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# Advances in Gynecologic Cancers:

# Hereditary Factors and Biomarker Testing

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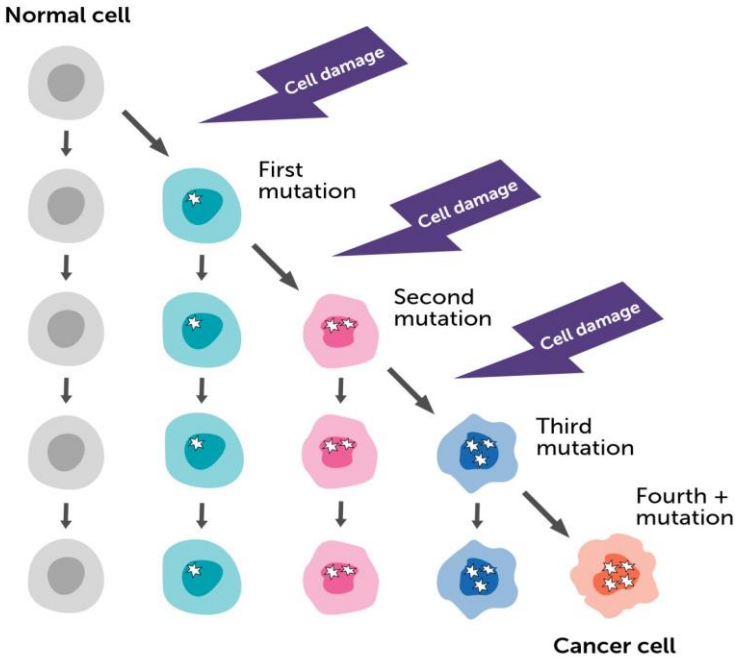
# Outline

- Germline (inherited) and somatic (tumor) genetic changes
- Hereditary Cancer
  - Genes associated hereditary gynecologic cancer
  - Impact on associated cancer risks
- Targeted Treatment Approaches
  - Current and new biomarkers associated with targeted therapies

# Germline and Somatic Genetic Changes

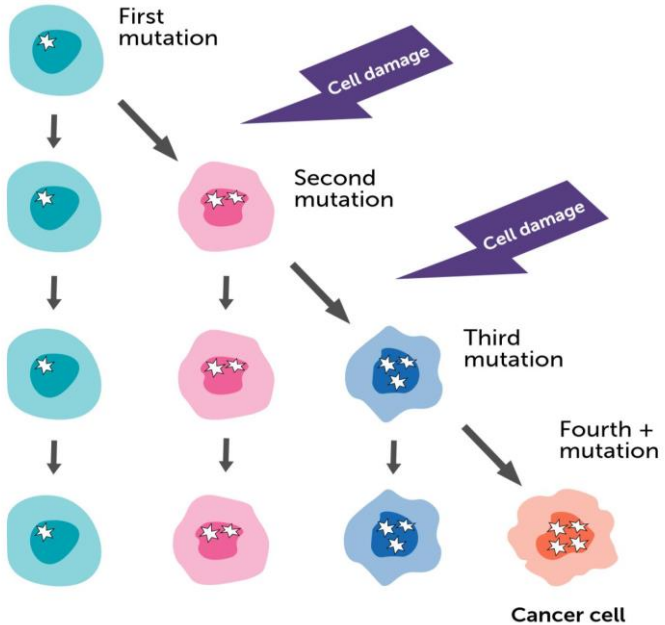
# All cancer is the result of genetic mutations

**With sporadic cancers,** many mutations build up in cells over time, eventually leading to cancer.




*Adapted from "Understanding Gene Testing" - NIH 1995*

**With hereditary cancers,** the first mutation is inherited and already present at birth. Additional mutations build up over time, leading to cancer.

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# Germline (hereditary) testing vs Somatic (tumor) testing

| | Germline Testing | Tumor Testing |
|---|---|---|
| Sample | Healthy cells, usually saliva or blood | Tumor cells from biopsy or surgery<br><br>* Dr. Chapman presented on circulating tumor DNA |
| Purpose | Learn cause of cancer and risk of future cancers for patient and family | Learn what makes the tumor grow and what treatments might work best |
| Often ordered by | Genetic Counselor or others | Oncologist |

# Hereditary Cancer Predisposition - Due to Germline Genetic Changes

# Hereditary Cancer is (not so) rare


- Ovarian cancer – 20%
- Endometrial (uterine) cancer – 5%
- Uterine sarcoma – unknown
- Cervical cancer – minimal inherited factors

# Somatic vs Germline Mutations

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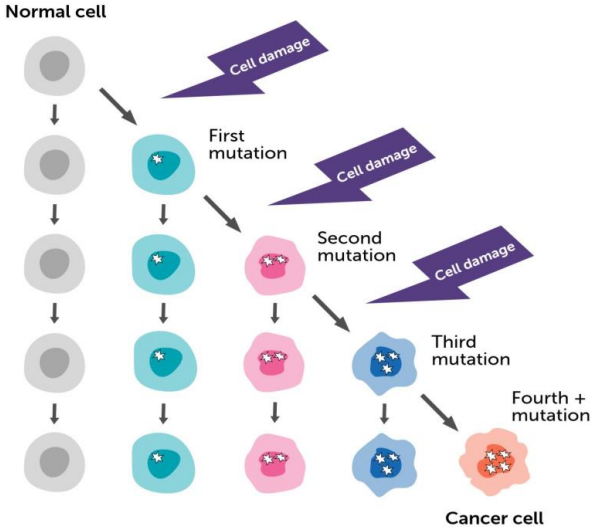


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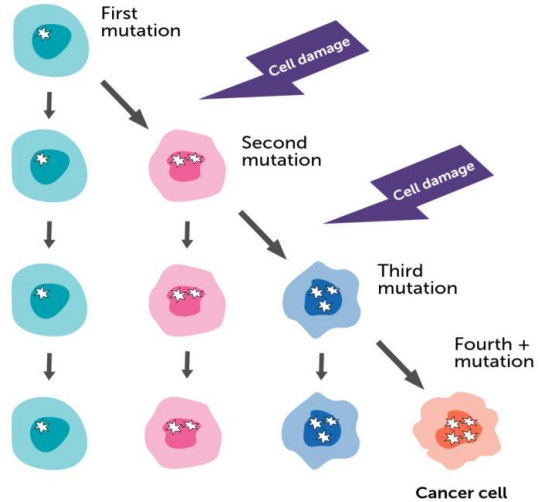


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## Inherited mutations cause:

- Early age at onset
- Multiple primaries
- Incomplete penetrance
- Dominant inheritance

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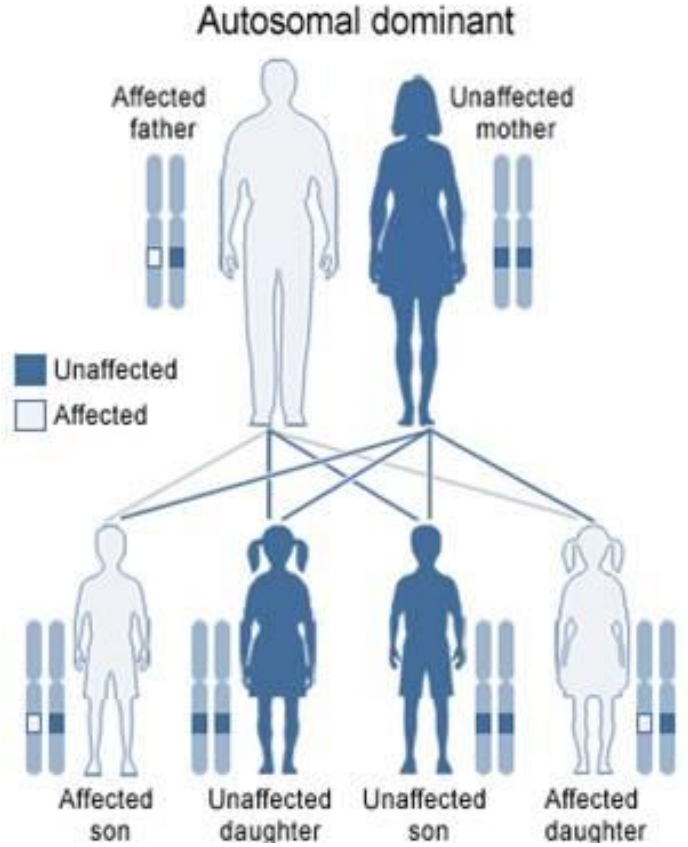


# Inheritance of Hereditary Cancer

http://www.in.gov/isdh/24477.htm

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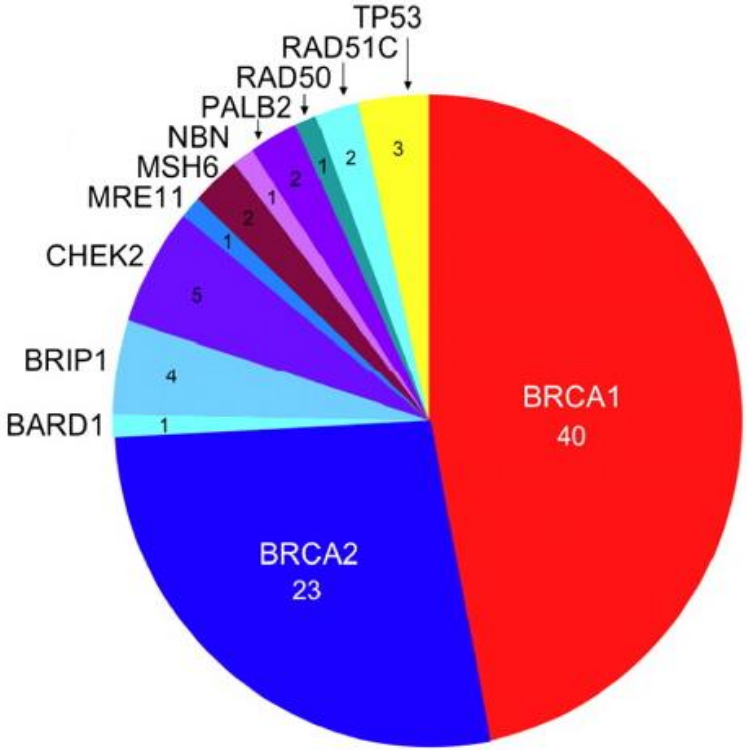
# Several Genes can Contribute to Hereditary Ovarian Cancer Risk




Proportions of patients with primary ovarian, fallopian tube, or peritoneal cancers with germline loss-of-function pathogenic variants



Walsh T et al. PNAS 2011;108:18032-18037

PNAS

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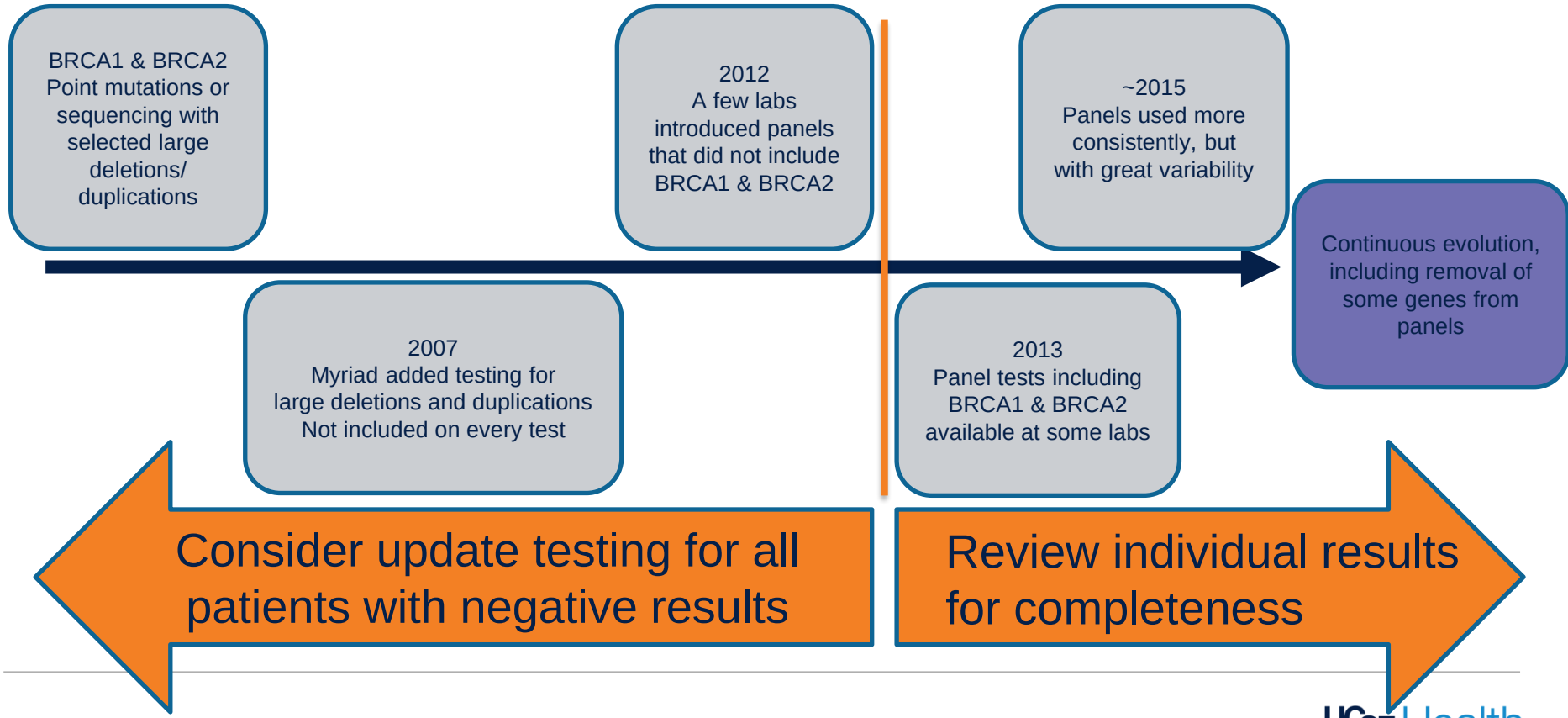
# Patients may need to be re-tested

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# Germline Genetic Testing - Results

| Types of Variants | |
|---|---|
| Pathogenic | Disease-causing “mutation” |
| Likely pathogenic | Usually treated clinically like pathogenic |
| Uncertain/ Unknown Significance | Encompasses large range – most will be benign, but some are suspicious |
| Likely benign | Treated clinically like benign, not reported |
| Benign | Not reported |

# Understanding Positive Results

- Is not a diagnosis of cancer!
- Increased chance of developing some cancers
  - Opportunity for early detection and prevention
- **Genes vary** in cancer risks and recommendations
- NCCN provides guidelines for management of many positive results

# Variants of Uncertain Significance (VUS)

**If I had a nickel for every time…**

- VUS are common with large multi-gene panels
  - (20-50%, depending on panel and population)

- VUS
  - Most turn out to be normal
  - Like negative result, we don't change screening or recommend testing relatives
  - "Normal until proven otherwise" – Nicola
  - There are many genetic differences between people, and most are normal. We do not understand all of the differences yet. When we see something rare, it is usually a normal variant, but can take time to figure out if it is normal or linked to cancer risk

# Targeted Treatment Approaches - Based on Somatic Genetic Changes

# Targeted Treatment Approaches

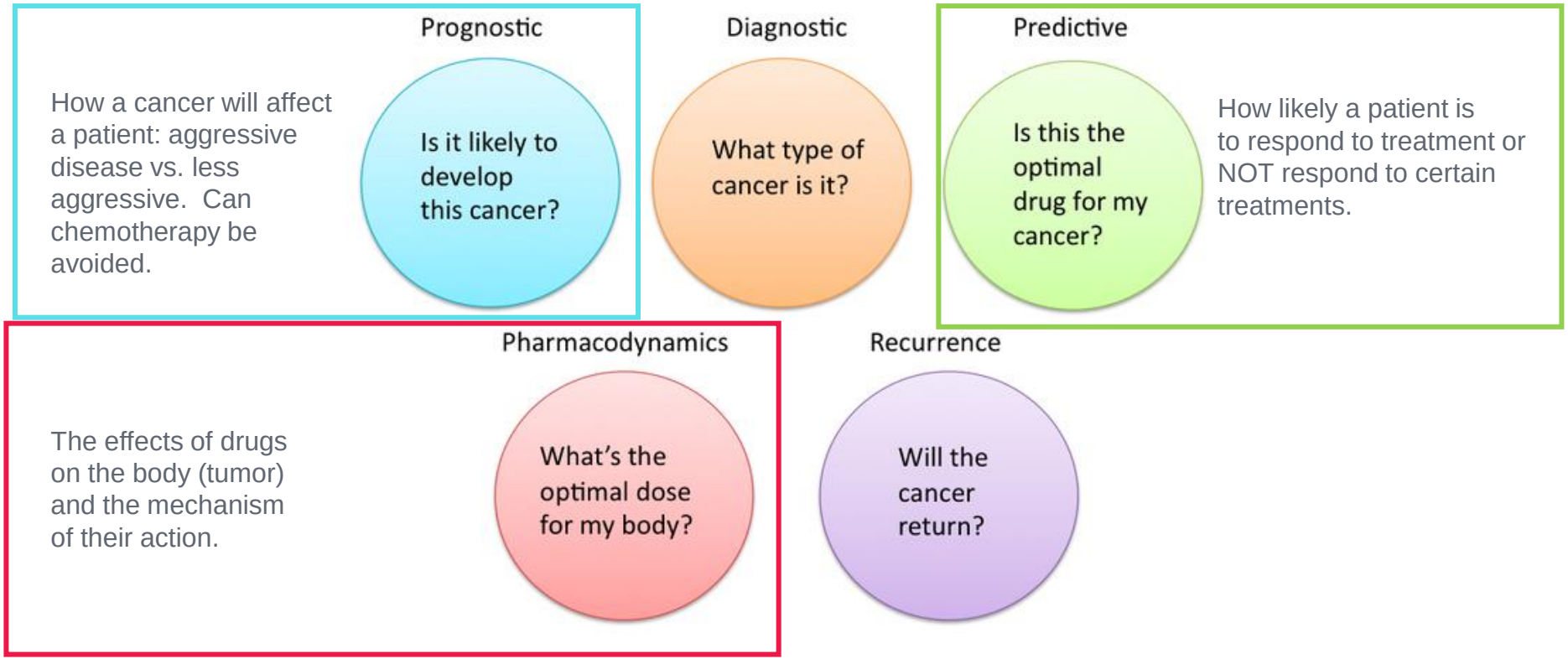
## What are Biomarkers

Each person's cancer has a unique pattern.

Certain proteins, DNA/RNA changes give us information about the aggressive nature, likelihood of response and overall prognosis for a patient.

This information helps to guide treatment decisions.

# Questions that can be answered by cancer biomarkers

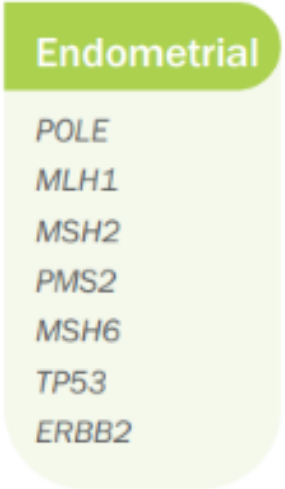


# Biomarkers in Endometrial Cancer

- MMR (Mismatch Repair) Proteins: Deficiencies in MMR proteins (e.g., MLH1, MSH2, MSH6, PMS2) are associated with Lynch syndrome and can influence treatment decisions, particularly the use of immunotherapy.
- POLE (Polymerase Epsilon): Mutations in the POLE gene are linked to a specific subtype of endometrial cancer with a favorable prognosis and may impact treatment strategies (de-escalate chemotherapy).
- TP53: Mutations in TP53 are often found in more aggressive forms of endometrial cancer and can guide the use of targeted therapies.
- HER2/neu: Overexpression or amplification of HER2 can be targeted with specific therapies like trastuzumab (Herceptin). Gene alterations in ERBB2 may also be considerations for targeted therapies.
- NTRK Gene Fusions: These fusions can be targeted with TRK inhibitors, which are effective in tumors harboring these alterations. (Larotrectinib/Entrectinib)
- Tumor Mutation Burden (TMB): High TMB can predict responsiveness to immunotherapy.

**Emerging Biomarkers (clinical trials)**

- JAG2, AURKA, PGK1, HRPT1: These genes are being studied for their potential roles as diagnostic, prognostic, or treatment biomarkers.



# Biomarkers in Ovarian Cancer

- BRCA1/BRCA2: Mutations (germline/tumor) in these genes can indicate a higher likelihood of response to PARP inhibitors, which are effective in treating ovarian cancer. (Lynparza/Olaparib)
- HRD (Homologous Recombination Deficiency): This includes BRCA mutations and other gene alterations that impair DNA repair (genomic instability), making tumors more susceptible to PARP inhibitors (increase response).
- TP53: Mutations in TP53 are common in high-grade serous ovarian cancers and can influence treatment strategies. (platinum-based)
- PIK3CA: Mutations in this gene can be targeted with PI3K inhibitors. (Alpelisib)
- Folate Receptor Alpha (Frα): Platinum resistant cancer to determine targeted therapeutics (mirvetuximab soravtansine)
- FOXL2: prognostic
- MSI (Microsatellite Instability): High MSI can predict responsiveness to immunotherapy. (Bevacizumab)
- NTRK Gene Fusions: These fusions can be targeted with TRK inhibitors, which are effective in tumors harboring these alterations. (Larotrectinib/Entrectinib)

**Emerging Biomarkers**

- ARID1A, PTEN, KRAS: These genes are being studied for their potential roles in targeted therapies and personalized treatment approaches.

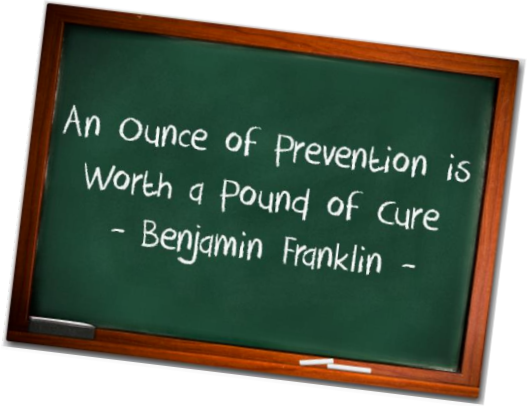
# Summary

- Germline/Hereditary Testing
  - Identifies people with increased risk for cancer
  - Allows for early detection, prevention, and targeted treatments
  - Different genes have different risks and recommendations

- Tumor Testing
  - Determines need for treatment
  - Determines ideal targeted therapy
  - Allows personalized approach to treat patients uniquely

# Supplemental

# Inherited risk for cancer



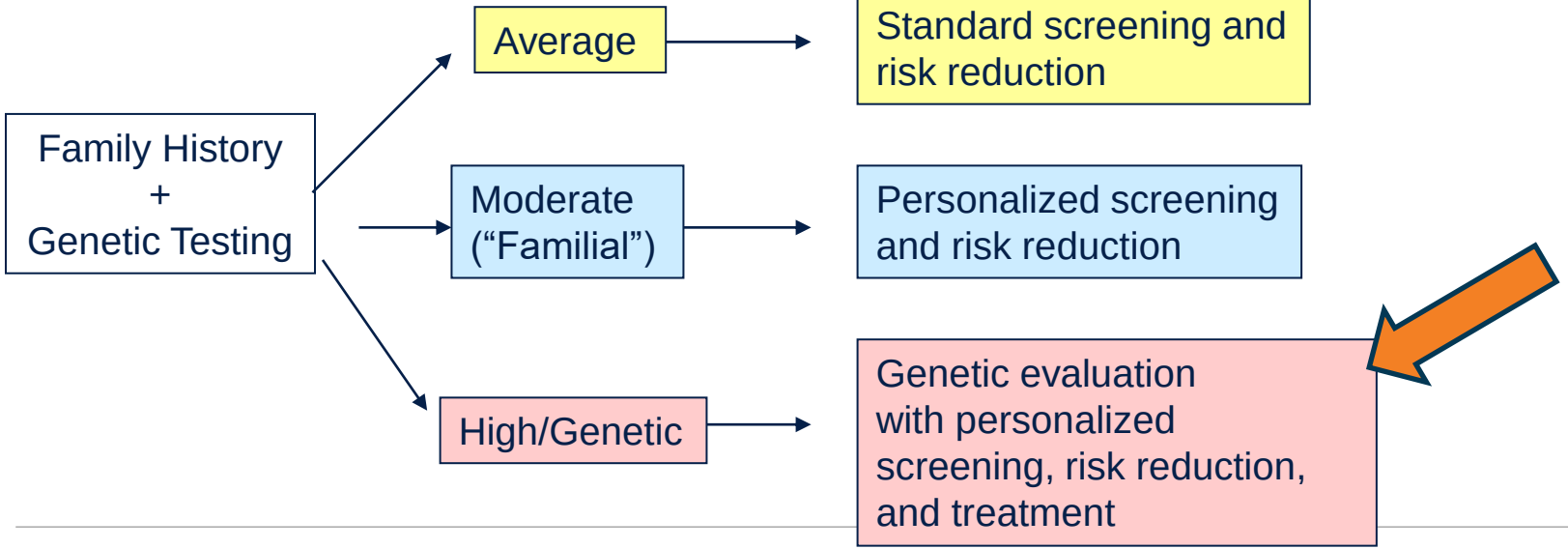

- (NOT SO) rare…

- BUT have great impact
  - Risk of cancer can be high e.g. 40% ovarian cancer risk with BRCA1 pathogenic variant
  - Multiple primary cancers are common

  - Opportunity for PREVENTION

# Identifying Hereditary Cancer is Important

**Genetic Risk Assessment = Personalized Medicine**



# Signs of Hereditary Cancer

- Early age of diagnosis
- Family history of the *same* or *related* types of cancer
  - eg. breast and ovarian; colon and endometrial
- Multiple primary cancers, including bilateral breast cancers
- Rare cancers
  - eg. Male breast, fallopian tube, triple-negative breast cancer
- Ancestry
  - eg. Ashkenazi Jewish and BRCA1 and BRCA2

# Germline Genetic Testing – How and Why?

- Testing done on healthy tissue - usually blood, saliva, cheek swabs
  - Patients with prior allogenic BMT or hematologic malignancy may require skin biopsy sample
- For healthy people, as well as those with cancer
- An inherited pathogenic variant is *not* a diagnosis of cancer
- Information can be used for early detection, prevention, and treatment of cancer
- Information can affect relatives

# Genes vary in cancer risks

| | Breast | Ovarian | Uterine | Other Cancers |
|---|---|---|---|---|
| BRCA1 | | | | Pancreas, prostate |
| BRCA2 | | | | Pancreas, prostate |
| BRIP1 | | | | |
| PALB2 | | | | Pancreas |
| RAD51C | | | | |
| RAD51D | | | | |
| Lynch Syndrome (MLH1, MSH2, MSH6, PMS2) | | | | Colon, small bowel, others |



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