Genetics and Breast Cancer: Common Factors

Greta Henry, MS, CGC
Genetic Counselor
Allina Health Cancer Institute

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Disclosure

- I have no conflicts of interest in relation to this program or presentation.

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Objectives

- Review genetic factors in cancer risk
- Recognize red flags of hereditary cancer syndromes
- Compare the utility of genetic counseling for affected versus unaffected patients
- Acknowledge other ways that patients may encounter genetic concepts or obtain their genetic data

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Cancer Genetics

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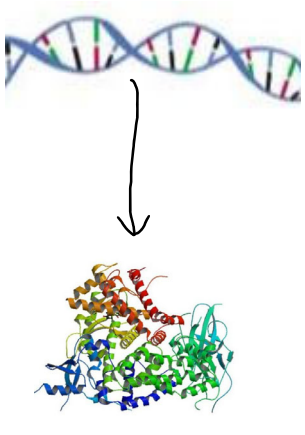
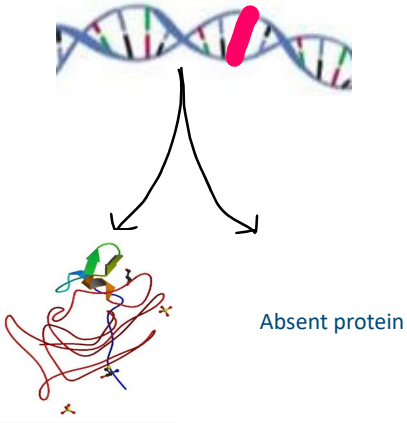
Mutation



Functional protein



Abnormal protein

Absent protein

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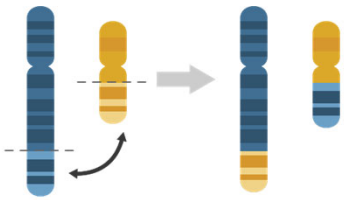
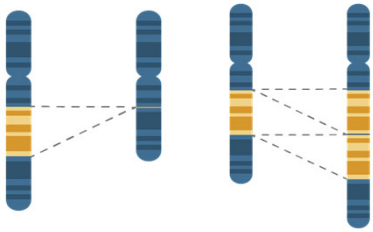
Types of Gene Mutations

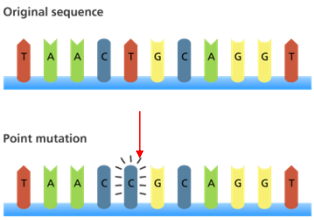
Translocation



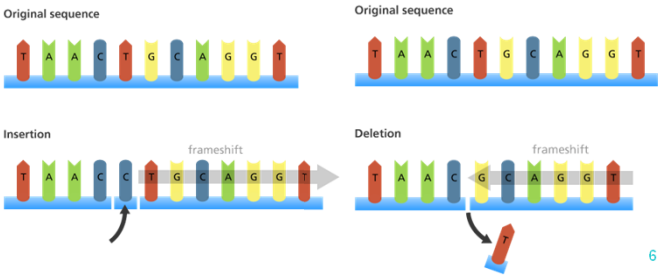
Deletion/duplication



Point Mutation



Insertion/deletion



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Uncontrolled Cell Division

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Cell Cycle Regulation

- DNA repair genes
  - Fix errors made during DNA replication
  - Inactivation leads to cancer development
  - Ex: *MLH1, MSH2, MSH6, PMS2*
- Tumor suppressor genes
  - Negatively regulate the growth of cells
  - Inactivation leads to cancer development
  - Ex: *BRCA1/2*
- Oncogenes
  - Play roles in cell cycle regulation
  - Activation leads to cancer development
  - Ex: *RET*

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Cancer: Genetic But Not Always Inherited

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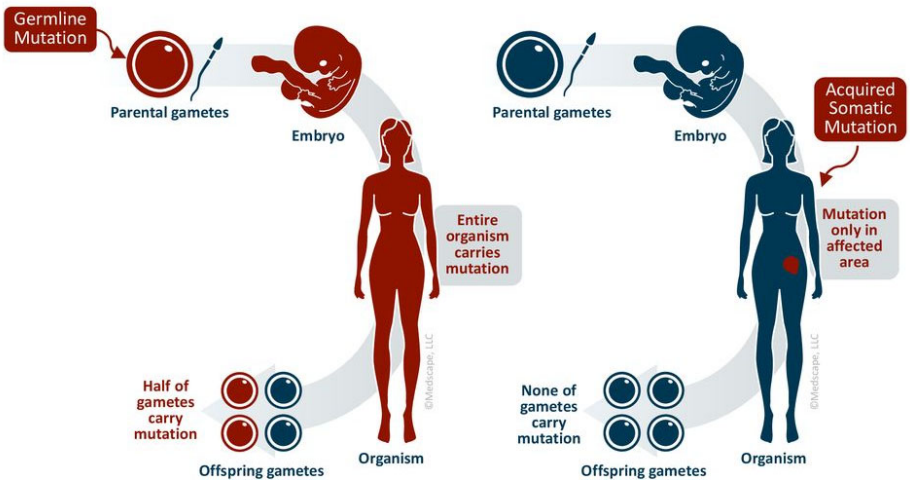
Germline Mutations vs Acquired



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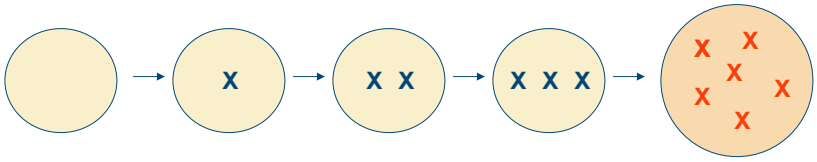
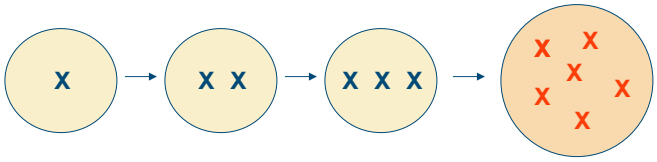
Sporadic Cancers



Cancerous Cell

Hereditary Cancers



Cancerous Cell

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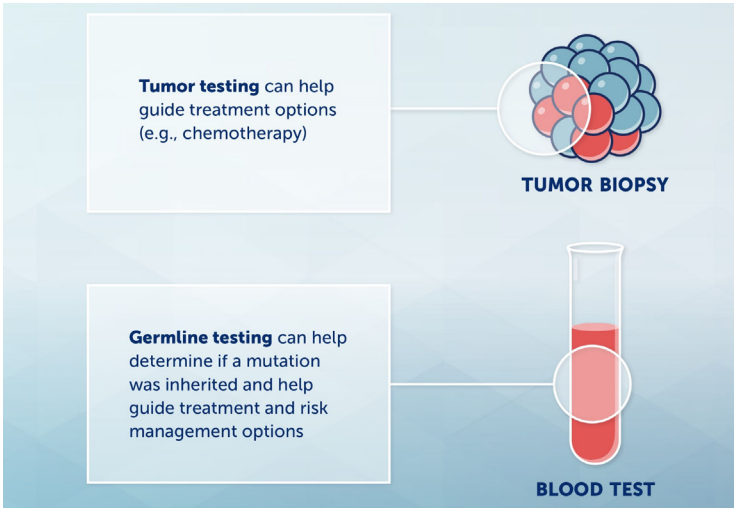
Genetic Testing



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Myriad Genetics

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Hereditary Breast Cancer Assessment

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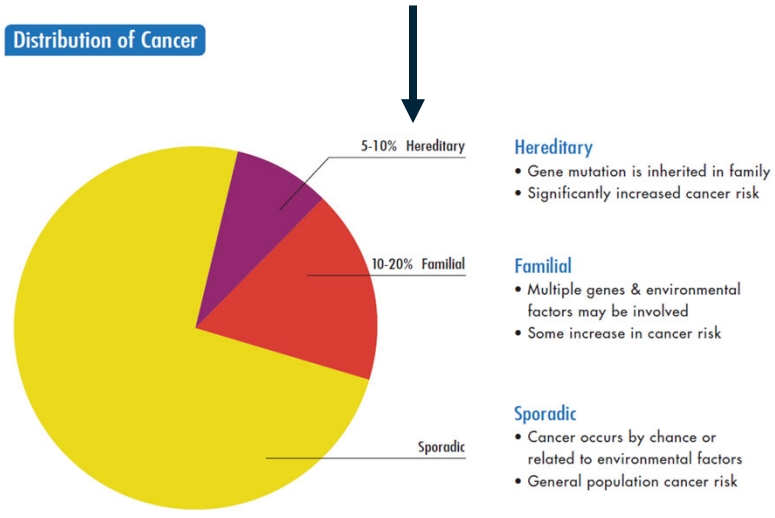

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Greenwood Genetics

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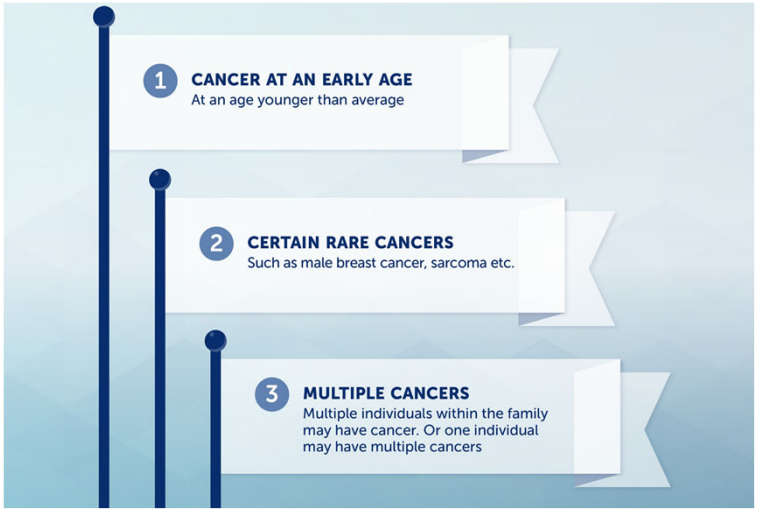
Hereditary Cancer Red Flags



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Genetic testing criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,f,g,h,i]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[m]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer NCCN Guidelines for Gastric Cancer
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - Family history[n]
      - ≥1 close blood relative[o] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

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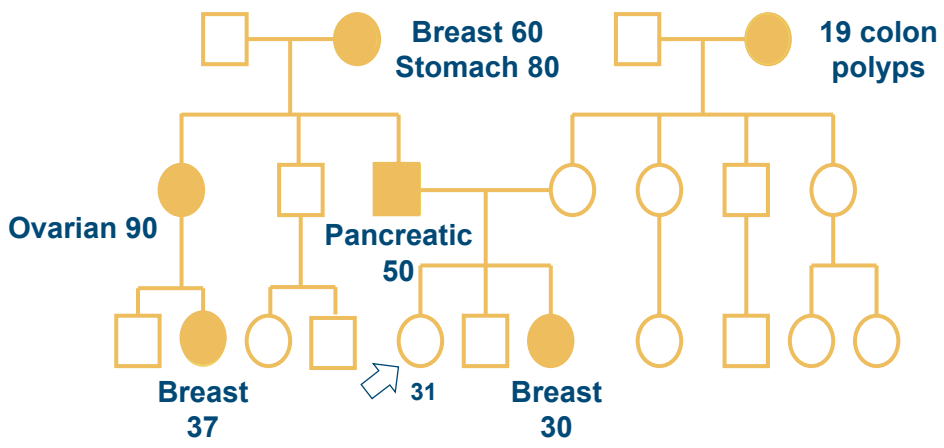
Family History Evaluation



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What is Genetic Testing

- DNA sequencing and deletion/duplication analysis of genes related to inherited cancer syndromes
- Multi-gene panels are commonly used to test for multiple genes at once

	GENES	BREAST & GYN	ENDOCRINE	GASTROINTESTINAL	GENITOURINARY	HEMATOLOGIC	NERVOUS SYSTEM/BRAIN	PROSTATE	SARCOMA	SKIN
INVITAE BREAST CANCER GUIDELINES-BASED PANEL / INVITAE BREAST CANCER STAT PANEL	ATM	■		■		■		■		
	BRCA1	■		■	■			■		
	BRCA2	■		■	■			■		■
	CDH1	■		■						
	CHEK2	■	■	■	■			■		
	PALB2	■		■				■		
	PTEN	■	■	■	■		■			■
	STK11	■		■						
	TP53	■	■	■	■	■	■	■	■	■
	NBN	■			■	■		■	■	
	NF1	■	■	■		■	■		■	

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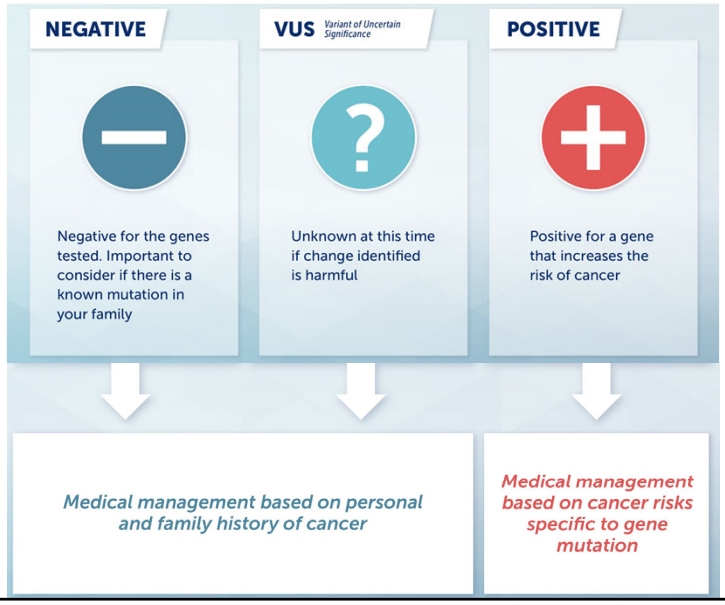
Potential Results of Genetic Testing



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Patient A: Newly diagnosed with breast cancer

- Referral placed by oncologist
  - The American Society of Breast Surgeons suggests that genetic testing for all diagnosed with breast cancer
- Scheduled in a “STAT” or “ASAP” context with a TAT of 2 weeks for results
- Max cost of $100 *(as of 2/11/2024)*
- Counseled on treatment implications, future risk reduction, and familial risk

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ASBrS 20

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Patient A: Newly diagnosed with breast cancer, PALB2+

RESULT: POSITIVE

One Pathogenic variant identified in PALB2. PALB2 is associated with autosomal dominant hereditary breast and pancreatic cancer and autosomal recessive Fanconi anemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PALB2	Gain (Exon 11)	copy number = 3	PATHOGENIC

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Patient A: Newly diagnosed with breast cancer, PALB2+

PALB2 gene	
Cancer risk	**Associated cancer management**
Breast cancer	Contralateral risk increased, consider bilateral mastectomy vs annual mammogram and breast MRI Consider PARP inhibitors
Ovarian cancer	Consider surgery to remove ovaries and fallopian tubes
Pancreatic cancer	Annual screening only recommended with family history of pancreatic cancer

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Cybulski 2015 Lancet Oncol; Kuchenbaecker et al 2017 JAMA and Graeser et al 2009 JCO; NCCN; Reiner et al 2018 JCO; Song et al 2020 Journal of Medical Genetics; Yang et al 2020 J Clin Oncol

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Patient B: Family history of breast cancer

- Referral often placed by PCP or OBGYN (GCs can self-refer)
- Scheduled in a “routine” or “ASAP” context
- $250 patient pay option (or insurance)
- Genetic testing discussion can be more nuanced
- Counseled on screening implications, future risk reduction, and familial risk
- Assessment and screening referral based on family history regardless of testing decision

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Patient B: Family history of breast cancer, PALB2+

RESULT: POSITIVE

One Pathogenic variant identified in PALB2. PALB2 is associated with autosomal dominant hereditary breast and pancreatic cancer and autosomal recessive Fanconi anemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PALB2	Gain (Exon 11)	copy number = 3	PATHOGENIC

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Patient 2: Family history of breast cancer, PALB2+

PALB2 gene		
Cancer risk	**Associated cancer management**	**Age to begin management**
Breast cancer	Annual mammogram and breast MRI Discuss option of risk-reducing bilateral mastectomy	Age 30
Ovarian cancer	Consider surgery to remove ovaries and fallopian tubes	Age >45
Pancreatic cancer	Annual screening only recommended with family history of pancreatic cancer	Age 50

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Patient 2: Family history of breast cancer, negative testing

RESULT: NEGATIVE

About this test

This diagnostic test evaluates 70 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

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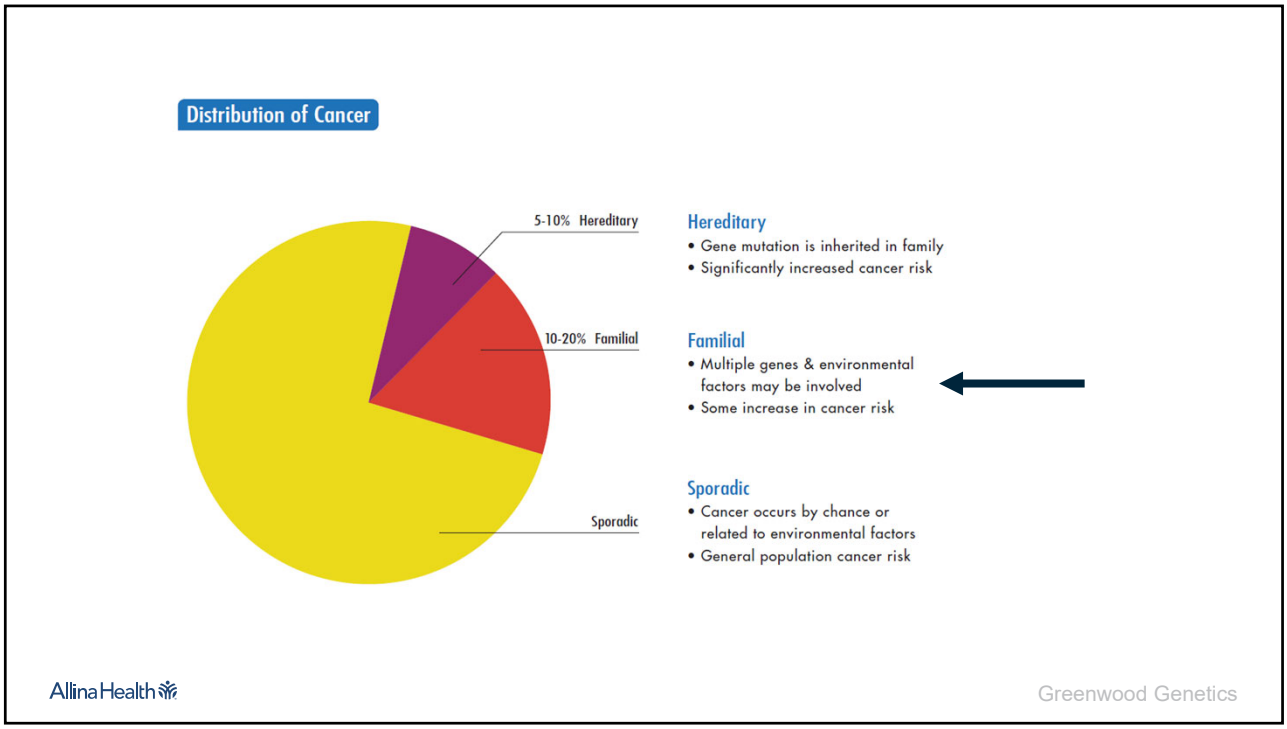

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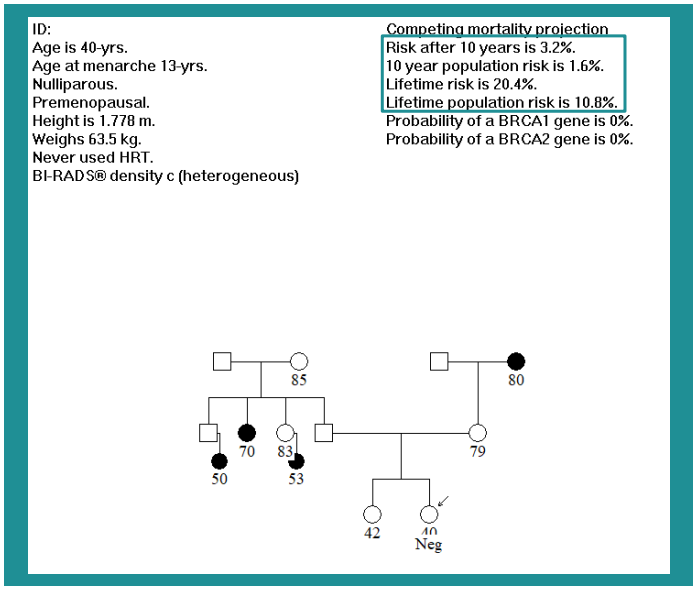
Risk Modeling

- IBIS risk model
  - Personal history (menarche, menopause, breast density, HRT, age at first child, etc)
  - Family history
  - Genetic test results
- Qualify for high-risk screening



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Other Sources of Genetic Results

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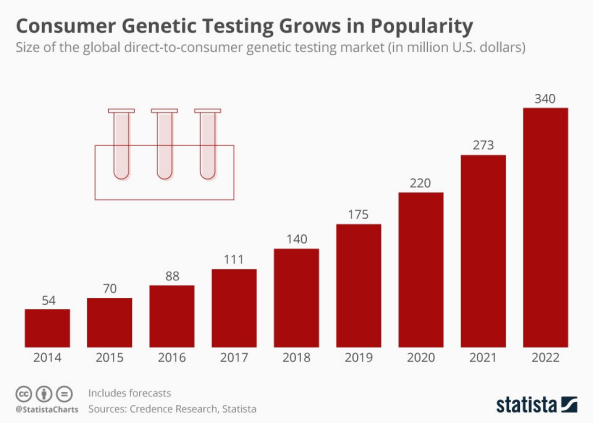
Direct to Consumer Tests

- **Who:**
  - 23andMe, AncestryDNA, FamilyTreeDNA, etc.
- **What:**
  - Tests for a selection of SNPs, think of these like flags or markers
  - Related to inherited conditions, health risks, drug responses, inherited traits, ancestry
  - Can link to family members who also did testing
- **Limitations**
  - Most risks are multifactorial
  - Clinician involvement not required
  - Unexpected results (APOE-4, 44-site BRCA1/2)
  - Overly reassured by results (44-site *BRCA1/2*)
  - Privacy concerns
  - Eurocentric data



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Population-based screening

What:

- Build genetic databases for research
- Same tech as clinical testing, more limited gene panels reported out
- Can provide non-comprehensive genetic screening to patients upon request
  - Familial hypercholesterolemia (FH), hereditary breast and ovarian cancer (HBOC), and Lynch syndrome
  - Some with pharmacogenomic results reported

Who:

- Tapestry Study at Mayo Clinic
- Helix Study at HealthPartners
- All of Us Research Program at NIH

Limitations:

- Patients may require more comprehensive testing

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Genetic Counseling

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AHCI Genetic Counselors

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Genetic Counseling

- Master's level training in medical genetics and counseling.
- Meet with individuals or families before and after genetic testing.
- All specialized in **oncology**, prenatal, cardiology, pediatrics, neurology, ophthalmology, psychiatry, and many other areas.
- In addition to different specialty areas, genetic counselors can have roles outside of seeing patients (research, education, industry, marketing, public health, etc).

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Summary

- Genetic testing for hereditary cancer is a complex, ever-evolving field
- Be careful to clarify when asking a patient “Have you had genetic testing?”
- Identifying a hereditary cause for cancer in a family can aid prevention/screening for the patient and family members
- Genetic counselors are here to help!

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Thank You!

greta.henry@allina.com

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