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

The proteins have specific jobs that help your body work normally.
WHAT HAPPENS WHEN THERE IS A GENETIC MUTATION?

NORMAL GENE

- HEALTHY PROTEIN

MUTATED GENE

- DAMAGED PROTEIN
HOW ARE GENES INHERITED?

MOTHER

Gene inherited from mother

Gene inherited from father

FATHER
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

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

Hereditary Cancer: 5-10%
Familial Cancer: 15-25%
Sporadic Cancer: 65%
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.

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**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)
TUMOR TESTING VS GERMLINE TESTING

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

**Germline testing** can help determine if a mutation was inherited and help guide treatment and risk management options
THE TWO-HIT HYPOTHESIS

INDIVIDUAL WHO DOES NOT CARRY A MUTATION

INDIVIDUAL WHO CARRIES A MUTATION
What are the common traits associated with hereditary cancer?

1. **CANCER AT AN EARLY AGE**
   At an age younger than average

2. **CERTAIN RARE CANCERS**
   Such as male breast cancer, sarcoma etc.

3. **MULTIPLE CANCERS**
   Multiple individuals within the family may have cancer. Or one individual may have multiple cancers
CANCER RISKS ASSOCIATED WITH BRCA1 & BRCA2

Female breast cancer risk to age 50
BRCA1: 28-51%
BRCA2: 23-28%

Second breast cancer within 5 years of first diagnosis
BRCA1: 20%
BRCA2: 12%

Ovarian cancer risk to age 50
BRCA1: 13-23%
BRCA2: 0.4-4%

Ovarian cancer risk within 10 years of breast cancer diagnosis
BRCA1: 12.7%
BRCA2: 6.8%
CANCER RISKS ASSOCIATED WITH LYNCH SYNDROME

GENES ASSOCIATED WITH LYNCH SYNDROME
- MLH1
- MSH2
- MSH6
- PMS2
- EPCAM

CANCERS KNOWN TO HAVE ELEVATED RISKS WITH LYNCH SYNDROME
- colorectal cancer
- endometrial cancer
- ovarian cancer
- gastric cancer
- small bowel cancer
- ureter/renal pelvis cancer
- pancreatic cancer
- hepatobiliary tract cancer
- central nervous system cancer
- sebaceous neoplasms
- prostate cancer

% RISK TO AGE 70
- 52-82%
- 10-69%
- Up to 20%
- 25-60%
- 16-71%
- Up to 15%

Elevated risk with MLH1, MSH2, MSH6, PMS2, and EPCAM (specific number unknown)
GENES ASSOCIATED WITH BREAST CANCER
and their associated risk ranges

- **BRCA1**: 46-87%
- **BRCA2**: 43-84%
- **PTEN**: 77-85%
- **PALB2**: 17-58%
- **CDH1**: 39-52%
- **ATM**: 17-52%
- **STK11**: 45-50%
- **CHEK2**: 23-48%
- **NBN**: 10.2-30%
- **BRCA1**: 46-87%
- **BRCA2**: 43-84%
- **PTEN**: 77-85%
- **PALB2**: 17-58%
- **CDH1**: 39-52%
- **ATM**: 17-52%
- **STK11**: 45-50%
- **CHEK2**: 23-48%
- **NBN**: 10.2-30%

General population risk to age 80: 10.2%

ELEVATED RISK OF BREAST CANCER, BUT NO DEFINED NUMBER AVAILABLE

- **TP53**
- **BARD1**
GENES ASSOCIATED WITH OVARIAN CANCER
and their associated risk ranges

- **BRCA1**: 39-63%
- **BRCA2**: 16.5-27%
- **STK11**: 18-21%
- **RAD51D**: 14.8%
- **MLH1**: 4-12%
- **MSH2**: 4-12%
- **EPCAM**: 4-12%
- **BRIP1**: 5.8%
- **RAD51C**: 6.7%

General population risk to age 80: 1.1%

ELEVATED RISK OF OVARIAN CANCER, BUT NO DEFINED NUMBER AVAILABLE

- **MSH6**
- **PMS2**
- **TP53**
GENES ASSOCIATED WITH COLORECTAL CANCER
and their associated risk ranges

General population risk to age 80: 3.4%

Biallelic MUTYH: 43-100%
APC: 70-99%
MLH1: 52-82%
MSH2: 52-82%
EPCAM: 52-82%
MSH6: 10-69%
BMPR1A: 40-50%
SMAD4: 40-50%
STK11: 39%
PMS2: UP TO 20%
PTEN: 9-16%
Monoallelic MUTYH: 3.4-10%

ELEVATED RISK OF COLORECTAL CANCER, BUT NO DEFINED NUMBER AVAILABLE

TP53
POLE
CDH1
POLD1
CHEK2
GREM1

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A PANEL APPROACH MAY CHANGE MEDICAL MANAGEMENT

even if it includes genes not associated with breast cancer

MUTATIONS IDENTIFIED BY A 25 GENE CANCER PANEL
in patients with a personal history of breast cancer

- **48.7%**: Hereditary breast and ovarian cancer syndrome-specific genes (BRCA1 and BRCA2)
- **10.3%**: Moderate-risk genes associated with breast cancer (PALB2, CHEK2, ATM, BRIP1*, BARD1, and NBN)
- **37.9%**: Other high-risk genes associated with breast cancer (PTEN, TP53, CDH1, and STK11)
- **3.1%**: Genes not associated with breast cancer (MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A, RAD51D, RAD51C, and SMAD4)

*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

**MUTATIONS IDENTIFIED BY A 25 GENE CANCER PANEL**
in patients with a personal history of ovarian cancer

- **65%** Hereditary breast and ovarian cancer syndrome-specific genes (BRCA1 and BRCA1)
- **10.3%** Moderate risk genes associated with ovarian cancer (RAD51C, RAD51D, and BRIP1)
- **16.5%** Genes not associated with ovarian cancer (ATM, BARD1, CHEK2, NBN, APC, and MUTYH)
- **8.2%** Other high-risk genes associated with ovarian cancer (MLH1 MSH2, MSH6, PMS2, and TP53)

Genes not associated with colorectal cancer (BRCA1, BRCA2, ATM, CHEK2*, BARD1, BRIP1, NBN, PALB2, and RAD51C)

Lynch syndrome specific genes (MLH1, MSH2, MSH6, PMS2, and EPCAM)

Other high-risk genes associated with colorectal cancer (APC and MUTYH)

MUTATIONS IDENTIFIED BY A 25 GENE CANCER PANEL
in patients with a Lynch Syndrome associated cancer

- 72.6% Lynch syndrome specific genes (MLH1, MSH2, MSH6, PMS2, and EPCAM)
- 22.2% Genes not associated with colorectal cancer (BRCA1, BRCA2, ATM, CHEK2*, BARD1, BRIP1, NBN, PALB2, and RAD51C)
- 5.2% Other high-risk genes associated with colorectal cancer (APC and MUTYH)

*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?

**GENETIC TESTING RESULTS**
- **Negative**
  - **Variant of uncertain significance**
  - **Deleterious or Suspected deleterious**

**IMPLICATIONS**
- **Medical management based on personal and family history of cancer**
- **Medical management based on cancer risks specific to gene mutation**
Management guidelines are put forth by professional societies such as the National Comprehensive Cancer Network (NCCN).

**WHICH GENES HAVE MANAGEMENT GUIDELINES?**

### GENES WITH MANAGEMENT GUIDELINES

<table>
<thead>
<tr>
<th>Gene 1</th>
<th>Gene 2</th>
<th>Gene 3</th>
<th>Gene 4</th>
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### IMPORTANT OTHER GENES

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

<table>
<thead>
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<tr>
<td>NBN</td>
<td>BARD1</td>
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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
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**
- a mutation that causes an increased risk of developing cancer - also known as **deleterious**
VUS: DATA NEEDED TO CONFIRM IF BENIGN OR HARMFUL
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.
Risk based on complex calculation

**MULTIPLE COMPLEX FACTORS**

- Genetic factors across genome
- Family history of cancer
- Personal clinical factors

**DISRUPTIVE GENE CHANGES**

Risk based on testing positive for one of these genes

28 genes

Risk based on complex calculation
RISK FACTORS:

Risk calculation

Risk calculation
Discuss management options
Discuss family members

Risk model to help determine breast cancer risk
Discuss management options
Discuss family members