

Hereditary Cancer: Identifying Risk, Empowering Prevention

Hereditary cancer genetics

Jen Jacober, MPH, MS, LCGC
Genetic Counselor
Ochsner Health System

Disclosures

Jennifer Jacober discloses **no relevant financial relationships** with any entity producing, marketing, re-selling, or distributing healthcare goods or services consumed by, or used on, patients during the past 24 months.

Learning Objectives

- Recognize key features of major hereditary cancer syndromes
- Be able to identify individuals who may benefit from genetic counseling.
- Describe the major components of genetic assessment and testing for hereditary cancer syndromes.
- Understand types of genetic testing results
- Discuss the benefits, limitations, and risks of genetic testing

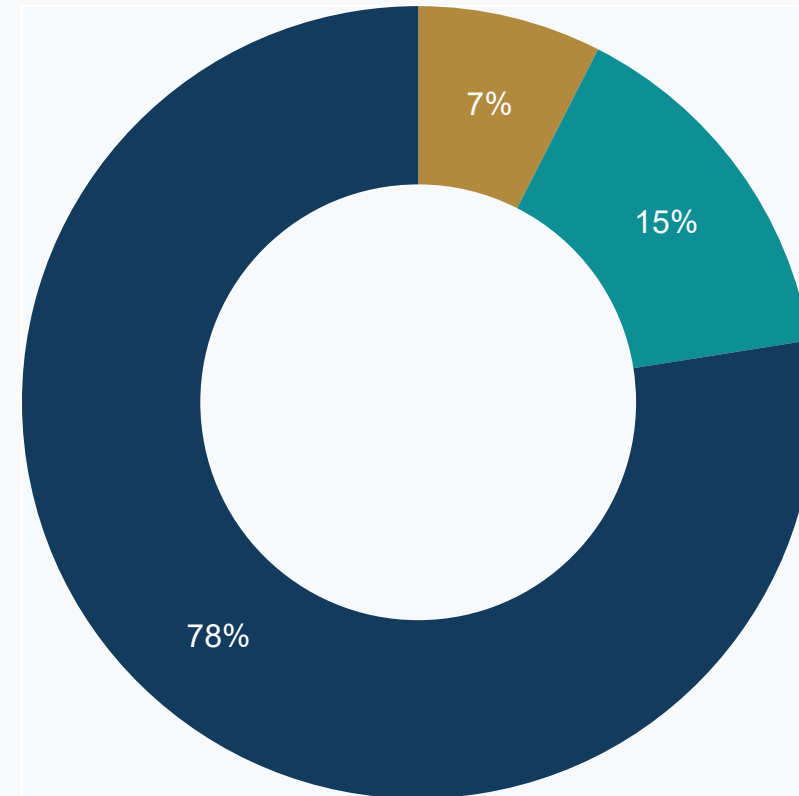
Cancer Overview

CANCER OVERVIEW

5–10% Hereditary

10–20% Familial

Up to 80% Sporadic



■ Hereditary ■ Familial ■ Sporadic

Features of Hereditary Cancer

- Unusually early age of cancer onset
- Multiple primary cancers in a single individual
- Bilateral cancer in paired organs or multifocal disease
- Clustering of the same type of cancer, or related cancers, in the same family
- Cancers in multiple generations
- Rare tumors
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Unusual cancer presentation
- Uncommon tumor histology
- Rare cancers associated with birth defects
- Individuals from certain geographic areas or ancestry groups

Features of Sporadic Cancer

- Most often thought to be multifactorial
- Negative genetic testing
- Common cancers such as breast, lung, colon
- Diagnosis at or around typical age
- No clear pattern of inheritance

When to Refer for Genetic Counseling?

- Suspicious personal or family history
- Pathogenic or likely pathogenic (P/LP) variant in a blood relative
- P/LP variant on somatic testing that could be of germline origin
- Ashkenazi Jewish ancestry
- Limited family history
- Genetic testing >5 years ago but especially if done prior to 2013
- ...or patient is just concerned or interested!

What is Genetic Counseling?

- Process of helping people understand and adapt to the implications of genetic contributions to disease.
- Often includes pre- and/or post-test counseling
- Ordering of genetic testing
- Interpreting and helping patients and their families understand genetic testing results
- Guiding patient decision making

Genetic Counseling: During a Session

- Elicit personal and family history
- Education regarding cancer genetics
- Determine the best test for the patient's needs
- Discuss benefits and limitations to testing
- Non-Directive
- Psychosocial Aspects

Decision Making

- Sometimes history is not concerning for hereditary predisposition
- Patient has insurance/out of pocket cost questions
- Concerns about how these results may impact their health or their family members' health
- Concern about impact on life insurance, long-term disability, long-term care insurance
- Anxiety, possibility to over-screen

Genetic Testing

- Doesn't always give a yes/no answer about heritability
- Interpretation depends on the patient's personal and family history
- Is this person the best person in the family to test?

Specimen Selection

WHY SPECIMEN CHOICE MATTERS

Individuals with certain hematologic conditions may have circulating leukocytes in the blood and saliva that contain somatic mutations at frequencies that could be mistaken for germline variants or interfere with the detection of true germline variants. Therefore, testing cultured fibroblasts from a skin punch biopsy is preferred.

Specimen Selection

- Skin punch biopsy is required for
 - Allogenic BMT/SCT
 - Active or recent leukemia, MDS, MPN, essential thrombocytosis/essential thrombocythemia, myelofibrosis, polycythemia vera, lymphoma (NHL, DLBCL, follicular lymphoma, Burkitt lymphoma, non-cutaneous T-cell lymphoma, cutaneous T-cell lymphoma with peripheral blood involvement, Waldenström macroglobulinemia), MGUS, myelophthisic anemia, transient abnormal myelopoiesis, systemic macrocytosis, and severe congenital neutropenia

Specimen Selection

- Blood, saliva, buccal specimens are acceptable for
 - Blood transfusion more than 2 weeks prior to specimen collection
 - Hematologic conditions in complete clinical AND molecular remission
 - Hodgkin lymphoma
 - Multiple myeloma, plasma cell myeloma, smoldering myeloma
 - Cutaneous T-cell lymphoma/mycosis fungoides without peripheral blood involvement

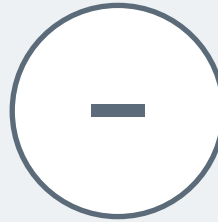
Possible Genetic Testing Results

POSITIVE



Positive

NEGATIVE



Negative

VUS



Variant of Uncertain
Significance (VUS)

Variants of Uncertain Significance (VUS)

- Very common
- Unclear if the variant disrupts the gene function or not.
- Unknown if the variant increases cancer risks or not
- We do not recommend changes to management based on VUSs in most cases
- In cancer, we do not test family members for these variants

Genetic Discrimination

The Genetic Information Nondiscrimination Act of 2008 (GINA).

GINA HELPS PROTECT

- ✓ **Most health insurance**
- ✓ **Employers with 15 or more employees**

GINA does not fully apply to active-duty military, veterans receiving VA care, or individuals using the Indian Health Service.

GINA DOES NOT COVER

- × **Life insurance**
- × **Disability insurance**
- × **Long-term care insurance**

Consider insurance planning before testing and seek individualized legal or financial guidance when needed.

Post-Test Counseling

- Explain results
- Assess risk based on results and personal/family history
- Create a personalized screening plan
- Place referrals
- Arrange for testing of at-risk relatives
- Follow up
 - Negative: To determine if updated testing is indicated
 - VUS: When VUS is reclassified (90% are reclassified as benign/likely benign)
 - Positive: Review updates to cancer risks and screening guidelines (CHEK2, MUTYH)

Hereditary Breast and Ovarian Cancer

- Genes: BRCA1, BRCA2
- Large tumor suppressor genes involved in DNA repair
- Common (1/400)
- 1/40 for individuals of Ashkenazi Jewish ancestry
- BRCA1 = 35% of hereditary breast cancer cases; BRCA2 = 25% of hereditary breast cancer

BRCA1 versus BRCA2

BRCA1

- More likely to be hormone receptor negative; ER/PR (-), HER2 Negative (triple negative)
- Earlier Onset
- Increased lifetime risk for ovarian cancer versus BRCA2
- Medullary breast cancer suggestive of a BRCA1 mutation

BRCA2

- More likely to be hormone receptor positive; ER/PR+
- Has increased risk for male breast cancer, pancreatic cancer, and prostate cancer compared to BRCA1
- Tendency to have later age of onset
- Biallelic mutations: Fanconi anemia

Gene-Associated Cancer Risks

	BRCA1	BRCA2	PALB2	CHEK2	ATM
Breast, female	60-72%	55-69%	32-53%	23-27%	21-24%
Breast, male	0.2-1.2%	1.8-7.1%	0.9%		
Ovarian	39-58%	13-29%	3-5%	No established association	2-3%
Prostate	7-26%	19-61%	Emerging evidence for increased risk	Emerging evidence for increased risk	Evidence for increased risk
Pancreatic, exocrine	<6%	3-10%	2-5%		5-10%
Melanoma, cutaneous	Conflicting evidence, possibly mildly elevated	Conflicting evidence, possibly mildly elevated			
Other cancers					Colon cancer 5-10%

Other BOPP Genes

- BARD1: Breast (17-30%)
- BRIP1: Ovarian (5-15%)
- CDKN2A: Pancreatic (>15%), melanoma (28-76%)
- RAD51C, RAD51D: Breast (20%), ovarian (10-20%)
- HOXB13

Breast Cancer Referral Indications

- Diagnosed at 50-years-old or younger
- Multiple primaries, bilateral, multifocal
- Triple negative
- Lobular with family history of diffuse gastric cancer
- Male breast cancer
- Ashkenazi Jewish ancestry
- Family History
 - ≥ 1 relatives with breast ≤ 50 , ovarian, pancreatic, male breast, advanced prostate cancer
 - Total of ≥ 3 relatives on the same side of the family with breast and/or prostate cancer (any age, stage)

Prostate Cancer Referral Indications

- Diagnosed ≤ 55 years
- High-risk, very-high-risk, metastatic
- Intermediate risk with intraductal/cribriform histology
- Ashkenazi Jewish Ancestry
- Family History
 - ≥ 1 relatives with breast ≤ 50 , ovarian, pancreatic, male breast, advanced prostate cancer
 - Total of ≥ 3 relatives on the same side of the family with breast and/or prostate cancer (any age, stage)

Ovarian and Pancreatic Cancer Referral Indications

OVARIAN

- Epithelial at any age and regardless of family history
- Non-epithelial (sex-cord tumor with annular tubules; SCC of the ovary, hypercalcemic type at any age)

PANCREATIC

- Exocrine at any age and regardless of family history

Colorectal and Gastric Cancer

Lynch Syndrome

- Genes: MLH1, MSH2, MSH6, PMS2, EPCAM
- Common (1/500)
- Most common cause of hereditary colorectal cancer (2-4% of cases)
- Cancers
 - Colorectal, endometrial, ovarian, gastric, pancreatic, urothelial, brain (glioblastoma), biliary tract, small intestine, sebaceous adenocarcinoma, keratoacanthoma
- Constitutional Mismatch Repair Deficiency (CMMRD)
 - Autosomal recessive condition

Lynch Syndrome Cancer Risks

	MLH1	MSH2/EPCAM	MSH6	PMS2
Colorectal	46-61%; 44years	33-52%; 44 years	10-44%; 42-69 years	8.7-20%; 61-66 years
Endometrial	34-54%; 49 years	21-57%; 47-48 yrs	16-49%; 53-55 years	13-26%; 49-50 years
Ovarian	4-20%; 46 years	8-38%; 43 years	<1-13%; 46 years	
Bladder	2-7%; 59 years	4.4-12.8%; 59 years	1-8.2%; 71 years	
Pancreas	6.2%; no data	0.5-1.6%; no data	1.4-1.6%; no data	
Gastric	5-7%; 52 years	0.2-9.0%; 52 years	<1-7.9%; limited data	
Brain	0.7-1.7%; no data	2.5-7.7%; No data	0.8-1.8%; 43-54 years	

Hereditary Diffuse Gastric Cancer (HDGC)

- Genes: CDH1, CTNNA1
- Most common gastric cancer syndrome (1-3% of gastric cancers)
- Risks (CDH1):
 - Lobular breast cancer (37-55%)
 - Diffuse gastric cancer (25-42%)



GI Cancer Referral Indications

- MMR-deficient
- Diagnosed before age 50
- Lynch syndrome cancers in multiple relatives or one before age 50
- Diffuse gastric cancer at any age

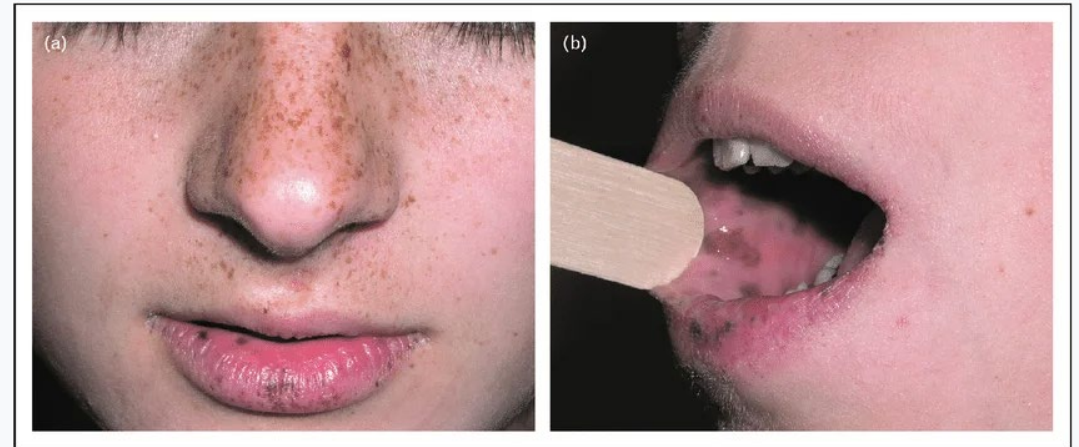
Polyposis Syndromes

Familial Adenomatous Polyposis (FAP)

- Gene: APC
- Most common hereditary adenomatous polyp syndrome
- High de novo rate: 20-30%
- Classic = >100 polyps beginning as early as 10 years old
- Attenuated = 10-100 polyps beginning at usual age (after age 40)
- Extracolonic features
 - Duodenal adenomas, papillary thyroid cancer, desmoid tumors
 - Multifocal/bilateral congenital hypertrophy of retinal pigment epithelial (CHRPE)

Peutz-Jeghers Syndrome (PJS)

- Gene: STK11
- Hamartomas in the gastrointestinal tract
- Mucocutaneous hyperpigmentation
- Cancer risks:
 - Breast (32-54%), colon (39%), gastric (29%), pancreatic (11-36%), cervical (>10%), uterine (10%), lung (7-17%), Sex-cord tumor with annual tubules, ovaries (>20%), Sertoli cell tumors, testes (9%)



Tacheci, Ilja & Kopacova, Marcela. (2021). Peutz-Jeghers syndrome. Current Opinion in Gastroenterology. 37. 245-254. 10.1097/MOG.0000000000000718.

GI Polyp Referral Indications

- 10 or more colorectal adenomas
- 5 or more serrated polyps with some adenomas
- Duodenal adenomas
- CHRPE
- Desmoid tumors
- Hamartomas
- Mucocutaneous hyperpigmentation

Multiple Endocrine Neoplasia

MEN1

- Gene: MEN1
- Benign and Malignant tumors
- Parathyroid adenoma/hyperplasia (95%)
- Pancreatic and duodenal NET
- Pituitary adenomas
- Surveillance begins at 8-15 years

MEN2

- Gene: RET
- Benign and malignant tumors
- Medullary thyroid cancer (98%)
- Pheochromocytoma
- Contraindication for GLP-1 receptor agonists due to MTC risk
- Surveillance may begin as early as age 6 months

Hereditary Paraganglioma / Pheochromocytoma Syndrome (PGL/PCC)

- Genes: SDHA, SDHAF, SDHB, SDHC, SDHD
- Benign and malignant tumors in adults and children
- Endocrine: Paragangliomas, pheochromocytomas
- Other: GIST, renal cell carcinoma
- SDHB has the greatest risks (PGL/PCC 20-60%)
- Surveillance begins at age 6-10 years for SDHB carriers and age 10-15 years for all other genes

Li-Fraumeni Syndrome (TP53)

- Gene: TP53
- Rare: 500 families in the US; 1000 families worldwide
- De novo rate: 7-20%
- High risk for multiple primary cancers beginning in childhood
- Core cancers: Adrenocortical, breast (>60%), CNS, osteosarcoma, soft tissue sarcoma
- Other cancers: Pancreatic (5%), prostate (25-50%)
- Surveillance may begin as early as infancy

Cowden Syndrome

- Gene: PTEN
- De novo rate 10-48%
- Cancers:
 - Breast (40-60%), endometrial, follicular/papillary thyroid, colon, RCC
- Other features:
 - Lhermitte-Duclos disease, macrocephaly, GI hamartomas and ganglioneuromas, trichilemmomas, oral papillomas, palmoplantar keratotic pits
- Surveillance begins at age 25

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

- Gene: FH
- Autosomal dominant HLRCC
- Cutaneous leiomyomas (present in 50%)
- Uterine leiomyomas (present in 90%)
- Renal cell carcinoma, aggressive (present in 15%)
- Autosomal recessive fumarate hydratase deficiency (FHD)
- Rare inborn error of metabolism, often fatal at birth
- Many FH variants can cause FHD but not HLRCC
- The most common one is L477dup

Renal Cell Carcinoma Referral Indications

- Diagnosed ≤ 46
- Bilateral or multifocal
- SDH-deficient RCC
- Personal and/or family history of
 - Mesothelioma
 - Uveal melanoma
 - Angiomyolipoma
 - Large uterine leiomyomas at a younger age than usual
 - Cutaneous leiomyomas

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Questions?

Thank you!

Contact: Jennifer.Jacober@ochsner.org