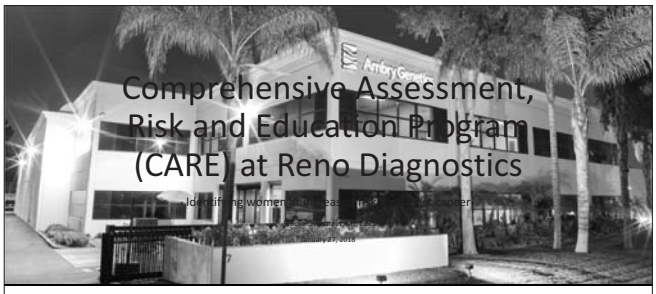
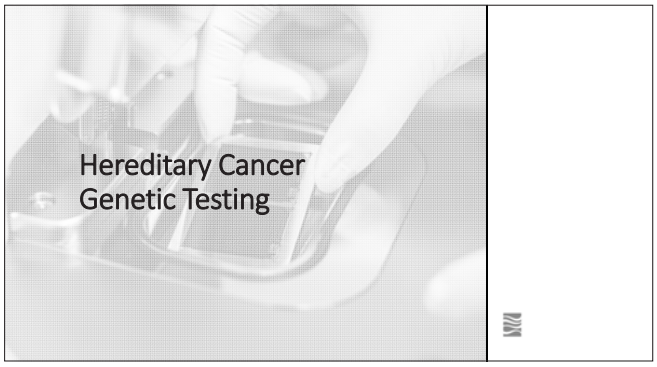


Agenda: Identifying "High-Risk" Women

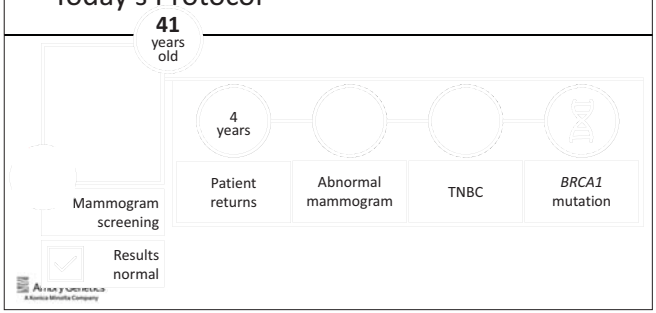
- Option 1: Utilize National Comprehensive Cancer Network (NCCN) guidelines
  - Personal history of cancer
  - Family history of cancer (including paternal side of the family)
  - Only identifying women with and without a hereditary cancer predisposition
- Option 2: Utilize breast cancer risk model
  - Personal risk factors
    - Breast density
    - Age of menarche
    - Parity
    - Hormone replacement therapy
    - Breast disease
  - Family history of cancer
  - Not identifying women with a hereditary cancer predisposition
- Option 3: Utilize both NCCN guidelines AND breast cancer risk models
  - Comprehensive approach to identify women who need increased breast screening

Disclosure

I am a full-time salaried employee at Ambry Genetics



Today's Protocol



Who to Test: Signs of Hereditary Cancer

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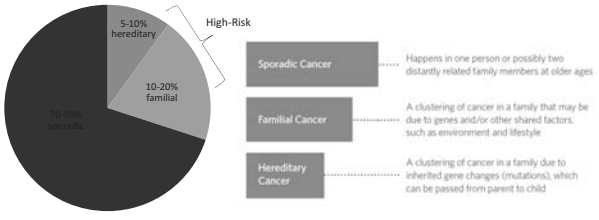
What Causes Cancer



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Key Syndrome: Hereditary Breast and Ovarian Cancer

FREQUENCY/CANCER RISK

Occurs in 1/400 individuals, or 1/40 individuals of Ashkenazi Jewish descent; Increased risks of breast, ovarian, pancreatic, male breast, and prostate cancer

FINDING ANSWERS THROUGH QUALITY GENETIC TESTING

Testing *BRCA1* and *BRCA2* through a quality laboratory can provide precise, actionable data to guide medical management

Hereditary Breast and Ovarian Cancer (HBOC)

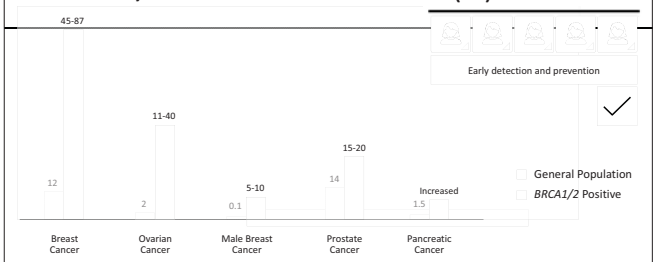
IMPACTS THE FAMILY

Sons, daughters, siblings, and parents should all be offered testing due to 50% chance of having mutation

ACTIONABLE

Screening and management guidelines exist, testing and management well covered by insurance companies nationwide

BRCA1/2 Lifetime Cancer Risks (%)



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Breast Cancer Genes with Medical Management Guidelines

Gene	*ATM*	*BRCA1/2*	*CDH1*	*CHEK2*	*PALB2*	*PTEN*	*TP53*	*NBN*	*NF1*
Breast Cancer Risks	**2-4 fold** increased risk for breast cancer	**45-87%** lifetime breast cancer risk	**39-52%** risk for lobular breast cancer	**2-fold** increased risk for breast cancer	**33-58%** lifetime breast cancer risk	**25-85%** lifetime breast cancer risk	Nearly 100% lifetime cancer risk, breast cancer risk increased	Moderately increased breast cancer risk	Moderately increased breast cancer risk
Consider Surgery	✓	✓	✓	✓	✓	✓	✓	✓	✓
Breast MRI +Mammo	✓	✓	✓	✓	✓	✓	✓	✓	✓
Option for PARPi therapy	✓	✓							
Other Cancer Risks	Pancreas Prostate	Ovarian Pancreas Prostate Melanoma Male breast	Diffuse gastric	Colorectal		Thyroid Uterine Melanoma	Sarcoma Brain Adrenocortical Leukemia Others		Malignant peripheral nerve sheath tumors GIST Others

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Genetic/Familial High-Risk Assessment: Breast and Ovarian. National Comprehensive Cancer Network. 2.2019

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Impact on Medical Management

- Annual breast MRI beginning between ages 25-29, annual MRI and mammogram at age 30
- Consideration of risk-reducing mastectomy
- Recommendation of risk-reducing oophorectomy
- Male breast cancer and prostate cancer screening for male mutation carriers
- Consider screening for pancreatic cancer and melanoma in certain individuals
- Option of PARP inhibitor therapy for patients with advanced ovarian cancer

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Selecting the Best Test: Benefits of Hereditary Cancer Panels

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Genetic Testing is Recommended by Key Professional Organizations


American Society of Breast Surgeons

Annals of Internal Medicine

U.S. Preventive Services Task Force

RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING FOR BRCA-RELATED CANCER IN WOMEN
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION


ACOG **supports** Ob-Gyns ordering testing

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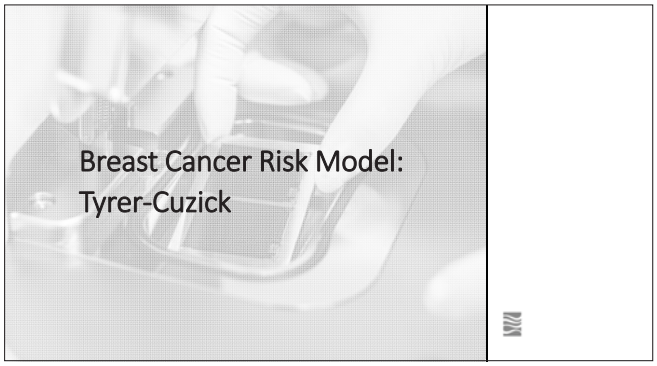
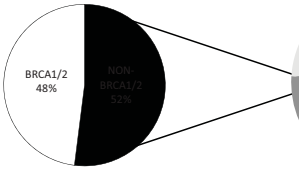
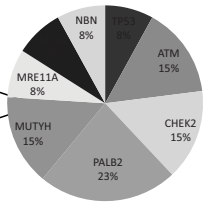


Importance of looking beyond *BRCA1/2*

Pathogenic Mutations in Panel Group



Distribution of Non-BRCA1/2 Mutations



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REFERENCE
Kapoor N., et al. Ann Surg Oncol. 2015

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What is Tyrer-Cuzick (TC)?

- Risk model used to calculate an **unaffected** woman's risk for breast cancer
- Incorporates personal and family history information
  - Personal: BMI, age at menopause, age at menarche, history of breast disease, breast density (Volpara), age at first live birth, HRT
  - Cancer family history: paternal and maternal
- Calculates lifetime breast cancer risk
- If TC lifetime breast cancer risk is ≥20%, patients are eligible for mammograms and breast MRIs
- Does NOT identify patients with hereditary cancer predisposition

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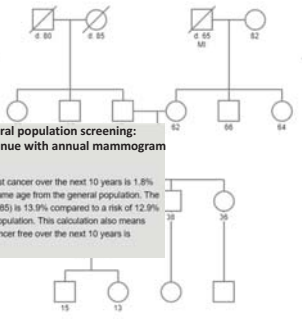
Case Example

TC Risk Score:
Current Age: 40
Weight: 135lbs
Height: 5'3"
Volpara: 13
Age at menarche: 1
Age at first live birth
No HRT
No menopause
No BRCA mutation
No breast disease
No Ashkenazi Jewis
No fam hx breast ca



Lifetime Risk:
This woman's Risk (to age 85): **13.9%**
Average woman (to age 85): **12.9%**

General population screening:
Continue with annual mammogram

This woman's estimated risk for developing breast cancer over the next 10 years is 1.8% compared to a risk of 1.6% for a woman of the same age from the general population. The lifetime risk for developing breast cancer (to age 85) is 13.9% compared to a risk of 12.9% for a woman of the same age from the general population. This calculation also means that this woman's chance of remaining breast-cancer free over the next 10 years is 98.2%.

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Screening Recommendations

- Lifetime breast cancer risk <15%
- Annual mammogram

- Lifetime breast cancer risk 15-19%
- Breast density, family history
- Annual mammogram + annual automated breast ultrasound

- Lifetime breast cancer risk ≥20%
- Personal and family history (TC model), hereditary breast cancer predisposition
- Annual mammogram + annual breast MRI

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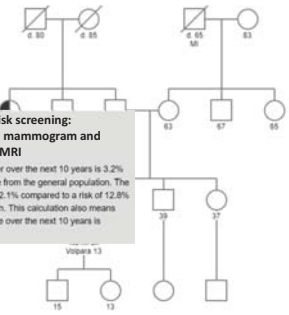
Case Example Cont.

TC Risk Score:
Current Age: 40
Weight: 142lbs
Height: 5'3"
Volpara: 13
Age at menarche: 1
Age at first live birt
No HRT
No menopause
No BRCA mutation
No breast disease
No Ashkenazi Jewis
Paternal aunt dx. breast cancer 68



Lifetime Risk:
This woman's Risk (to age 85): **22.1%**
Average woman (to age 85): **12.8%**

High-Risk screening:
Annual mammogram and Breast MRI

This woman's estimated risk for developing breast cancer over the next 10 years is 3.2% compared to a risk of 1.8% for a woman of the same age from the general population. The lifetime risk for developing breast cancer (to age 85) is 22.1% compared to a risk of 12.8% for a woman of the same age from the general population. This calculation also means that this woman's chance of remaining breast-cancer free over the next 10 years is 96.8%.

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Comprehensive Assessment, Risk and Education Program (CARE) at Reno Diagnostics

- Goal: Identify women at increased risk for breast cancer earlier
- Benefits of program:
  - Provide personalized cancer risk information
  - Make recommendations for increased screening
  - Identify at-risk family members

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Combining hereditary genetic testing and breast cancer risk model to identify patients at increased risk for breast cancer

Comprehensive Assessment, Risk and Education Program (CARE) at Reno Diagnostics

Identification	Pre-test education	Genetic testing	Results	Post-test counseling	Documentation
Using Ambry's High-Risk Screening Tool	How genetic testing can guide early detection and prevention	Ordered through Ambry for qualified individuals	Patient test results delivered to ordering provider	Genetic counseling to review next steps	Increase quality, decrease liability assessment

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Other Genes Possibly Associated with Breast Cancer

BRIP1 *RAD51C* *RAD51D*	*BARD1*	Lynch syndrome genes (Possible)
Possible breast cancer risk	**Possible breast cancer risk**	**Recent research indicates possible association with increased breast cancer risk (especially *MSH6*)**
Significantly increased risk of ovarian cancer Risk-reducing oophorectomy is appropriate	Possible increased risk for ovarian cancer	Increased colorectal cancer risks, other GI risks, endometrial and ovarian cancer risks, manage based on Lynch syndrome guidelines

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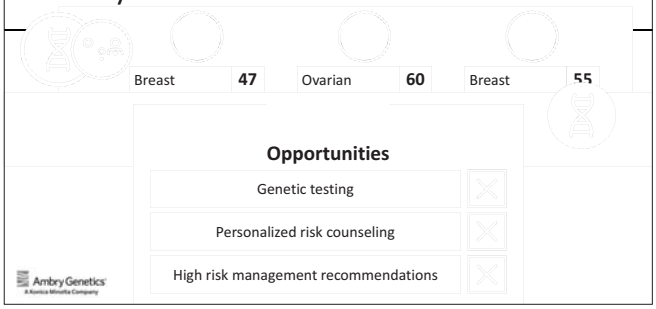
Today's Protocol



Opportunities

- Genetic testing
- Personalized risk counseling
- High risk management recommendations

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