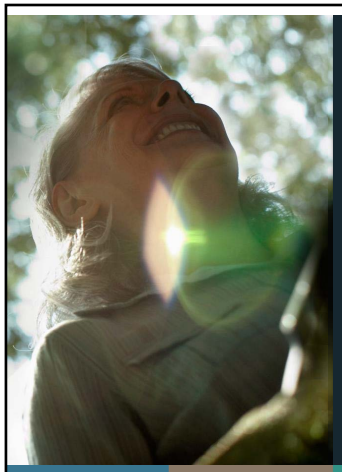

Identifying your risk for hereditary breast or ovarian cancer

David Andorsky, MD
Breanna Roscow, MS, CGC
303-993-0161

Boulder Community Health

ROCKY MOUNTAIN CANCER CENTERS™

Outline

Boulder Community Health

- Genetics and biology of hereditary cancer syndromes
- BRCA1 and BRCA2
- Genetic counseling and testing
- Genes related to breast cancer
- What to do with a positive genetic testing result
- Your questions

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What causes cancer?

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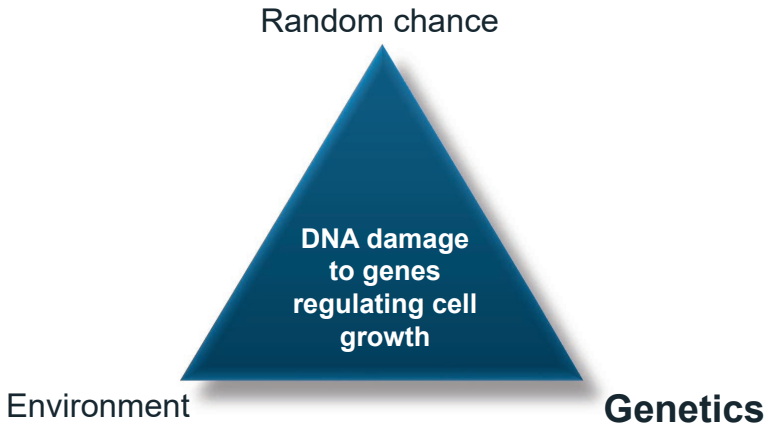

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Genetics 101

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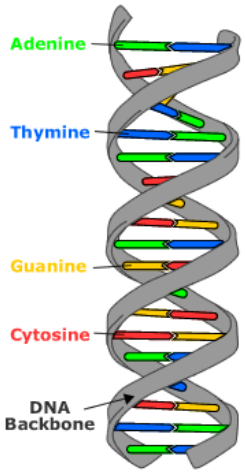

- Genes contain the instructions for building and regulating all living organisms
- Genes are encoded by long strings of chemical “letters” (base pairs) in molecules of DNA found in the nucleus of each cell

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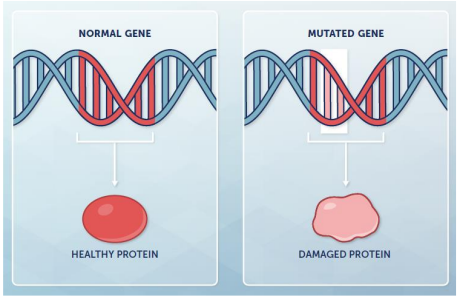
Genetic variation

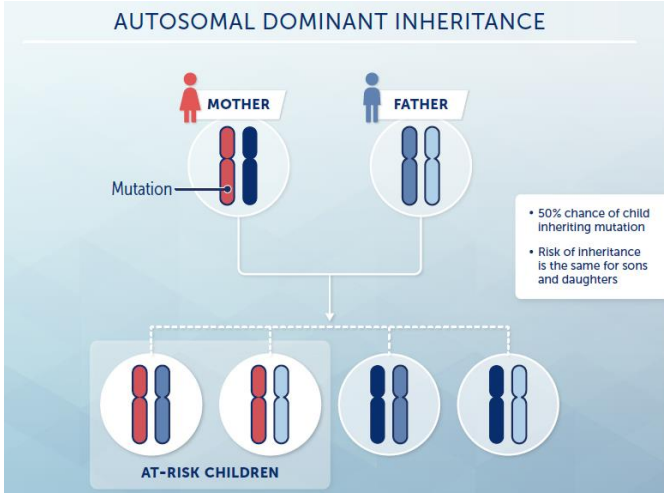
- Subtle differences in DNA sequences give rise to the diversity of life.
- Variations can be:
  - Wild type – the most common variant
  - Benign – less common but not harmful
  - Deleterious – giving rise to disease

Hereditary Mutations



Examples
- The fat cat ate the rat (Normal)
- The _atc ata tet her at (deletion)
- The ffa tca tat eth era t (insertion)
- Tha fat cat ate the rat (point mutation)
- The cat fat ate the rat (Rearrangement)
- The fat cat. (stop codon)

How can cancer be inherited?



BRCA1 and BRCA2

- Involved in DNA repair
  - DNA needs to be copied in its entirety each time a cell divides
  - BRCA1, BRCA2, and many other proteins correct DNA damage that occurs over time
- Deleterious mutations in BRCA1 or BRCA2 cause cells to accumulate more errors in DNA

BRCA1 and BRCA2

- Many errors are benign variants…..
- ….. But occasionally an error can alter genes responsible for cell growth
- It is these secondary mutations that ultimately give rise to cancer

BRCA1 and BRCA2

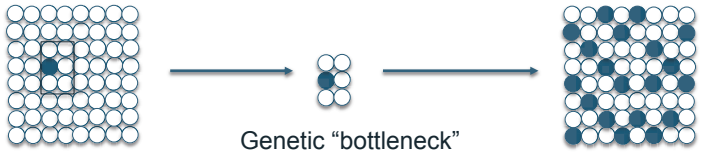
- You only need 1 defective copy of BRCA1 or BRCA2 to increase cancer risk
- Cancers arise later in life (because it takes decades for the right combination of errors)
- Some patients with BRCA1 or BRCA2 mutations never develop cancer (because there is some random chance involved in which errors occur)

BRCA mutations and Ashkenazi Jews

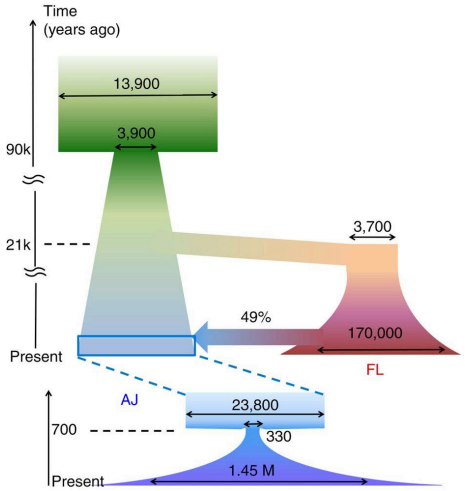
- BRCA1 and BRCA2 mutations are found in people of all ethnic/racial backgrounds
- 3 specific mutations are found with greatly increased frequency in Ashkenazi Jews
  - BRCA1: 185delAG, 5382insC
  - BRCA2: 6174delT
  - 1:33 to 1:56 affected individuals
- BRCA1 founder mutation also found in other Jewish populations

The founder effect

- A very small population may become enriched for rare genetic variants by chance



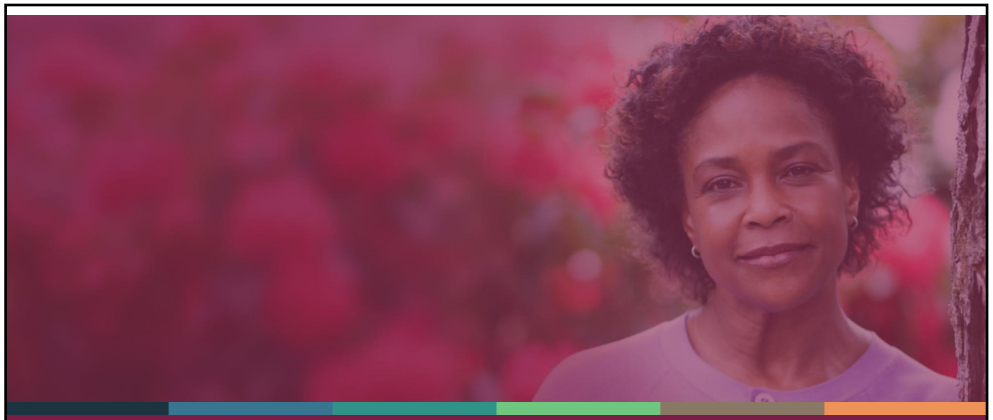
Ashkenazi Jewish genetic history



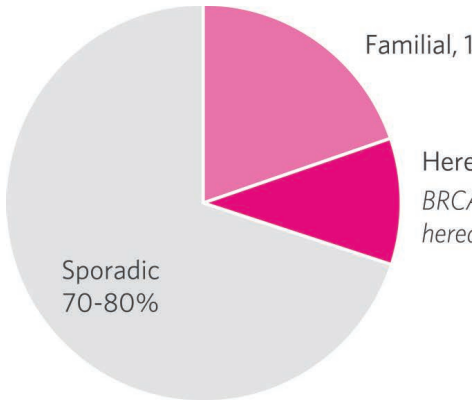
Cancer genes with Jewish founder mutations:

- BRCA1
- BRCA2
- CHEK2
- GREM1
- APC

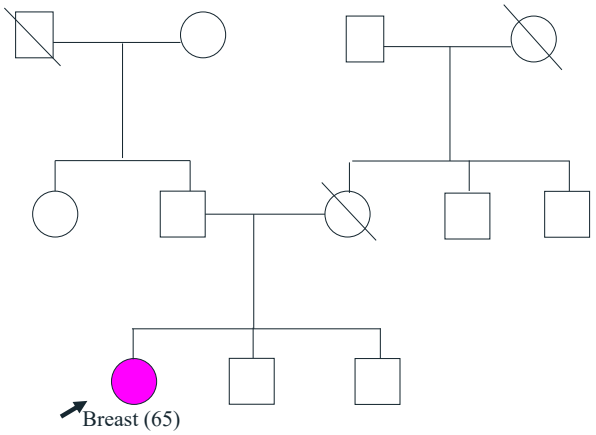
Carmi S, et al. *Nature Communications* **5**, : 4835 (2014)



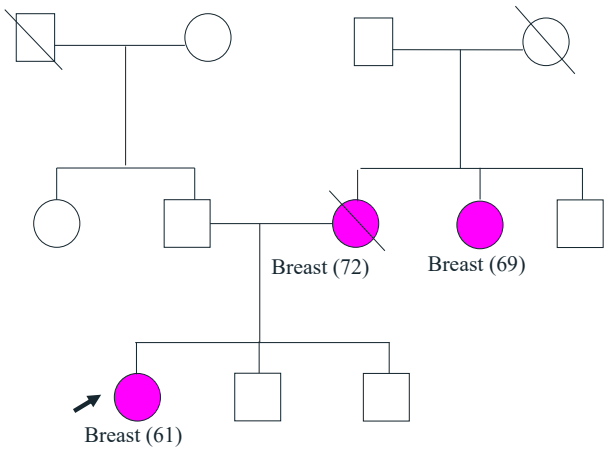
You may have seen….



Sporadic Cancer



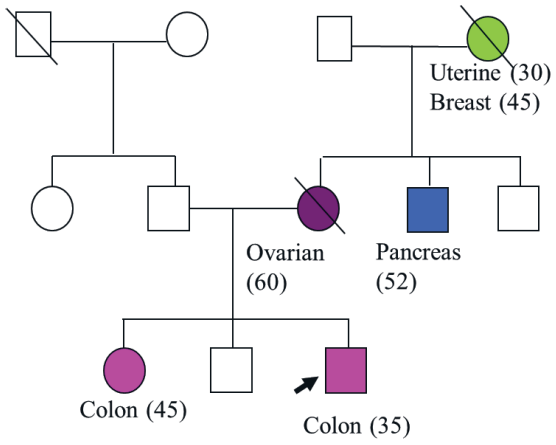
Familial Cancer



When do we suspect hereditary cancer?

Multiple	2 OR MORE primary cancers in the same person	3 OR MORE cancers on the same side of the family	10 OR MORE colorectal polyps in a person's lifetime
Young	ANY OF THE FOLLOWING CANCERS DIAGNOSED ≤50Y: Breast, colorectal, uterine		
Rare	CANCER OF SMALL BOWEL, URETER, MALE BREAST CANCER, OVARIAN CANCER		
Ancestry	ASHKENAZI JEWISH AND HISTORY OF BREAST OR PANCREATIC CANCER		

Hereditary Cancer



Genetic Counseling vs. Genetic Testing

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- **Genetic counseling**:
  - Appointment to assess cancer risks
  - Discuss genetic testing options
  - Interpret genetic testing results
  - Create a personalized management/screening plan

- **Genetic testing**:
  - Blood or saliva test that can show if you inherited an abnormal gene (mutation) that increases your risks for certain cancers
  - Testing is performed by a specialized laboratory
  - Results take ~ 3 – 4 weeks

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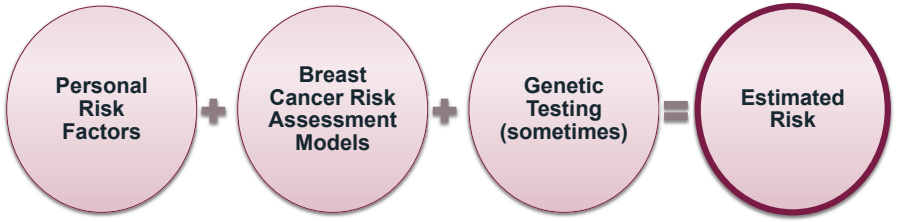
How do we estimate breast cancer risk?

Boulder Community Health



- Genetic testing may not be needed by everyone
- Can still use family history / personal history to estimate risk
- May qualify for increased screening

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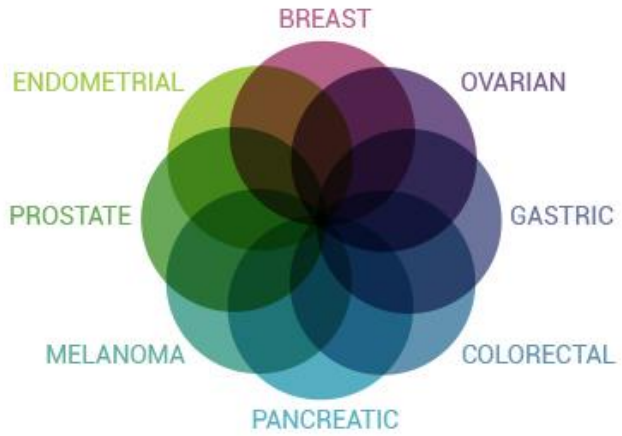
Boulder Community Health



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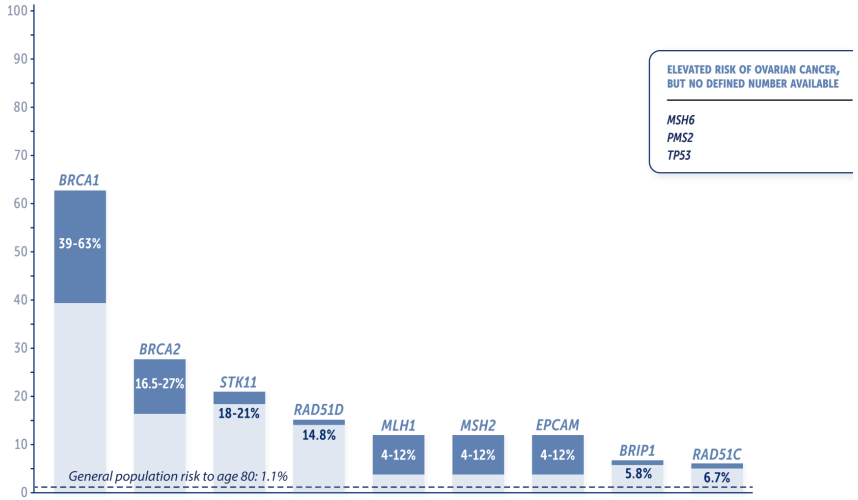
GENES ASSOCIATED WITH BREAST CANCER

and their associated risk ranges

Rocky Mountain Cancer Centers

GENES ASSOCIATED WITH OVARIAN CANCER

and their associated risk ranges



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Breast Cancer Genes

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PALB2	ATM	CHEK2
• Breast • Pancreatic • Possibly other cancers	• Breast • Pancreatic • Possibly ovarian and other cancers	• Breast • Prostate • Colon • Possibly other cancers

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Genetic Test Results

Boulder Community Health

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

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Boulder Community Health

GINA

Genetic Information Non-Discrimination Act

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

Colorado has protections for long-term and short-term disability insurance, but NOT life insurance

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BRCA1/BRCA2 Management in Women

Boulder Community Health

Breast

- Annual Screening
  - Self breast exam - start at 18
  - Clinical breast exam - start at 18
  - Breast MRI – start at 25
  - Mammogram – start at 30
- Risk Reduction
  - Consider bilateral mastectomy
  - Chemoprevention (Tamoxifen)
- Considerations
  - Screening during pregnancy
  - Nursing
  - Recovery from mastectomy
  - Insurance coverage

Ovarian

- Screening
  - Transvaginal ultrasound
  - CA-125

  Limited usefulness
- Risk Reduction
  - Oophorectomy:
    - BRCA1 35-40
    - BRCA2 40-45
  - Chemoprevention (birth control)
- Considerations
  - HRT
  - Salpingectomy alone?
  - Cost of over treating?

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BRCA1/BRCA2 Management in Men

Boulder Community Health

Breast

- Annual Screening
  - Self breast exam – start at 35
  - Clinical breast exam – start at 35
  - Consider mammogram

Prostate

- Annual Screening
  - PSA and prostate exam – start at 45

Men and women:

No specific guidelines for **pancreatic cancer** or **melanoma**, but may be individualized based on family history

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NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Genetic/Familial High-Risk Assessment: Breast and Ovarian

NCCN Guidelines Index
Table of Contents
Discussion

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	See Li-Fraumeni Syndrome Management

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Recent Updates

Boulder Community Health

- American College of Radiology (ACR) and Society of Breast Imaging (SBI) now recommend that **ALL** women should be evaluated for breast cancer risk no later than age 30.
  - Specifically names populations at higher risk:
    - Black women
    - Women of Ashkenazi Jewish

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Recent Updates – 23andMe

Boulder Community Health

23andMe Granted First FDA Authorization for Direct-to-Consumer Genetic Test on Cancer Risk

March 6, 2018

Authorization allows 23andMe to report on BRCA1- and BRCA2-related genetic risk for breast, ovarian and prostate cancer

- Only analyzes the 3 AJ founder mutations in BRCA1 and BRCA2.
- Hundreds of other known BRCA mutations are **NOT** analyzed.
- FDA states “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."
- The test has a minimum analytical sensitivity of 95%.

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