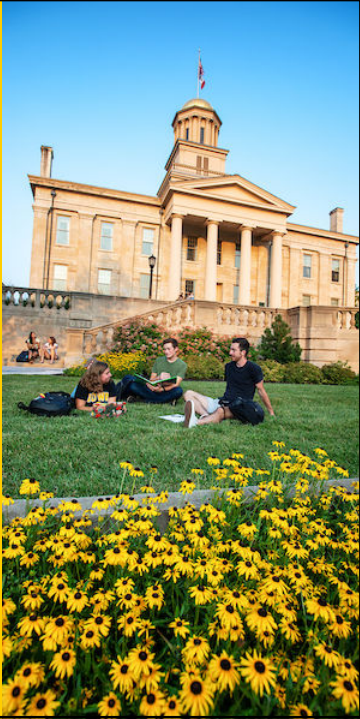


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Cancer Genetic Risk Assessment: The Basics

Morgan Jansen, MPAS, PA-C, CGRA



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Disclosures

I have no disclosures.

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Learning Objectives

1. Determine the components required to complete cancer genetic risk assessments.
2. Recognize family histories that are concerning for hereditary cancer syndromes and understand when patients qualify for genetic testing for hereditary cancer syndromes.
3. Understand the basics of calculating lifetime breast cancer risk utilizing various risk assessment models.
4. Utilize patients' calculated lifetime breast cancer risk to determine and employ appropriate breast cancer screening.

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Components of Cancer Genetic Risk Assessment

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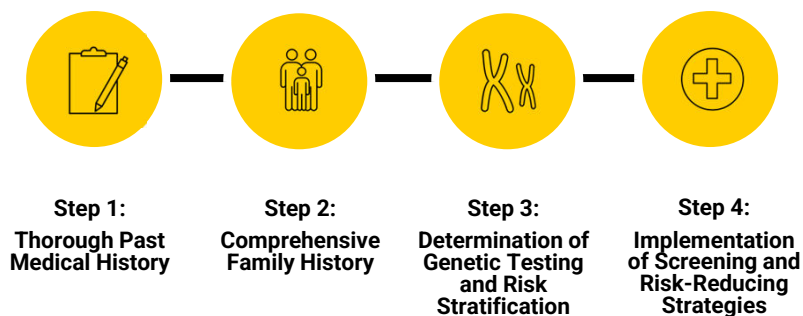
What is Cancer Genetic Risk Assessment (CGRA)?

- Definition: a clinical evaluation used to identify individuals who may have an increased risk of developing cancer due to hereditary susceptibility or other factors
 - Susceptibility may include:
 - Germline mutations (e.g. hereditary cancer syndromes like *BRCA1/2*)
 - Cancer risk secondary to other factors (lifestyle, familial factors beyond known germline mutations, breast density, etc.)
 - CGRA includes cancer risk stratification and may or may not include genetic testing for hereditary cancer syndromes
- The goal of CGRA is to determine which individuals may be at higher risk for cancer *and then* utilize this information to inform strategies for cancer screening and risk-reduction

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Components of CGRA

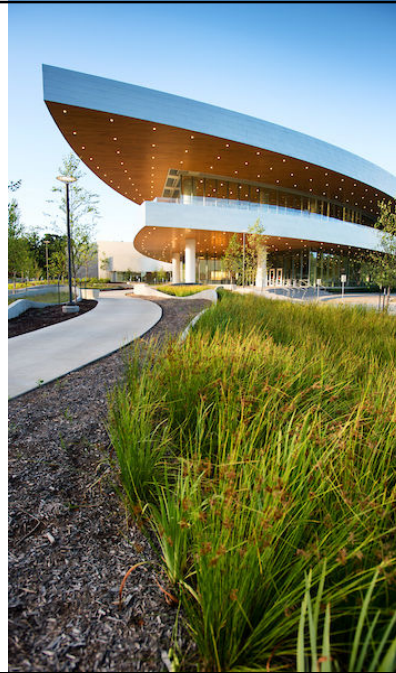


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Components of CGRA: Past Medical History

- Personal history of cancer or other medical conditions
- History of biopsies
- History of exposure to cancer-causing agents
- Reproductive history
- Lifestyle/social history
- Surgical history
- Known prior genetic testing



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Components of CGRA: Family History

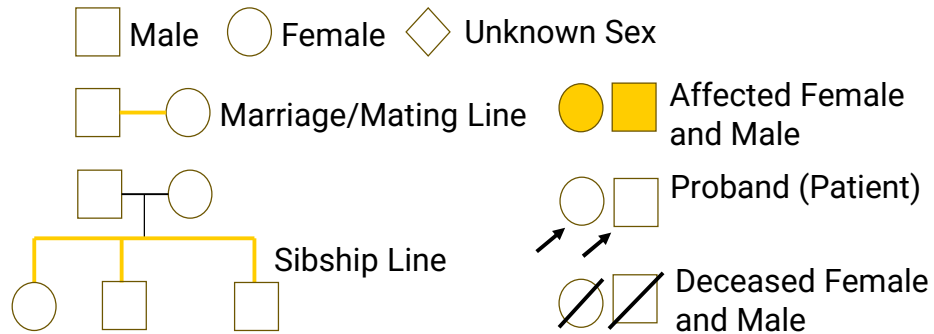
- Detailed family history of cancers and tumors
 - Family history should include information regarding:
 - Both unaffected and affected persons
 - Male and female relatives
 - First-, second-, and third-degree relatives if possible
 - Current age and/or age of death
 - Ethnicity
 - Detailed cancer and tumor history including:
 - Type of cancer (including stage and/or grade)
 - Unilaterality or bilaterality
 - Age of diagnosis
 - Treatment received (if any)
 - Known prior genetic testing
- Detail is KEY to any cancer genetic risk assessment; however, it is reasonable to work with patients regarding their knowledge and to assume “best guesses”

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Components of CGRA: Family History and the Pedigree

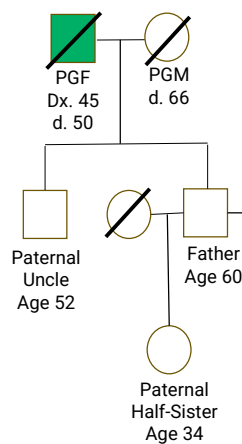
- Pedigree: family tree or chart used to document family history of cancers and/or tumors
- Pedigree symbols:


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Pedigree Example

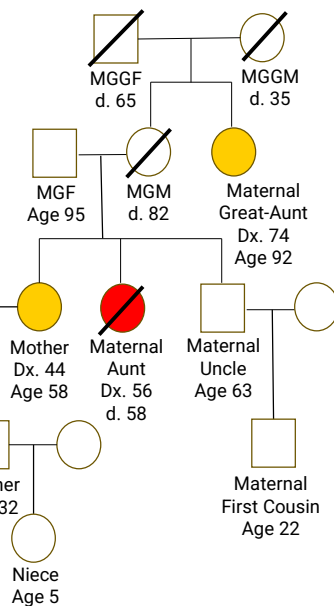
GERMAN ANCESTRY



LEGEND

- Uterine Cancer
- Breast Cancer
- Colon Cancer

IRISH ANCESTRY


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Hereditary Cancer Syndromes

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What are hereditary cancer syndromes?

- Germline genetic mutations which increase the risks for certain types of cancer
- Hereditary cancer syndromes may be:
 - Dominant vs. recessive (or both!)
 - Increase risk of a singular type of cancer vs. multiple types of cancer
 - Note: Hereditary cancer syndromes do NOT guarantee that a patient will develop cancer; rather they increase the risk of cancer in comparison to the general population

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Many Hereditary Cancer Syndromes

- Hereditary breast and/or GYN cancer (ovarian, endometrial) syndromes:
 - *ATM, BARD1, BRCA1/2, BRIP1, CDH1, CHEK2*, Neurofibromatosis type 1 (*NF1*), *PALB2*, Cowden Syndrome (*PTEN*), Lynch Syndrome (*MLH1, MSH2, MSH6, PMS2*), *RAD51C/D, STK11, TP53*
- Hereditary pancreatic cancer syndromes:
 - *CDKN2A, BRCA1/2, PALB2*, Lynch Syndrome (*MLH1, MSH2, MSH*), *ATM, TP53*
- Hereditary prostate cancer syndromes:
 - *H0XB13, BRCA1/2, ATM, TP53*
- Hereditary colon cancer syndromes:
 - Lynch Syndrome (*MLH1, MSH2, MSH, PMS2*), Cowden Syndrome (*PTEN*), *STK11*
- Skin cancer syndromes
 - *CDKN2A, BRCA2*

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Who should be tested?

- National Comprehensive Cancer Network (NCCN) provides specific guidelines regarding patients who may be at risk for hereditary cancer syndromes, as well as recommendations for which patients should be offered genetic testing



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General Guidelines for Testing

Multiple family members with the same type of cancer

For example, NCCN recommends offering testing for breast cancer susceptibility genes in patients with a family history of ≥ 3 diagnoses of breast and/or prostate cancer on the same side of the family (including the patient)

Cancer clusters that are consistent with a hereditary cancer syndrome

For example, patients with a family history of colon cancer, endometrial cancer, and ovarian cancer on one side of the family would be good candidates to test for Lynch Syndrome

Additionally, patients with a family history of breast cancer, ovarian cancer, and pancreatic cancer on one side of the family would be good candidates for test for *BRCA1/2*

Young age at diagnosis

To illustrate, NCCN recommends offering testing for breast cancer susceptibility genes in patients with a personal or family history of breast cancer diagnosed at $\leq$ age 50

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General Guidelines for Testing

Rare and/or high-risk cancers

To illustrate, NCCN recommends offering genetic testing for those with a personal or family history of pancreatic cancer, ovarian cancer, male breast cancer, or metastatic prostate cancer

Ethnicity

For example, NCCN recommends offering genetic testing for hereditary breast/ovarian cancer syndromes for individuals with Ashkenazi Jewish ancestry

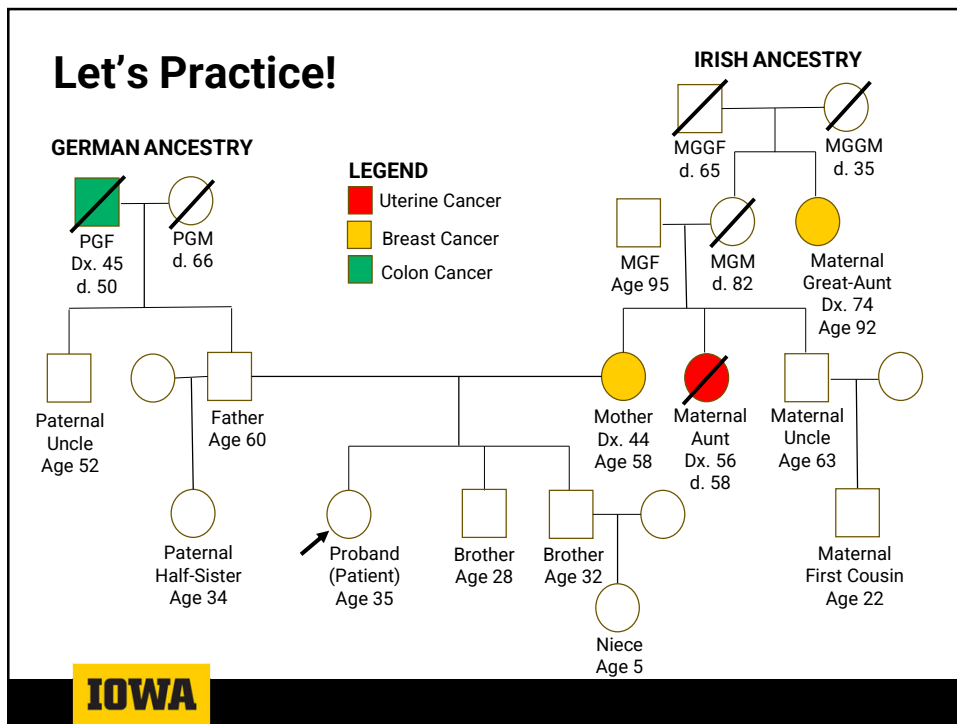
Known family history of hereditary cancer syndrome

Patients with a known family history of hereditary cancer syndromes should be offered genetic testing if they have not previously had testing

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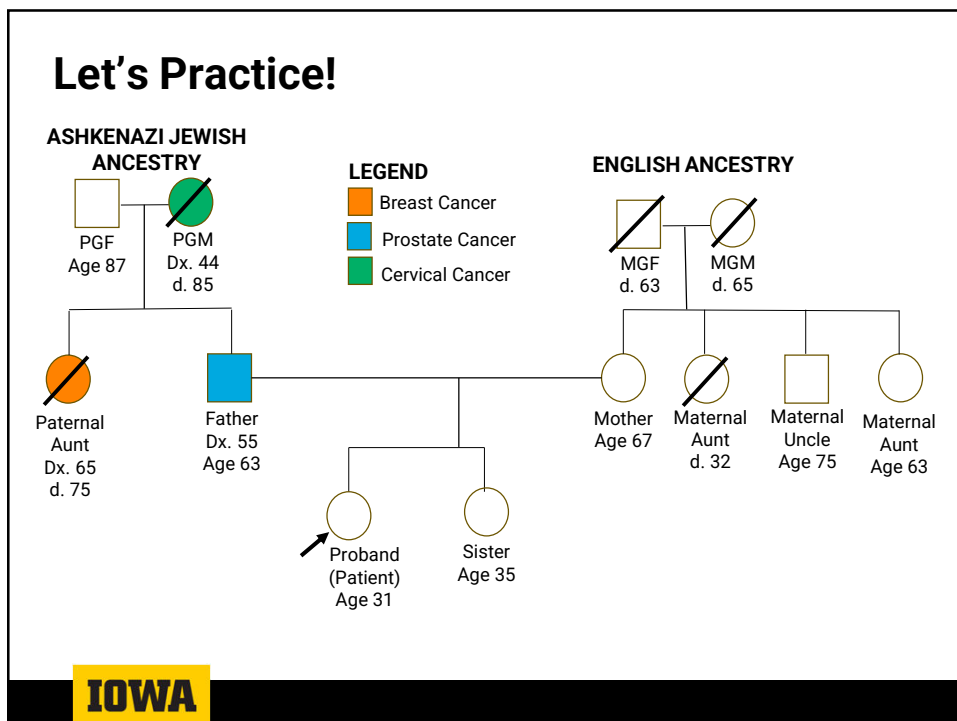
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Let's Practice!



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Let's Practice!



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“I’m worried my patient may have a hereditary cancer syndrome... Now what?”

- Whenever possible, it is recommended that a clinician *with experience in cancer genetics* be involved with counseling the patient regarding genetic testing options, as well as review of results
 - Genetic testing is complex; results may be negative, positive or “somewhere in between”
 - Additionally, genetic testing has implications not only on possible cancer risk, but also socially (e.g. insurance)
- Qualified individuals may include:
 - Genetic Counselors
 - Clinical Geneticists
 - Oncologists and/or cancer surgeons
 - Oncology nurses
 - APPs with additional certification/experience (e.g. CGRA)

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**WHEN IN DOUBT,
REFER IT OUT!**

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Positive Results

- Patients who return with positive genetic testing results for a hereditary cancer syndrome should be managed according to NCCN guidelines
 - Note: NCCN guidelines change FREQUENTLY, and therefore should be consulted before proceeding with any screening modalities and/or risk-reducing treatments/surgeries

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Calculating Breast Cancer Risk

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Breast Cancer and Risk Factors

- Breast cancer is the most common type of cancer in women worldwide
- 1 in 8 women will develop a breast cancer in their lifetime and average lifetime risk (LTR) of breast cancer out to age 85 is 12-13%
- There are multiple risk factors that affect breast cancer risk:

– Age at menarche	– Breast density	– Prior breast biopsies
– Age at menopause	– Current age	– Ethnicity
– Age at parity	– Menopausal status	– Hereditary cancer syndromes
– BMI	– Use of hormonal contraceptives *	– Use of MHT (HRT)

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Calculating Breast Cancer Risk

- Breast cancer risk can be calculated using multiple algorithms:
 - Gail Model
 - Tyrer-Cuzick Risk Assessment Score
 - CanRisk/BOADICEA
 - ASK2ME
- Each algorithm has pros and cons, and no algorithm is perfect
- Remember: These are risk *estimates* and these estimates *can change over time*

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Gail Model

- Can be accessed online for free (through National Cancer Institute, MDCalc, etc.)
- Pros:
 - Rapid
 - Easy-to-use
- Cons:
 - Not as comprehensive
 - May underestimate risk, particularly for those in minority groups (specifically Black/African American, Hispanic women born outside of the US, and American Indian/Alaska native) or those with family history of breast cancer in second- or third-degree relatives

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Gail Model

Included

- Patient's age
- Race/ethnicity
- Personal history of breast biopsy
- Age at menarche
- Age at parity
- First-degree relatives with history of breast cancer

NOT Included

- Prior genetic testing results
- Personal history of breast cancer
- Personal history of chest radiation
- BMI
- Menopausal status
- Breast density
- Second- or third-degree relatives
- Family history of other cancers
- Hormonal contraceptive usage
- MHT (HRT) usage
- Non-affected family members
- Lifestyle factors (e.g. alcohol use, smoking, etc.)
- Prior risk-reducing surgeries
- Male patients

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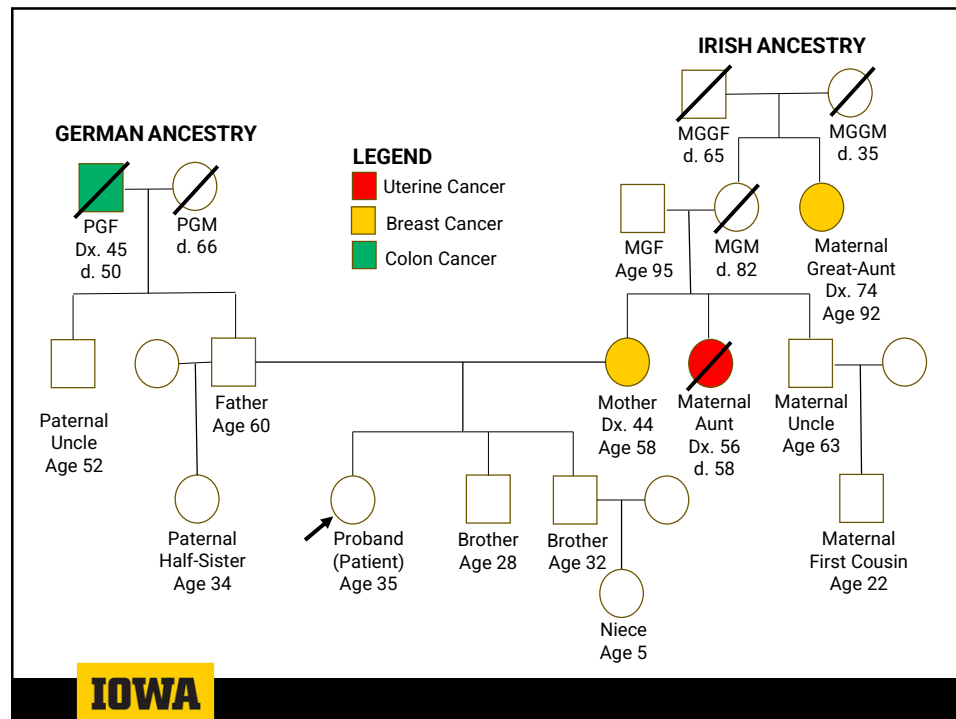
Let's Practice!

A 35 year old G2P2002 female presents to your office to discuss her family history of breast cancer. She does not have a personal history of breast cancer, and no one in her family has been tested for hereditary cancer syndromes, including herself. You obtain the following information:

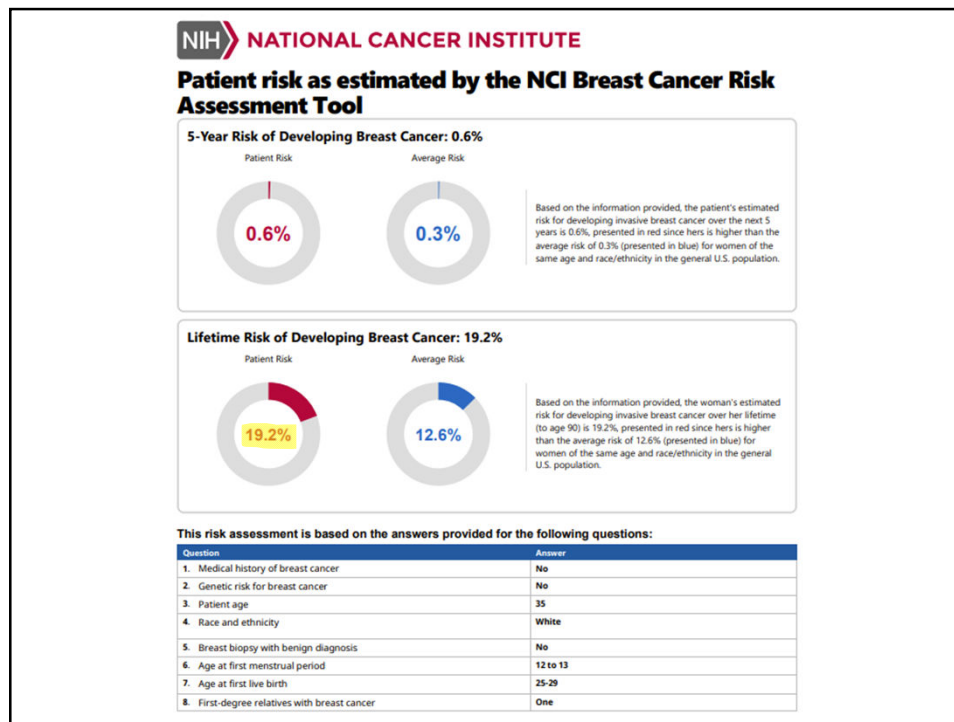
- Menarche: age 12
- Age at first birth: 26
- No prior history of breast biopsy
- Height: 5' 6" (167 cm)
- Weight: 195 lbs (88 kg)

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Tyrer-Cuzick Model

- Can be accessed online for free
- Pros:
 - Easy-to-use
 - Relatively rapid (though does require additional family history)
- Cons:
 - More comprehensive
 - May overestimate risk, particularly in those with history of certain breast biopsies
 - Not always straightforward

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Tyrer-Cuzick Model

Included

- Patient's age
- Personal history of breast biopsy
- Age at menarche
- Age at parity
- First- and second-degree relatives with history of breast cancer
- First- and second-degree relatives with history of ovarian cancer
- Non-affected family members
- BMI
- Menopausal status
- Breast density
- Prior *BRCA1/2* genetic testing results
- MHT (HRT) usage

NOT Included

- Race/ethnicity
- Prior genetic testing results for non-*BRCA* mutations
- Personal history of breast cancer
- Personal history of chest radiation
- Third-degree relatives
- Family history of cancers that are NOT breast or ovarian cancer
- Lifestyle factors (e.g. alcohol use, smoking, etc.)
- Hormonal contraceptive usage
- Prior risk-reducing surgeries
- Male patients

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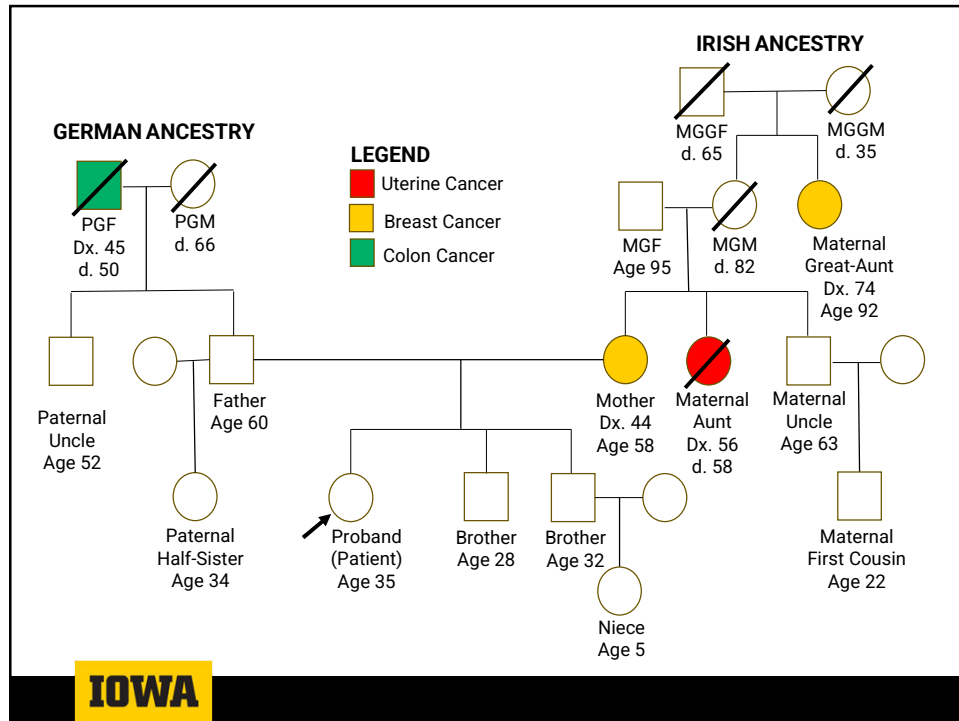
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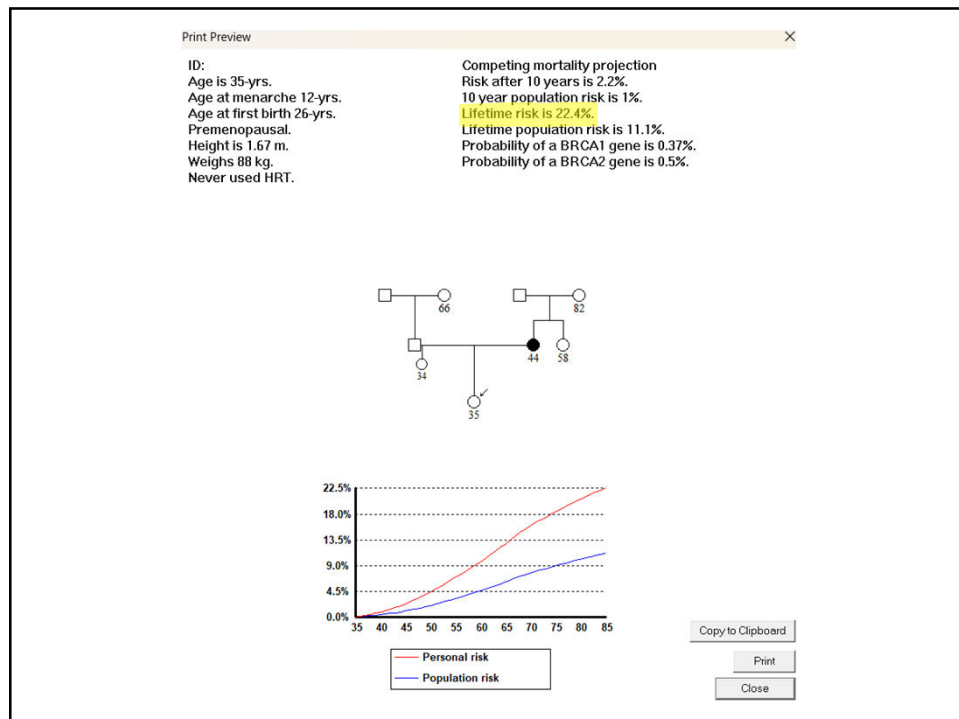
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- Age at first birth: 26
- No prior history of breast biopsy
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Breast Cancer Screening

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Risk Stratification

- Average (population) lifetime risk (LTR) of breast cancer out to age 85 is 12-13%
- Intermediate LTR of breast cancer out to age 85 is 14-19.9%
- High LTR of breast cancer out to age 85 is $\geq 20\%$

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Average and Intermediate Risk Patients

- Breast cancer screening guidelines for average and intermediate risk patients vary across organizations:
 - **American College of Obstetricians and Gynecologists (ACOG), American College of Radiology (ACR), National Comprehensive Cancer Network (NCCN)**
 - Annual mammogram starting at age 40
 - U.S. Preventative Services Task Force (USPSTF)
 - Biennial (every 2 years) mammogram starting at age 40
 - American Cancer Society (ACS)
 - Consider annual mammograms between age 40-44 (shared decision making) with recommendation to start at age 45
 - Switch to biennial mammograms at age 55

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High-Risk Patients

- Patients who are high-risk for breast cancer are recommended to undergo intensive breast surveillance, which involves:
 - Annual screening mammogram staggered with annual breast MRI
 - Recommended to start at age 40 or 10 years prior to the earliest breast cancer in patient's family (whichever is earlier)
- Intensive breast surveillance has been shown to be *equal to risk-reducing mastectomy* in preventing patients from dying of breast cancer

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Helpful Links

- National Comprehensive Cancer Network (NCCN):
<https://www.nccn.org/>
 - Note: Account is required to access NCCN guidelines, but it is free to make one
- Gail Model: <https://bcrisktool.cancer.gov/calculator.html>
- Tyrer-Cuzick Model: <https://ems-trials.org/riskevaluator/>

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Many Thanks

Thank you to the individuals who have guided and mentored me to becoming a competent CGRA practitioner:

Kathryn Huber-Keener, MD, PhD

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Providers of City of Hope

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