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Ovarian Cancer Genetics

Jeff Dungan, MD
Brittany DeGreef, MS, CGC
Cancer Genetics Program
Northwestern Medicine
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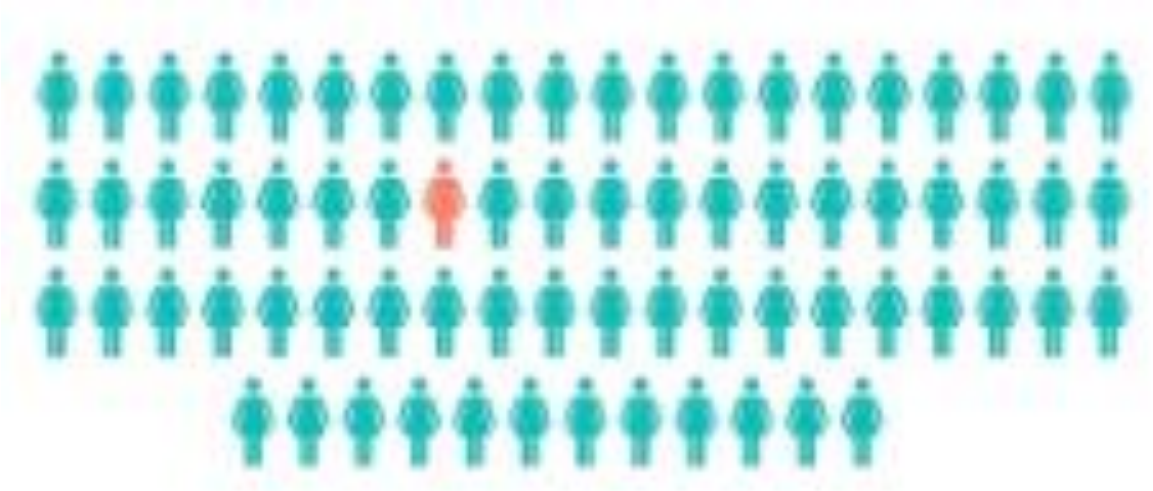
Disclosure

- We have no disclosures.

Ovarian Cancer Risk in General Population

1 out of 72 women will develop ovarian cancer in their lifetime (1.4%)



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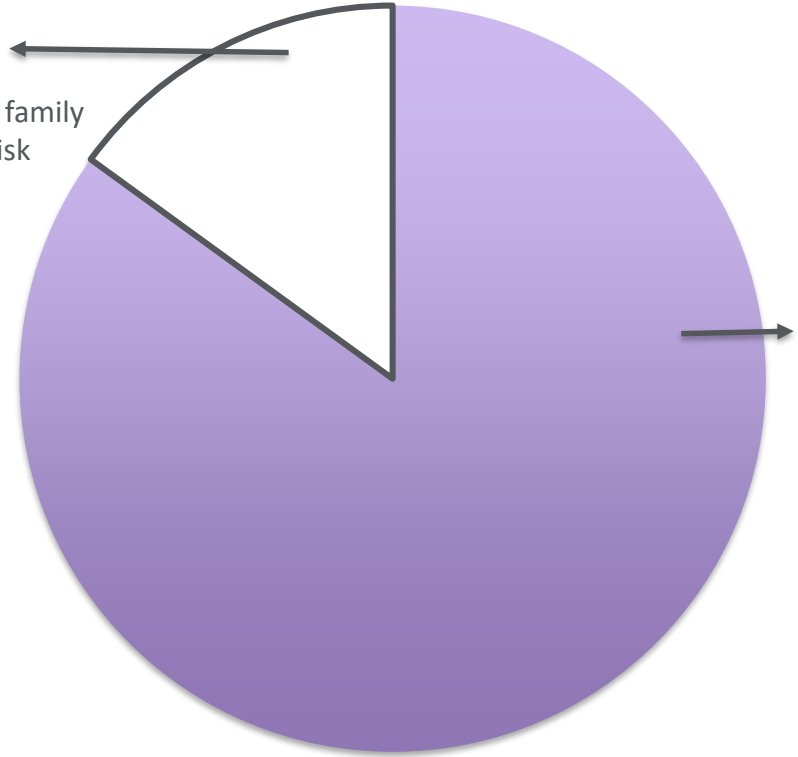
Ovarian Cancer

Hereditary: 15%

- Gene mutation is inherited in family
- Significant increased cancer risk
- Ex: *BRCA1* and *BRCA2*



Sporadic/Familial ~85%

Sporadic

- Cancer occurs by chance or related to environmental factors
- General population cancer risk

Familial

- Multiple genes and environmental factors
- Some increase in cancer risk

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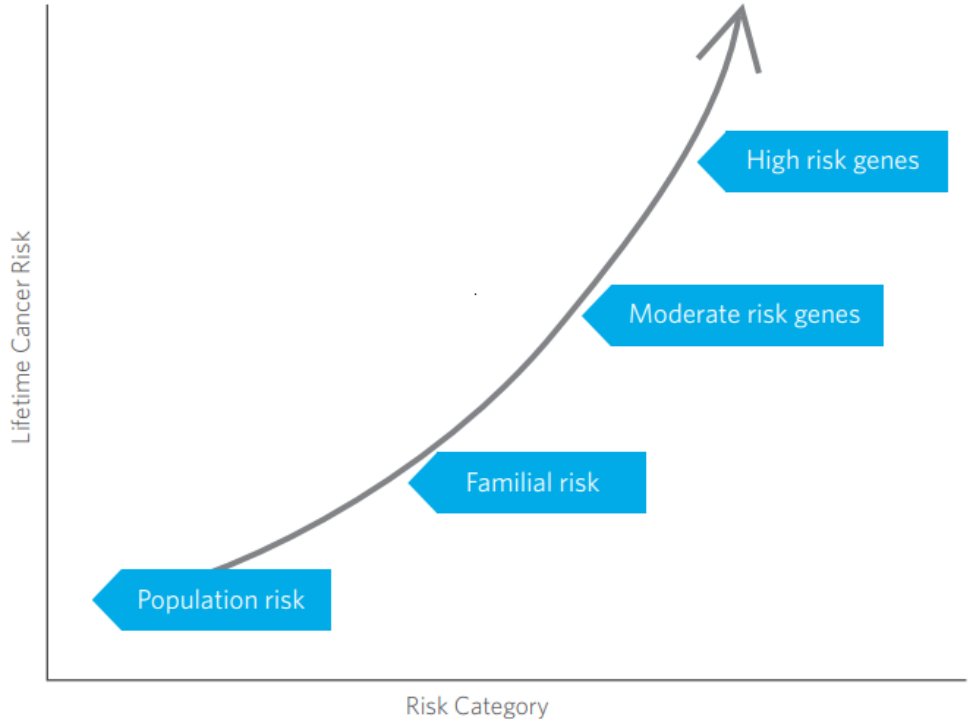
Cancer Risks by Gene Type



Ex: *BRCA1* and *BRCA2*

Ex: *RAD51C/D* and *BRIP1*

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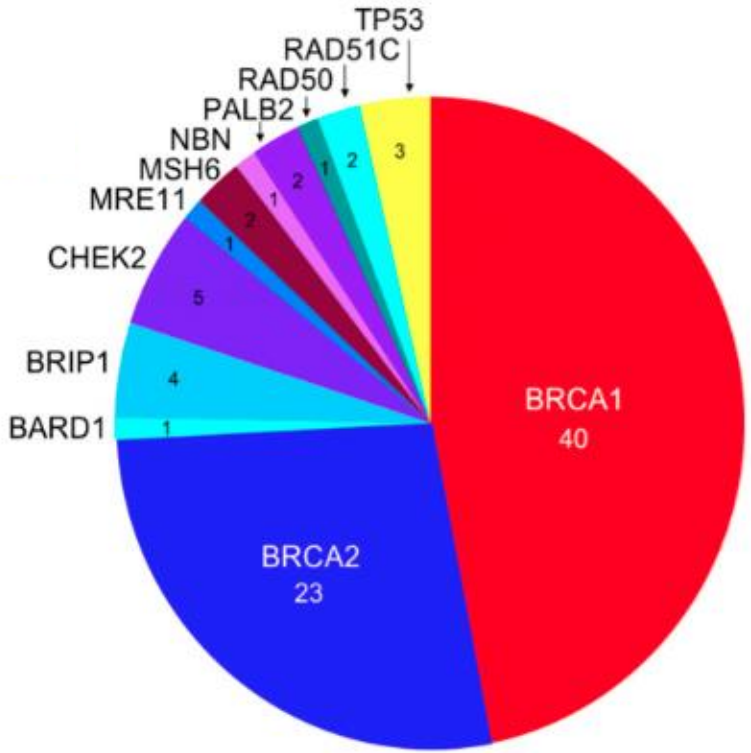
Retrieved from Ambry Genetics Counseling Aids

Causes of Hereditary Susceptibility to Ovarian Cancer



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WalshT et al. *Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing.* Proc Natl Acad Sci 2011;108:18032–7.

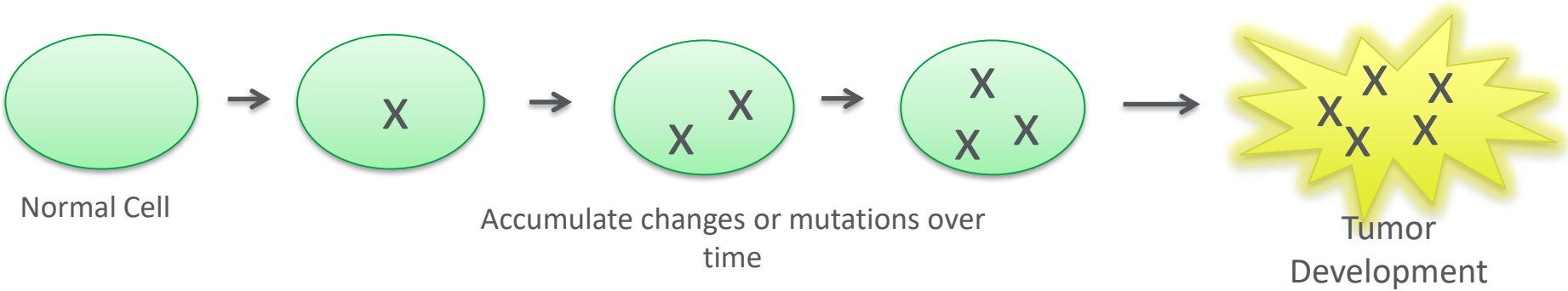
Features of Hereditary Cancer Syndromes

When To Suspect Inherited Syndrome

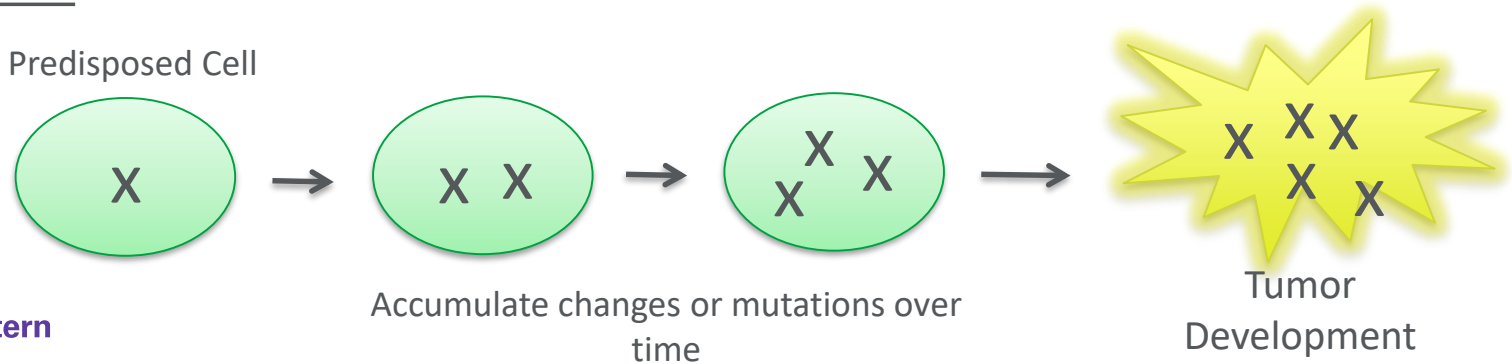
- **Early ages of diagnosis** (may vary based on cancer type)
  - Ovarian and Pancreatic Cancers: ≤ 60 years old
  - Breast cancer: ≤ 45 years old
  - Uterine and Colon Cancers: ≤ 50 years old
- **Multiple generations affected with cancer**
- **Multiple primary cancers in a single individual**
  - Also: bilateral tumors (bilateral breast, bilateral kidney, etc.)
- **Same or Related Cancers in two or more close relatives**
  - Ex: breast and ovarian; colon, ovarian, and uterine; melanoma and pancreatic
- **Rare cancers/tumors**
  - Male breast cancer
  - Paraganglioma/pheochromocytoma
- **Known cultural/ancestry groups at higher risk**
  - Ashkenazi Jewish

How Cancer Forms

Sporadic Cancer



Hereditary Cancer



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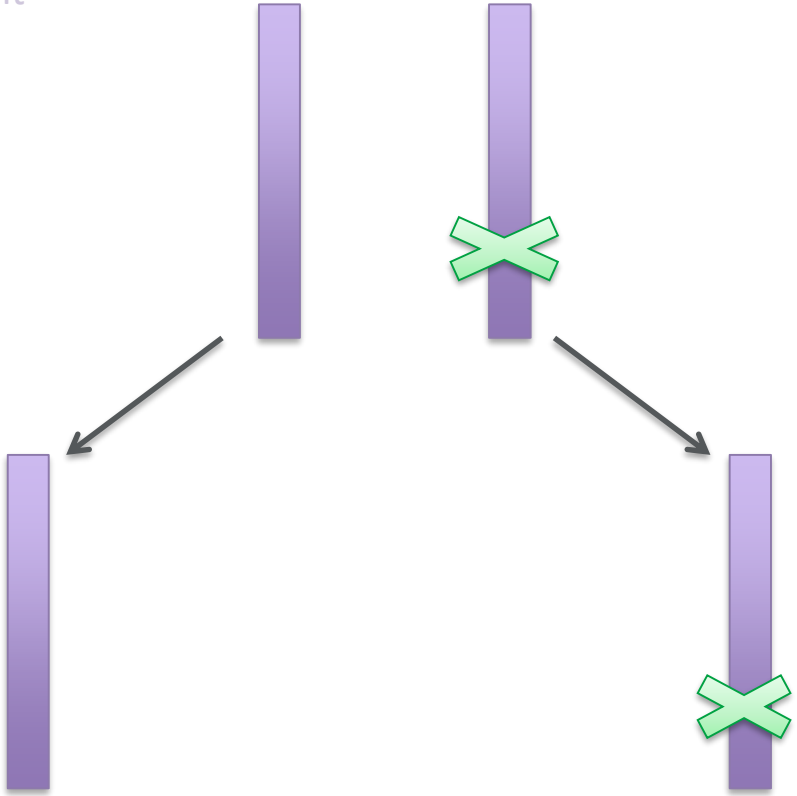
Inheritance

Autosomal Dominant

50% chance to pass on the working copy of the gene



50% chance to pass on the non-working copy of the gene

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Hereditary Cancer Syndromes

Associated with an Increased Risk of Ovarian Cancer

	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	Lynch Syndrome	Other/Moderate Risk Genes for Ovarian Cancer
Genes	*BRCA1* and *BRCA2*	*MLH1, MSH2, MSH2, PMS2, EPCAM*	*BRIP1, RAD51C, RAD51D*
Ovarian Cancer Risk	25-45%	10-15%	5-15%
Other Cancer Risks	Female/Male Breast (50-60%, up to 6%) Prostate (15%) Melanoma (5%) Pancreatic	Colon (up to 80%) Uterine (50-60%) Gastric (up to 13%) Urinary Tract (up to 7%) Pancreatic (up to 6%)	Unknown?

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HBOC Medical Management Recommendations

Adapted from NCCN guidelines, Version 2.2019

Cancer Type	Cancer Risk	Medical Management Recommendations
Ovarian	25-45%	**SCREENING:** • **Limited clinical utility (not encouraged)** • Transvaginal ultrasound/CA-125 blood testing q 6 mos **RISK REDUCTION:** • Bilateral salpingo-oophorectomy (BSO) • Recommended after childbearing (L30s-e40s) • Ovarian cancer risk reduction: 96% • Breast cancer risk reduction: 50%

Lynch Syndrome: Medical Management Recommendations

Adapted from NCCN Guidelines, Version 1.2018

Cancer Type	Cancer Risk	Medical Management Recommendations
Uterine	**General: 50-60%** *MLH1/MSH2*: 25-60% *MSH6*: 16-26% *PMS2*: 15%	• Education on symptoms (abnormal bleeding, postmenopausal bleeding) **SCREENING: (limited)** • Consider endometrial biopsies every 1-2 years • Transvaginal ultrasound at clinician's discretion **RISK-REDUCTION:** • Prophylactic hysterectomy (timing based on completion of childbearing, gene mutation)
Ovarian	Varies *MLH1*: 11-20% by age 70 *MSH2*: 15-24% by age 70 *MSH6/PMS2*: limited data	**SCREENING:** • **Limited clinical utility (not encouraged)** • Transvaginal ultrasound/CA-125 blood testing q 6 mos **RISK REDUCTION:** • Bilateral salpingo-oophorectomy (BSO) • Timing based on completion of childbearing, gene mutation

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Moderate Risk Ovarian Cancer Genes

BRIP1, RAD51C, RAD51D

- Approximately 15% lifetime risk of developing ovarian cancer
- Current data limited, no established guidelines
- Consider risk-reducting bilateral salpingo-oophorectomy
  - Evidence insufficient to recommend optimal age for procedure
    - Following natural menopause?
  - Discussion with providers ~age 45-50
  - May be modified based on family history of ovarian cancer (if present)
- Other cancers?
  - Insufficient evidence
  - TBD

Ovarian Cancer Risk Reduction

HBOC and Lynch Syndrome

- Birth control pills
  - 5 years of use: 27% reduction
  - 15 years of use: 60% reduction
- First full-term pregnancy < age 25; number of pregnancies
- Breast-feeding
- Bilateral tubal ligation/hysterectomy
- Prophylactic salpingo-oophorectomy
  - Risk of primary peritoneal cancer remains

Non-Epithelial Ovarian Cancer Syndromes

Peutz Jeghers Syndrome (*STK11* gene)

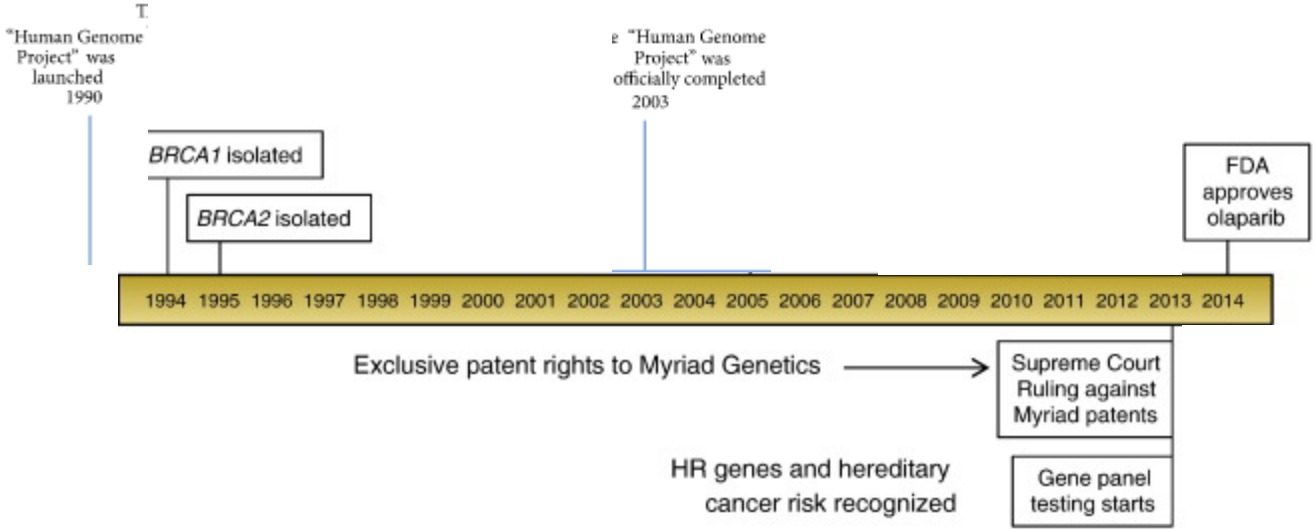
- **Increased risk for following cancers:**
  - Small bowel
  - Pancreas
  - Colon
  - Breast
  - Others
- **Sex cord ovarian tumors with annular tubules (SCTAT) – 36% related to PJS**
  - Granulosa cell ovarian cancer
  - Cervical adenoma malignum

DICER1 Related Cancer Syndrome

- **Increased risk of following:**
  - Pleuropulmonary blastoma (usually diagnosed in childhood and most common tumor)
  - Multinodular thyroid goiter or thyroid nodules
  - Embryonal rhabdomyosarcoma of uterus/cervix
  - Cystic nephroma (benign tumor of kidney)
  - Others
- **Ovarian sex cord tumors**
  - Sertoli Leydig cell tumor of ovary
  - Juvenile Granulosa cell tumor

What if I already had negative *BRCA1* and *BRCA2* testing?

It depends on the year performed and comprehensiveness of analysis



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Adapted from: Walsh C. Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy, Gynecologic Oncology, 137 (2015) 343-350

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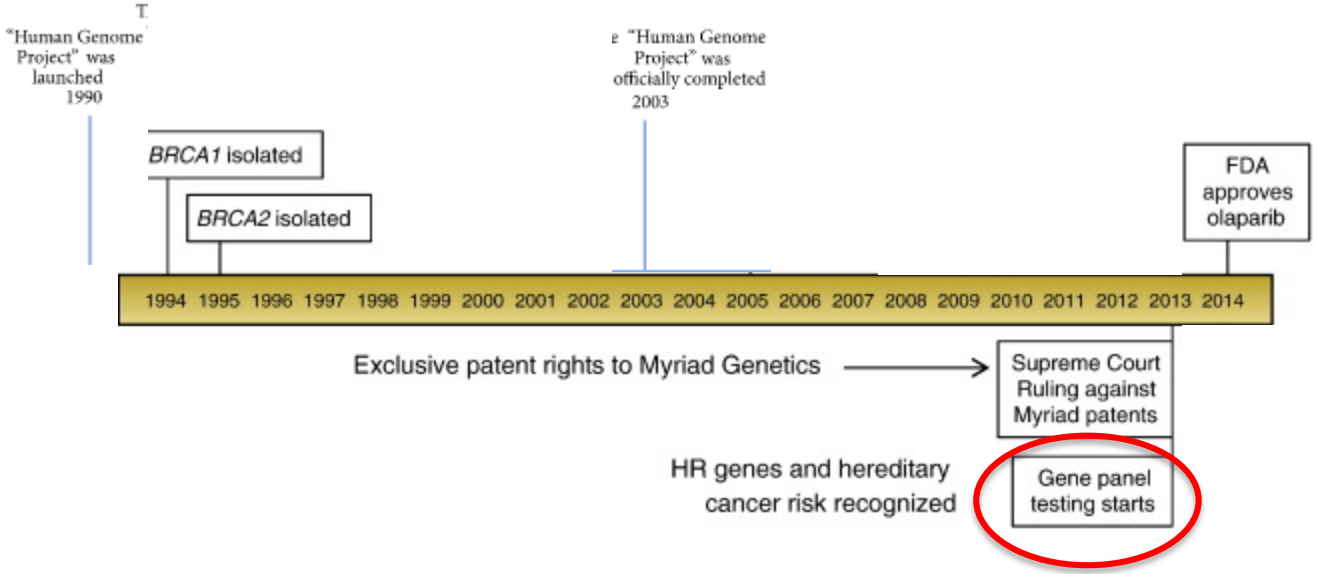

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AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTT
CAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTC
AGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTCAGTCACT
GCAGTCAGTCAGTACGTTGCACCGTGACAGTCAATTGCACCGTGACAGTCACGTAGTCACT

- Sequencing Analysis
  - Reads through each letter one by one
  - Picks up approximately 95% of mutations in *BRCA1/2*

What if I already had negative *BRCA1* and *BRCA2* testing?

AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTT
CAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTC
AGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTCAGTCACT
GCAGTCAGTCAGTACGTTGCACCGTGACAGTCAATTGCACCGTGACAGTCACGTAGTCACT

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AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTT
CAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTC
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AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTT
CAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTC
AGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTCAGTCACT
GCAGTCAGTCAGTACGTTGCACCGTGACAGTCAATTGCACCGTGACAGTCACGTAGTCACT

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What if I already had negative *BRCA1* and *BRCA2* testing?

AGCTGTTCAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTT
CAAGTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAAAAT
GTCAGTCACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAAAGCTGTTCAAGTCAGTC
ACTGCAGTCAGTCAGTACGTTGCACCGTGACAGTCAATTGCACCGTGACAGTCACGTGACT

- Deletion/Duplication Analysis
  - Looks for large amounts of letters that are missing or added
  - Picks up approximately 5% of mutations in *BRCA1* or *BRCA2*

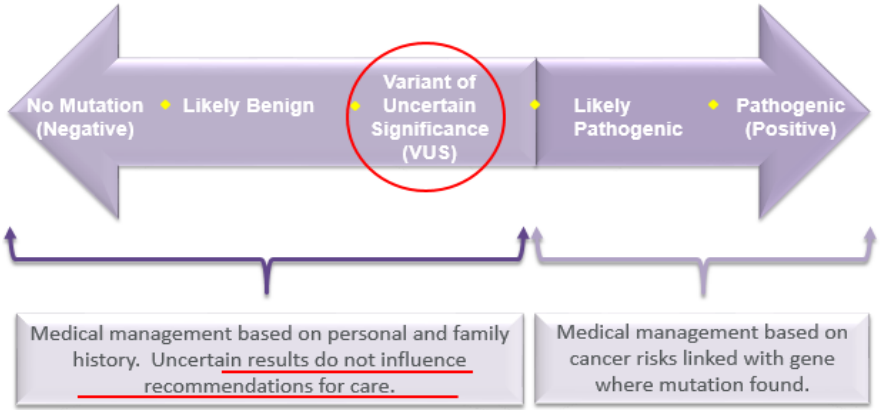
What if I already had negative *BRCA1* and *BRCA2* testing?

Are there other genes related to ovarian cancer?

- Gene panels…
  - Includes more than one gene related to specific indication such as ovarian cancer
    - High risk genes: Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)
    - Moderate risk genes: *BRIP1, RAD51C, RAD51D*
    - And many more…
- Changing yearly, even monthly

Genetic Testing: Possible Results

- **Positive**
- **Negative**
  - **Vs. Uninformative negative**
- **True Negative**
- **Variant of Uncertain Significance (VUS)**
  - "Inconclusive"/"Uncertain"
  - Management based on personal and family history
  - Encourage patient to periodically re-contact for updates
  - Do not recommend that relatives undergo genetic testing



Graphic Courtesy of Haley Pace, MS, CGC

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All of my genetic testing was negative, now what?

- Management based on personal and family history of cancer
- First degree female relatives (daughters, sisters, mothers):
  - *Consider ovarian cancer screening program* (research protocol only)
    - Includes Trans-vaginal ultrasound and CA-125 level
- **Consult with physicians/genetic counselors periodically for updated genetic testing and recommendations**

Benefits of Genetic Testing

- Provide an explanation for your personal or family history of cancer
- Evaluate your risk of developing future cancers
- Make informed medical decisions, including treatment, surveillance, and preventive options
- Potential use of other chemotherapy options
  - Ex: PARP inhibitors
- Qualify you for participation in clinical trials or research studies
- Identify other at-risk relatives for whom genetic testing is recommended
- Always changing and evolving – periodically check-in with genetics

Drawbacks to Genetic Testing

- Will results make a difference in my care?
- May be inconclusive
- Risk for developing cancer not always established
- What interventions are available?
- Psychosocial implications

Tumor DNA Testing

Also called somatic testing

- Uses next generation sequencing (many, many genes)
- Testing performed to look for DNA mutations *within* cancer cells/tumor only
  - Different from germline/inherited testing (testing we just reviewed)
- Typically performed to look for treatment targets or response to treatment
- Incidentally can find a genetic mutation that you were born with (inherited mutation)
- Rapidly evolving… (stay tuned)

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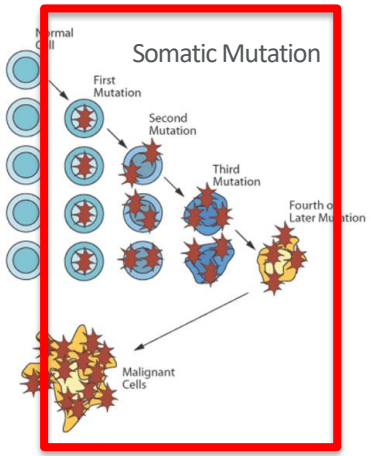
Sporadic Vs. Hereditary Cancer

Somatic vs Germline Mutations

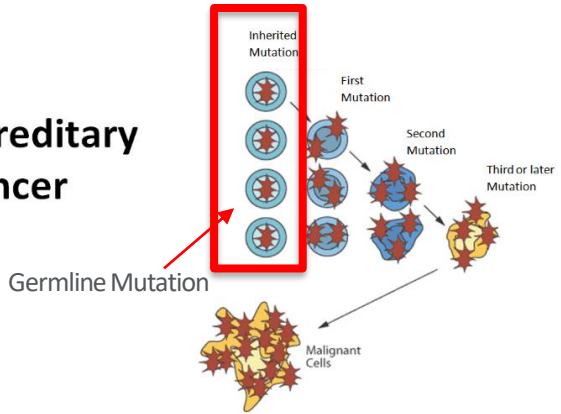
Genomic Testing



Sporadic Cancer

- Only present in tumor/cancer
- NOT inherited

Genetic Testing



Hereditary Cancer

- Present in every single cell
- Inherited in families
- From conception, at higher risk for specific malignancies

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Other Considerations…

- Genetic Information Nondiscrimination Act (GINA) passed in 2008
- Family planning options and reproductive risk implications
- Openness or willingness to communicate with family members
  - Family letter
- Psychosocial Implications
- Patient advocacy groups

Genetic Discrimination

- **Genetic Information Nondiscrimination Act (GINA)**
  - Federal Law, passed in 2008
  - Separate from the Affordable Care Act (ACA)
- Two major provisions
  - **Health insurance discrimination is ILLEGAL**
  - **Employment discrimination is ILLEGAL**
- Exceptions:
  - Life Insurance companies
  - Long Term disability companies
  - Companies with fewer than 20 employees
- For more information: www.ginahelp.org

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Family Letter Example

Dear family:

I am writing this letter to inform you that I recently had genetic testing and was diagnosed with a condition called hereditary breast and ovarian cancer syndrome (HBOC) which affects families. This letter contains information about HBOC, how it might affect you, and how to find out if you have this condition also.

People who have HBOC have increased cancer risks. Specifically women have increased risks for breast cancer and ovarian cancer, and men have increased risks for prostate cancer and male breast cancer. It is recommended that anyone with HBOC have increased screening for these cancers which helps detect cancers earlier when they are more easily treated, and in some cases, prevent them altogether.

Hereditary breast and ovarian cancer syndrome is caused by a mutation in a gene that can be inherited in families. The specific mutation identified in me was in the ***BRCA**** gene (***). Genetic testing is available for you to see if you carry this same mutation. You can take this letter to your doctor, or contact the genetics team at Northwestern Cancer Genetics to discuss this further and find out how to get tested in your area. You can also find a genetic counselor near you by going to the following website: www.nsgc.org and using the "Find a Genetic Counselor" tool.

If you or your doctors have additional questions, the Northwestern Cancer Genetics team would be happy to discuss this further. You can reach a member of the Cancer Genetics Team at 312-472-0518 or 312-472-0523.

Sincerely,

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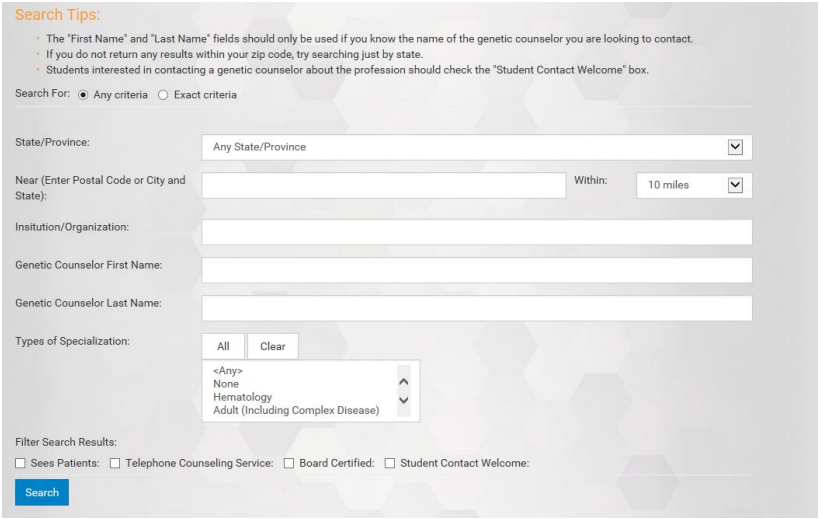
Find a Genetic Counselor Near you

http://www.aboutgeneticcounselors.com/



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Thank You

Email: cancergenetics@nm.org
Scheduling: (312) 695-0320

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