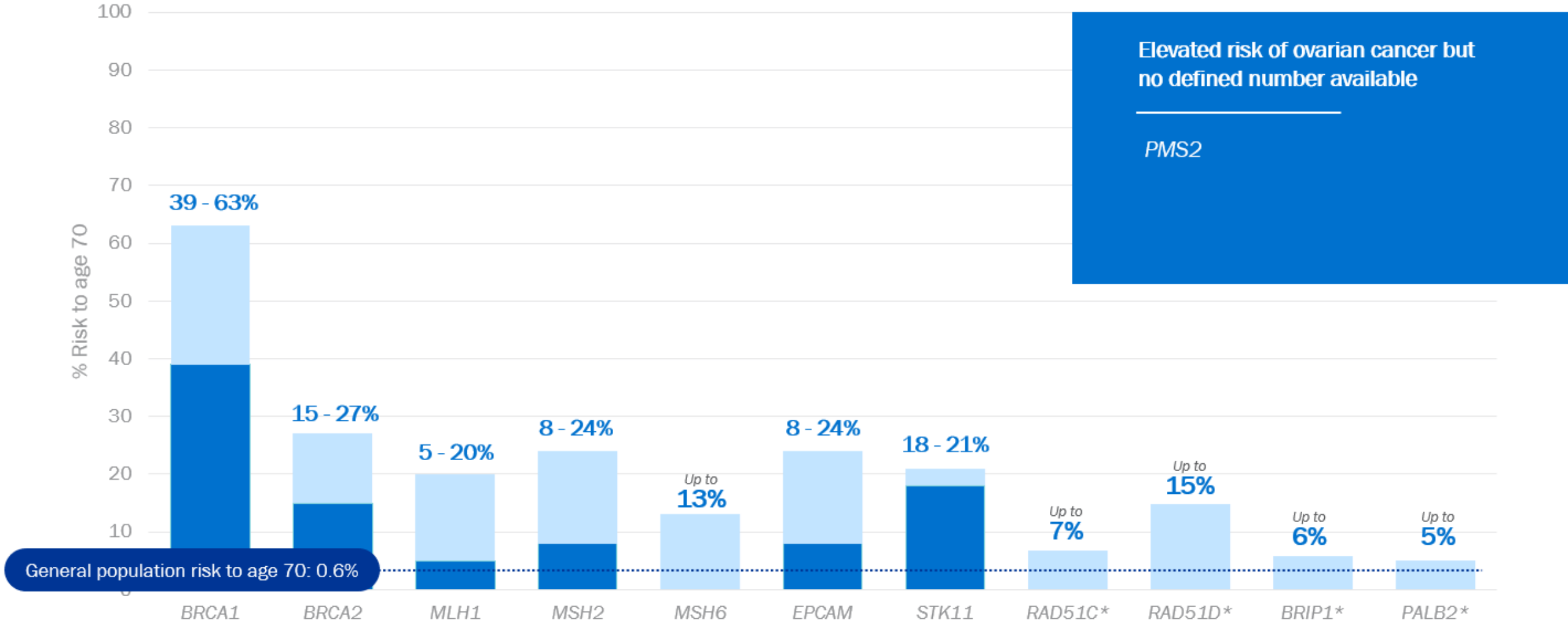

BRCA1/BRCA2 Cancer Risks

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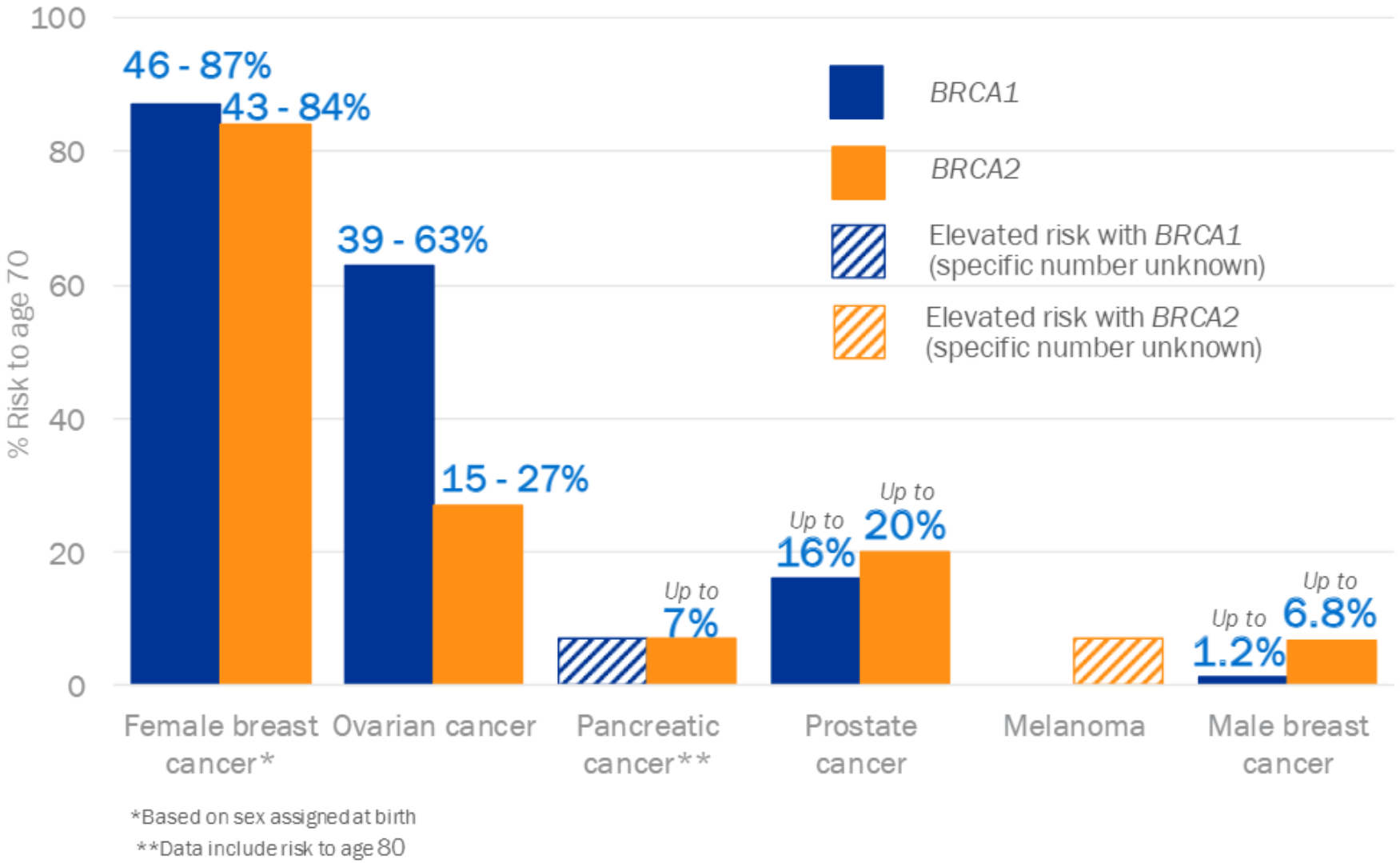

*Based on sex assigned at birth

**Data include risk to age 80

BRCA1/BRCA2 Cancer Risks

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	BRCA1	BRCA2
Female breast cancer* risk to age 50	28 - 51%	23 - 35%
Second breast cancer within 5 years of first diagnosis	8.9% - 20%	3.9% - 12%
Ovarian cancer risk to age 50	8 - 23%	0.4 - 4%
Ovarian cancer risk within 10 years of breast cancer diagnosis	12.7%	6.8%

Cancer Risks for Men

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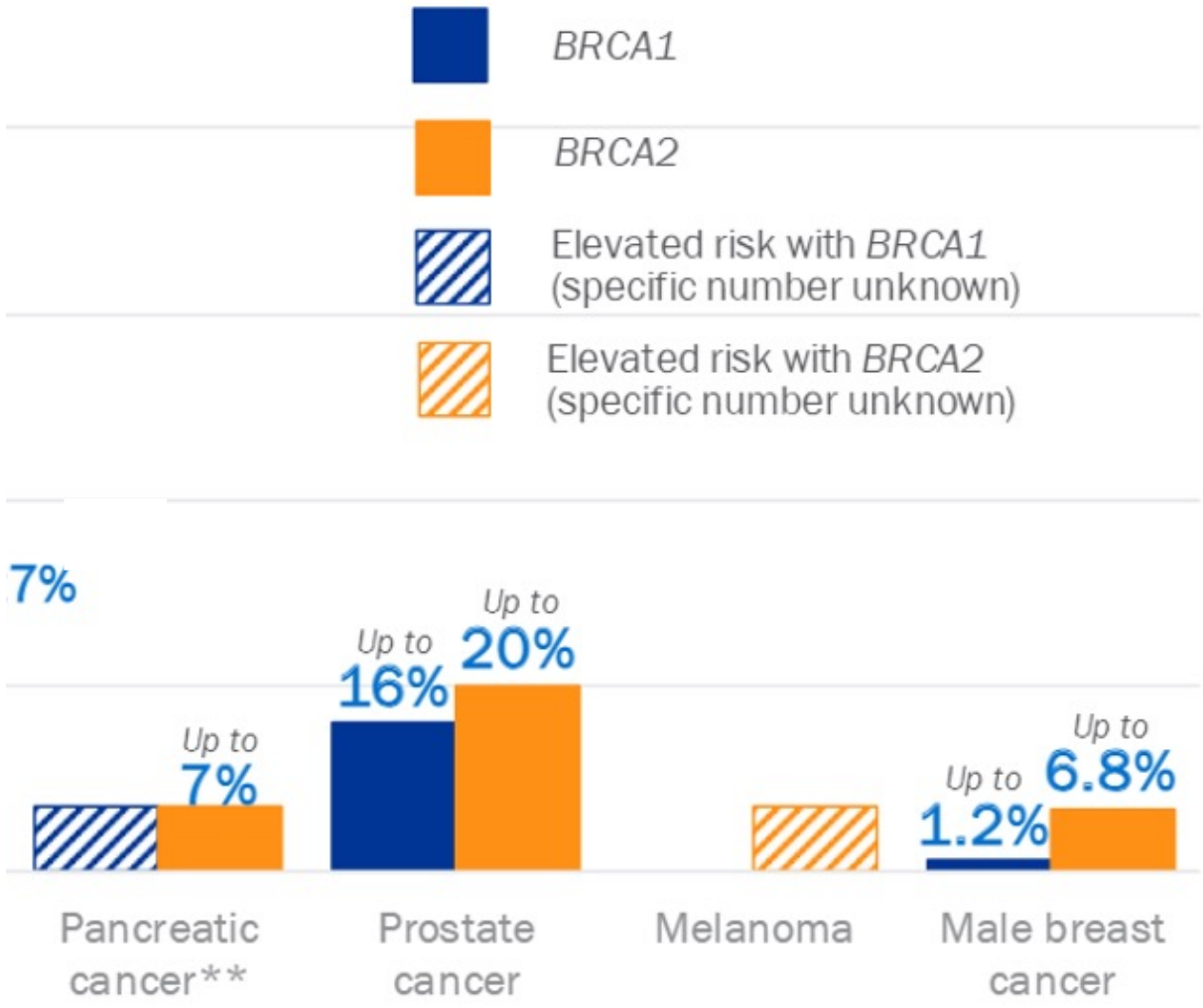
- Hereditary breast cancer doesn't just affect women.
- Men can be at risk too!
  - Male breast cancer
  - Prostate cancer
  - Pancreatic cancer
  - Melanoma
  - Other cancers
- Men have the same risk to pass a mutation to their children.



Breast Cancer Risk Management

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- Female breast cancer surveillance:
  - Breast awareness starting at age 18
  - Clinical breast exam every 6-12 months starting at age 25
  - Annual breast MRI starting at age 25
  - Annual mammogram (in addition to breast MRI) starting at age 30
- Male breast cancer surveillance:
  - Breast self-exam training and education starting at age 35
  - Annual clinical breast exam starting at age 35
  - Consider annual mammogram starting at age 50 (BRCA2 carriers)
- Management can be customized based on the age of cancer onset in the family.

Surgical Options for Breast Cancer Risk Reduction

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Initial dx	2nd breast cancer risk	Ovarian cancer risk	Management recommended	Management benefits
Localized **Sporadic** Breast cancer	2% after 5 years[9] Up to 11% by age 70	<1% 10 years after breast cancer dx[11]	Lumpectomy with radiation[10]	Risk reduction from lumpectomy with radiation[10]
VS				
Localized **Hereditary** Breast cancer	20% after 5 years[1] Up to 64% by age 70[2]	Up to 13% 10 years after breast cancer dx[3] Up to 35% 20 years after breast cancer dx[3]	Bilateral mastectomy Prophylactic BSO Chemoprevention[4]	Mastectomy reduces breast cancer risk as much as 90%[5] Reduces the risk of contralateral breast cancer by as much as 53%[6] Oophorectomy reduces 2nd breast cancer risk as much as 68%[7] Oophorectomy reduces ovarian cancer risk as much as 96%[8]

Medication Options for Breast Cancer Risk Reduction

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Selective Estrogen Receptor Modulators (SERMs)

- Tamoxifen 20 mg/d (>35 yo)
- Raloxifene 60 mg/d (post-menopausal)

Aromatase Inhibitors*

(AIs; post-menopausal)

- Exemestane 25 mg/d
- Anastrozole 1 mg/d

Risk-Reducing Agent

~50% Risk Reduction (ER+)

FOR 5+ YEARS

Surveillance for Ovarian Cancer

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- Screening tests that have been studied
  - Pelvic Exam
  - Transvaginal Ultrasound
  - CA-125 assay
- Concerns with these methods
  - Finding ovarian cancer by the methods above may not improve health
  - False-negative tests can occur
  - False-positives tests can occur
- Transvaginal ultrasound combined with CA-125 could be considered for BRCA1/2 carriers, although benefit is uncertain

Medication for Ovarian Cancer Risk Reduction

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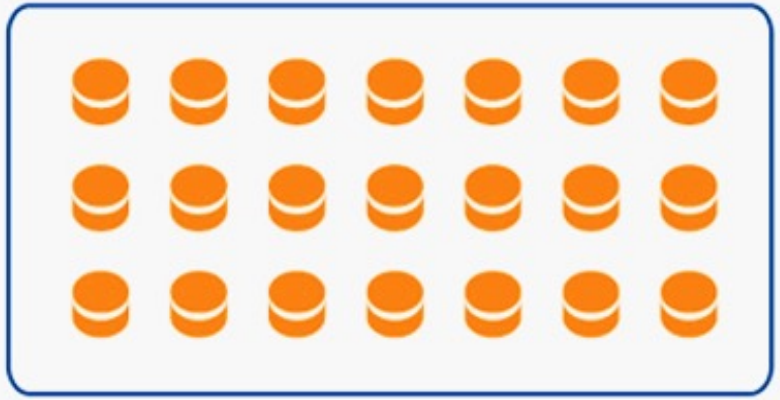
Ovarian Cancer Risk-Reducing Agents

- If childbearing not completed

ORAL CONTRACEPTIVE PILLS

- Combined Estrogen and Progestin



50%

Risk Reduction
for 5+ Years

Risk Reduction Benefits

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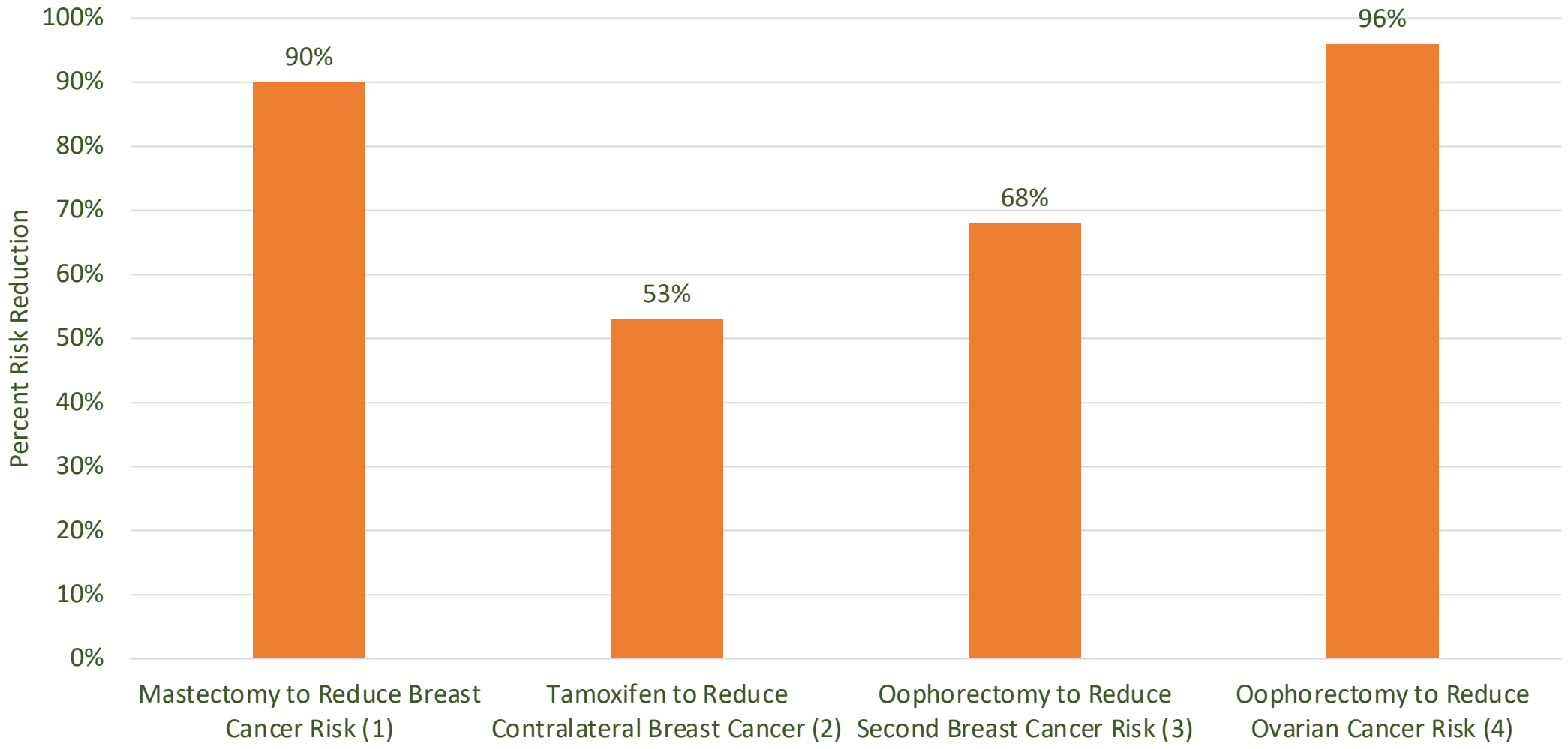

1. Hartmann LC, et al. *Proc Am Assoc Ca Res* 2000
2. Gronwald, et al. *Int J Cancer* 2006
3. Kauff ND, et al. *N Engl J Med* 2002
4. Rebbeck TR, et al. *N Engl J Med* 2002

Moving Beyond Risk Reductions

Boulder Community Health

- Individuals with a diagnosis of breast or ovarian cancer and a known BRCA mutation may benefit from targeted therapies.
  - PARP inhibitors target the defect in cell division resulting from BRCA mutations
  - Available as treatment for both breast and ovarian cancers

How Do PARP-inhibitors Work?

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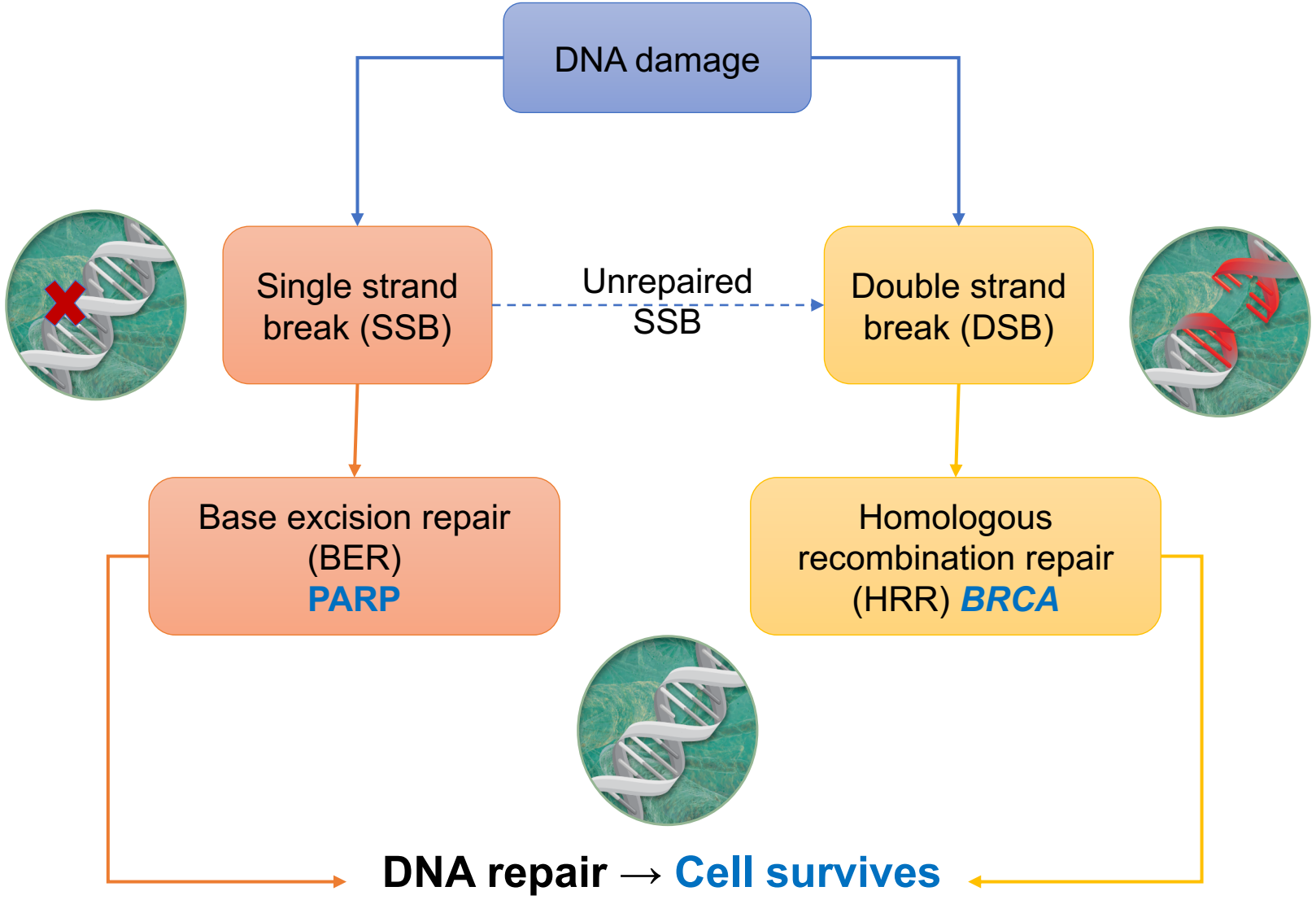

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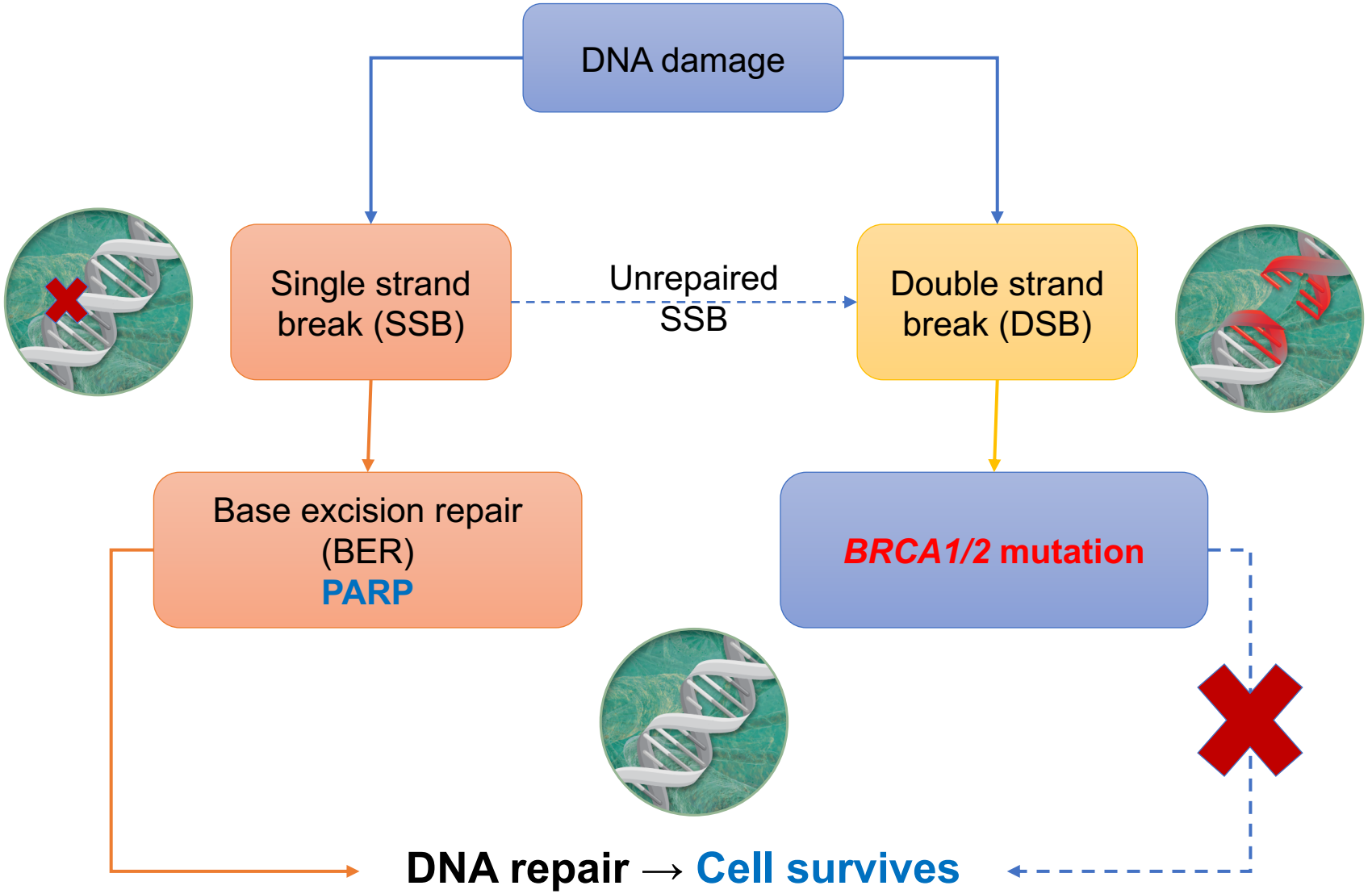

How Do PARP-inhibitors Work?

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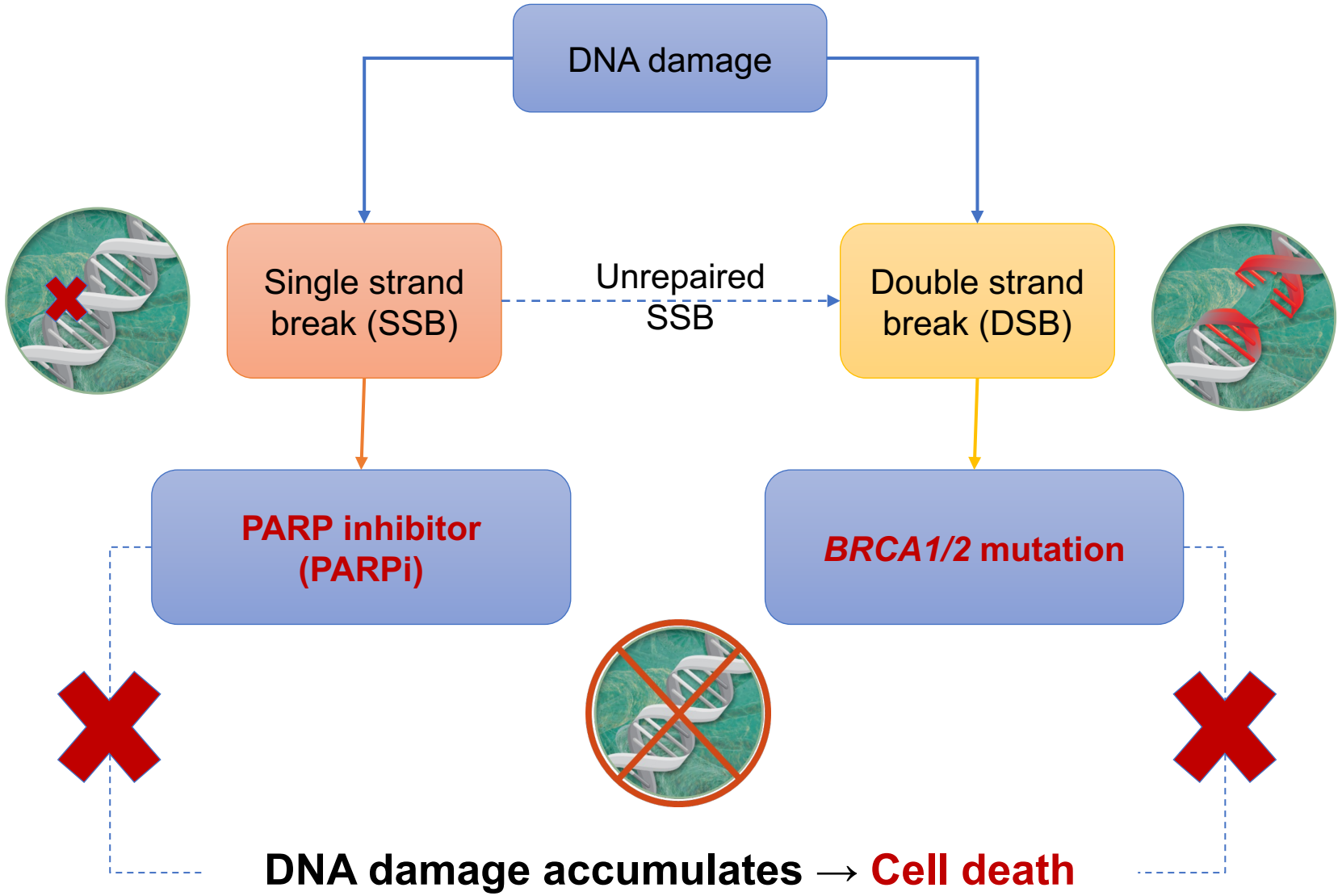

Moving Beyond Risk Reductions

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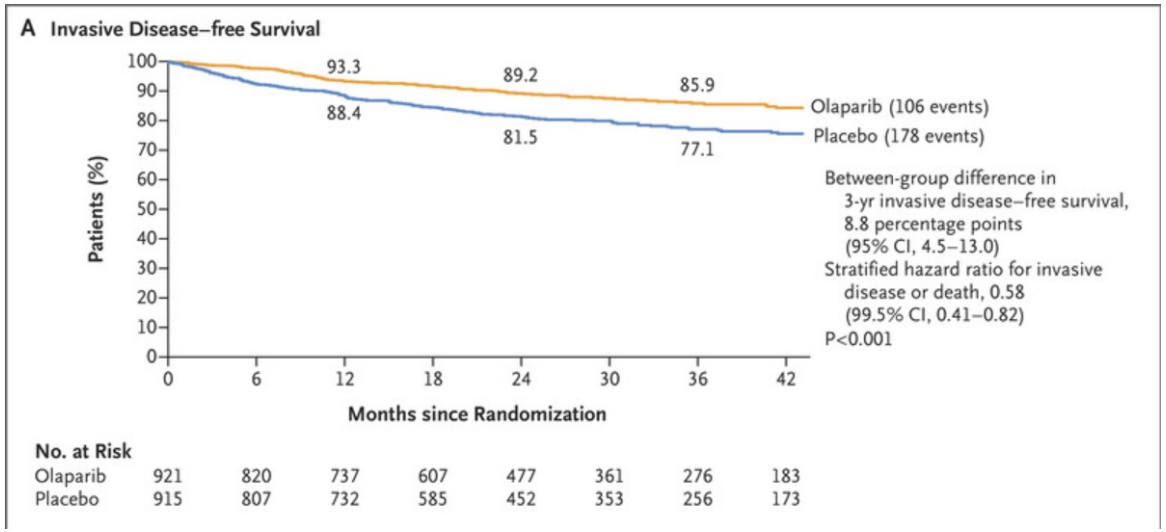
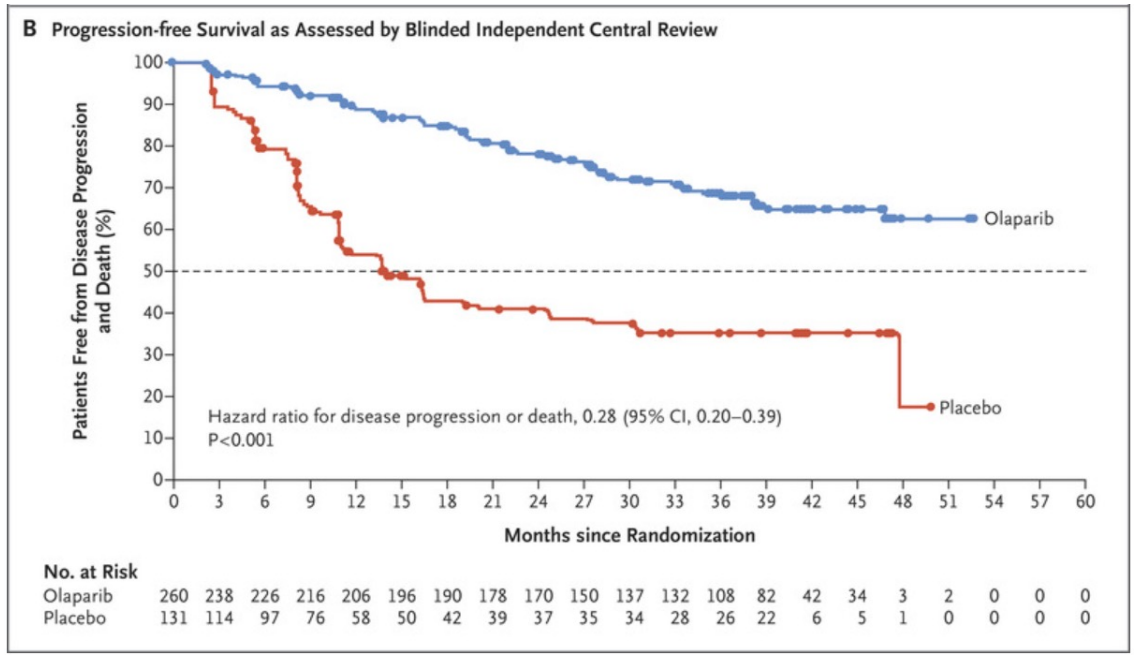
OlympiA Trial
Localized Breast Cancer



(Tutt ANJ, et al. 2021)

SOLO1 Trial
Advanced Ovarian Cancer



(Moore K, et al. 2018)

Seeking Care

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- If you're concerned about possibly having hereditary cancer in your family, what should you do?
  - Speak to your doctor
  - Ask if a referral is right for you
  - Collect your family history information

Image: brightpink.org

Tips for Collecting Family History

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- Document **as many relatives as you are able to**
  - First-degree = parents, siblings, children
  - Second-degree = aunts, uncles, grandparents
  - Third-degree = cousins, great-aunts, great-uncles
- Make note of **current age** or **age at death** for each relative
- **List <u>ANY</u> cancers and/or tumors** and what age they were diagnosed
  - Colon polyps and benign tumors count!
- Ask if a cancer was **metastatic** and/or what the primary cancer was
  - Note: brain, bone, liver and lung are common sites of metastases

Ask whether family members have ever had genetic testing and if so whether you can have a copy of their results

Tips for Collecting Family History

Boulder Community Health

- Example Family History:
  - Mother, alive at age 65, diagnosed with breast cancer at age 60.
  - Maternal aunt, died at age 72, colon polyps x5, all after age 50.
  - Paternal grandmother, died at age 80, diagnosed with uterine cancer at age 55.
  - Sister, alive at age 38, skin cancer diagnosed at age 38.
  - Paternal uncle, alive at age 60, diagnosed with prostate cancer at age 58, metastasized to liver.
  - Maternal aunt, died at age 63, diagnosed with lung cancer at age 62, 20 year + history of tobacco use.

Thank you!

Boulder Community Health

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