Introduction to Cancer Genetics

Sarah Austin, MS, CGC

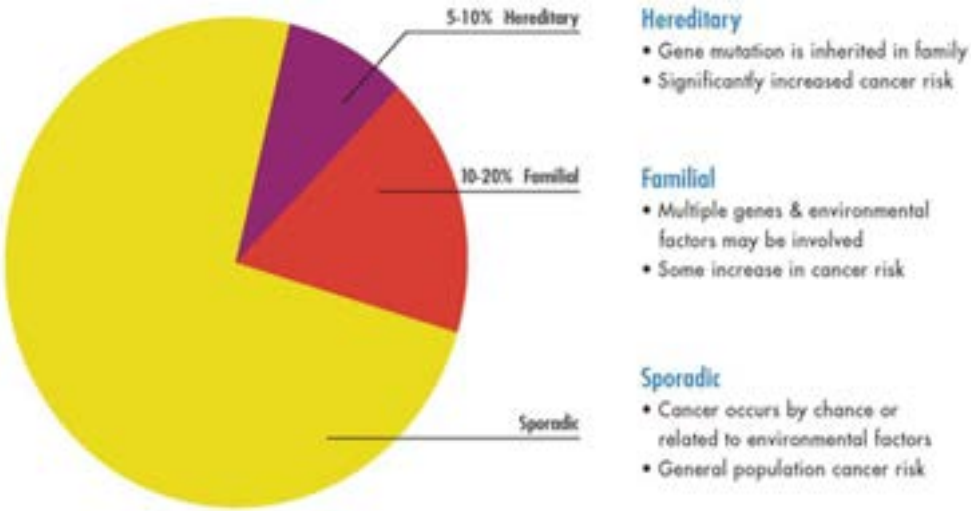
No conflict of interest to disclose

Genetic testing for inherited cancer risk

https://youtu.be/9wbj48f6o5c

Cancer Genetics

- Genetic testing is most beneficial for those with suspected **hereditary** risk
- Factors that raise suspicion for hereditary risk can be found through review of family and medical history
  - Earlier onset cancer
  - Certain cancer sites
  - Multiple family members over multiple generations with same cancer (or cancers linked by same gene)
- Some cancers almost always be environmental (NMSC, Lung, HNSCC)



Hereditary Cancer Testing

Goal:

To better understand cancer risk for individuals and their relatives

Three main benefits:

1. Increased cancer screening/surveillance
2. Inform treatment decisions (surgical options, targeted therapy)
3. Knowledge for family members (cancer surveillance and reproductive options)

Three types of results:

1. Positive – pathogenic variant (mutation) identified
2. Negative – does not rule out all familial risk
3. Variant of uncertain significance (VUS) – ~80-90% reclassified to benign

When Should a Person Consider Genetic Testing?

Personal and/or family history of:

- Young age at cancer diagnosis
  - Before age 50 for most common cancers (breast, endometrial, colon)
- Multiple primary cancers in a single individual such as:

Bilateral breast cancer	Colon and endometrial cancer
Breast and ovarian cancer	Melanoma and pancreatic cancer

- Rare or unusual cancers
  - Ovarian or pancreatic cancer, childhood cancers, sarcoma
- Multiple family members with cancer (same or different types)
- Certain physical features or findings on screening procedures (ex. many polyps on colonoscopies)
- Family member with positive genetic testing results

Specific cancer types and clinical features may warrant genetic evaluation/testing

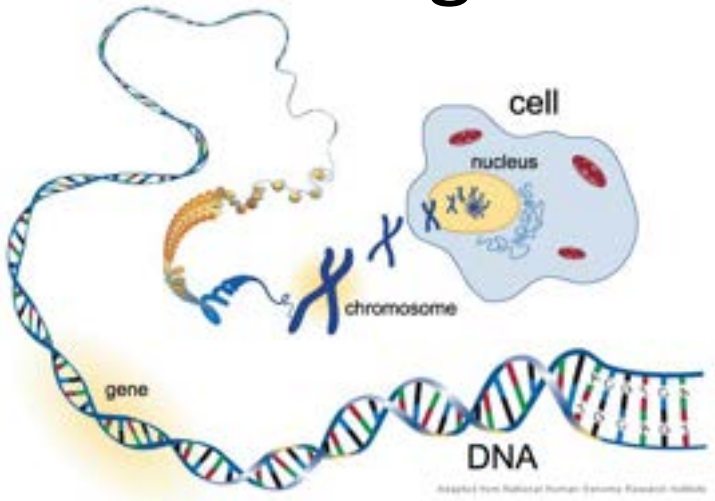
NCCN guidelines have the most up to date criteria for genetic evaluation

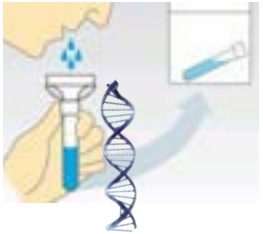
Tumor type	**Clinical history**
Breast	Age <50, bilateral tumors, triple negative cancer, metastatic, AJ ancestry
Colorectal	Age <50, multiple primary tumors
Endometrial	Age <50, multiple primary cancers
Pancreatic	Any personal/family history
Prostate	Age <50, metastatic, AJ ancestry
Ovarian	Any personal/family history

Important Points to Remember

- ~10% of cancers are caused by inherited risk
- Cancer risk can be inherited to and from both males and female
  - Both sides of the family matter
- For most inherited cancer syndromes, the risk for cancer is not 100% (reduced penetrance)
  - Cancer can appear to “skip” a generation, but an inherited pathogenic variant cannot

How does germline genetic testing work?





Multi-gene panel testing

- Most clinical labs offer options that range from one gene to 80+ genes
- Updated technology allows us to offer more complete testing for lower cost
  - In early 2000's testing included 1-2 genes and cost $1000+
  - Now can test for multiple genes through one test for ~$250
- One sample needed
- Recommended for most "red-flag" cancer types by NCCN

Summary

- 5%-10% of cancers are due to hereditary risk
- Genetic testing can impact cancer screening, treatment, and risk for other relatives
- Certain cancer types and patterns of cancer in a family can help identify individuals at higher risk
- Changes to technology have allowed us to test for more genes at a lower cost

What is genetic counseling?

The process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources and research
- Counseling to promote informed choices and adaptation to the risk or condition

Family history collection for clinicians

Andrea Murad, MS, CGC

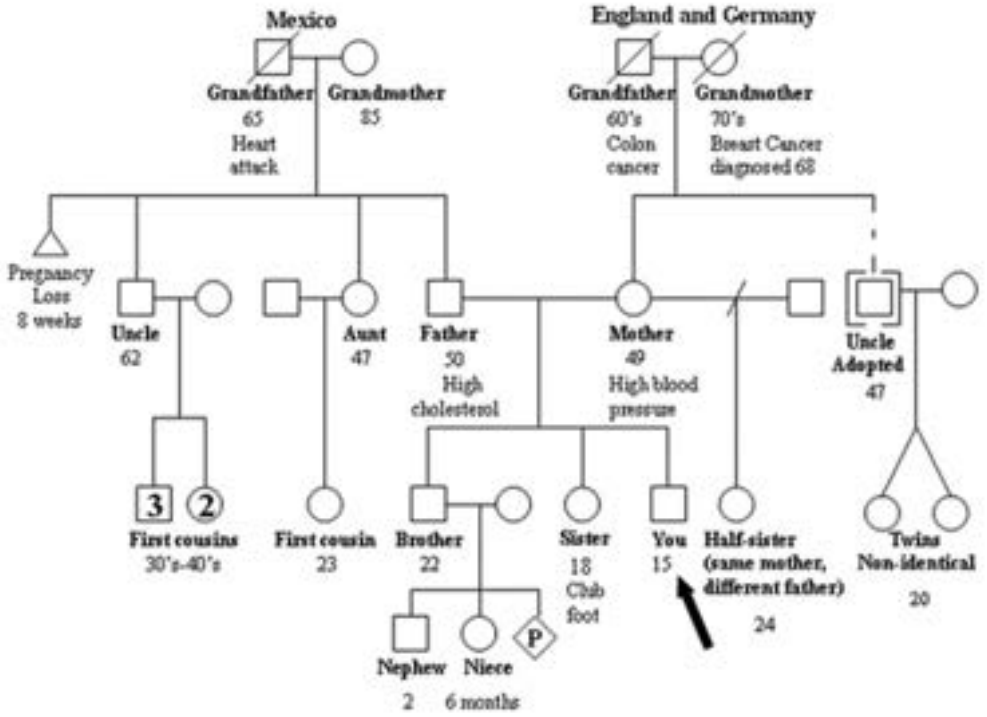
Disclosures

No conflicts of interest to disclose

Gathering a family history

What is family health history and why is it important?

- Medical and health information about a person & blood relatives
- Give clues to conditions that may run in a family
- Helps identify individuals who are at an increased risk of developing those conditions



Important information to collect

Information on both maternal and paternal relatives

- Age or estimate if exact age is unknown
- If deceased, age of death (or estimate/decade of life) and cause of death
- Cancer history of all first, second and third degree relatives
  - This includes parents, siblings, children, grandchildren, grandparents, aunts/uncles and first cousins
  - Make note of type of cancer or where it originated
  - Age of diagnosis (or estimate/decade of life)
- Have any family members undergone genetic testing for cancer
- Make note of any lifestyle or environmental exposures that could contribute to cancer risk
- Make note of any blood related family members who have married each other

Documenting family health history

Important to document the type of cancer and not just “cancer”

Important to document what side of the family the relative is from

- Paternal Aunt is better than Aunt
- Maternal Grandmother is better than Grandmother

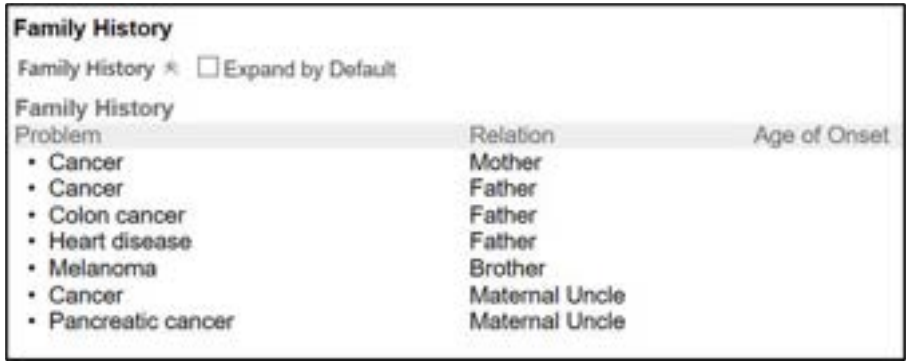
If multiple individuals with the same relation have cancer, important to document who you are referring to

- For example, if patient has 3 sisters and you list: sister with breast cancer; sister with ovarian cancer; sister with colon cancer this is unclear
- Better to document: Sister 1 with breast and ovarian cancer; Sister 2 with colon cancer; Sister 3 no history of cancer.

Family health history documentation examples

Less helpful/useful documentation:

FHx: No family history of ovarian, breast, colon, prostate cancer. No family history of bleeding or clotting disorders. Her family history includes Breast cancer in her maternal grandfather and mother, Colon cancer in her paternal grandmother.



Family History

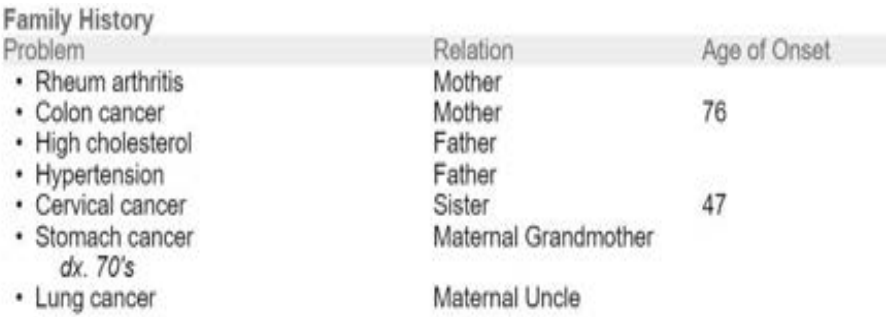
Family History ☆ ☐ Expand by Default

Family History

Problem	Relation	Age of Onset
• Cancer	Mother	
• Cancer	Father	
• Colon cancer	Father	
• Heart disease	Father	
• Melanoma	Brother	
• Cancer	Maternal Uncle	
• Pancreatic cancer	Maternal Uncle	

Helpful documentation:

FHx: Assessed family history of cancer in first and second degree relatives. Notable for breast cancer in her maternal grandfather (diagnosed age 60) and mother (diagnosed age 44). Colon cancer in her paternal grandmother (age at diagnosis unknown).



Family History

Problem	Relation	Age of Onset
• Rheum arthritis	Mother	
• Colon cancer	Mother	76
• High cholesterol	Father	
• Hypertension	Father	
• Cervical cancer	Sister	47
• Stomach cancer *dx. 70's*	Maternal Grandmother	
• Lung cancer	Maternal Uncle	

Hereditary cancer syndromes - Lynch syndrome and Gastrointestinal syndromes

Marie-Louise Accardo, MS, CGC

Conflicts of Interest

No conflicts of interest to disclose.

Overview

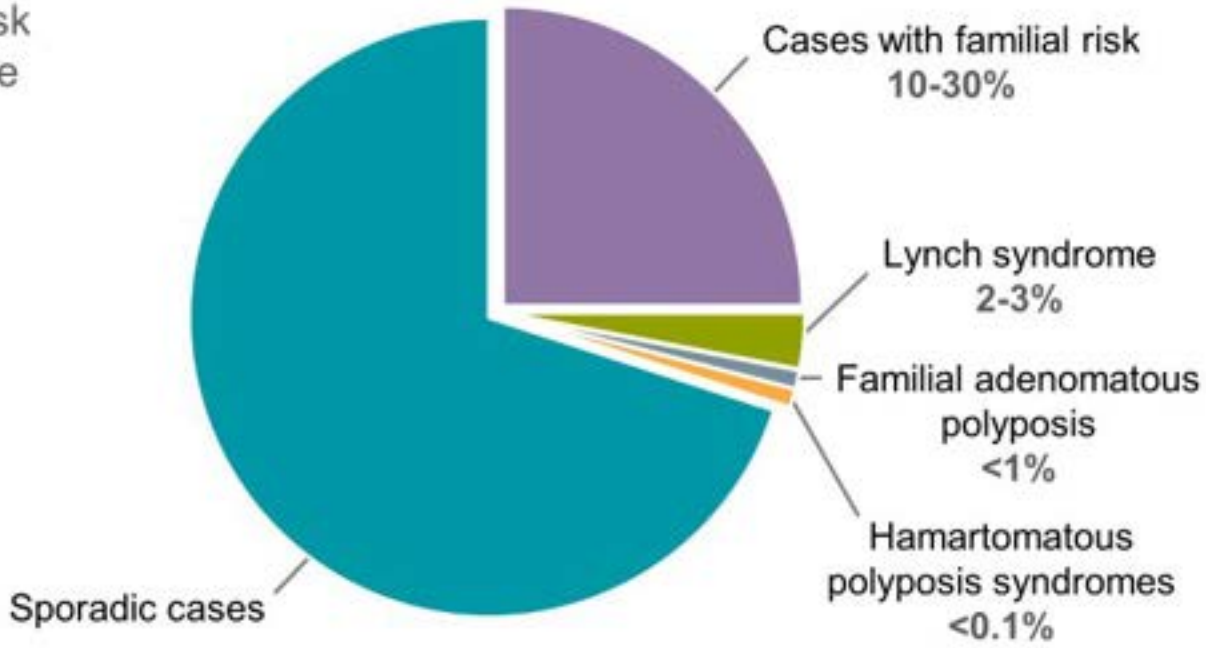
- Overview of Lynch syndrome
- Overview of hereditary polyposis syndromes
- When is genetic testing is indicated?

Hereditary colorectal cancer

Sporadic: Environmental risk factors or unexplained cause

Familial: Combination of environmental and genetic risk factors

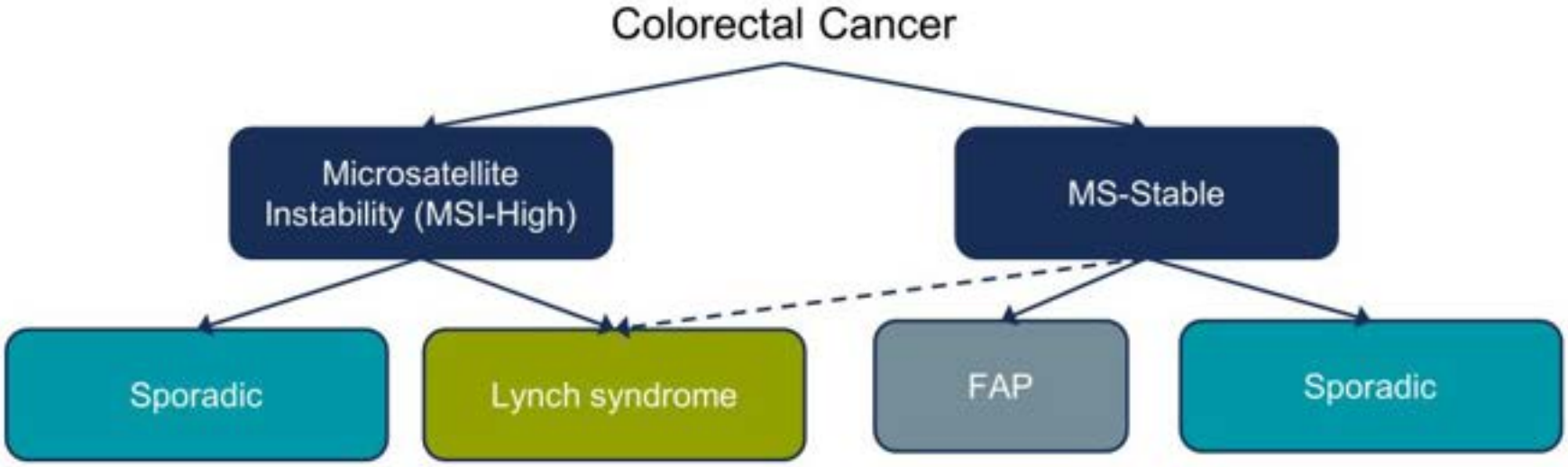
Hereditary: Single major genetic risk factor (Mendelian condition)



Mismatch repair genes

- Genes belong to DNA mismatch repair (MMR) pathway
- Work to recognize and correct replication errors in newly synthesized DNA "spell checkers"
- Mutations in MMR genes lead to microsatellite instability
- >90% of Lynch syndrome-associated tumors are MSI-High and/or lack expression of at least one of the MMR proteins by immunohistochemistry (IHC) staining
- 10-15% of sporadic tumors exhibit abnormal IHC and are MSI-High

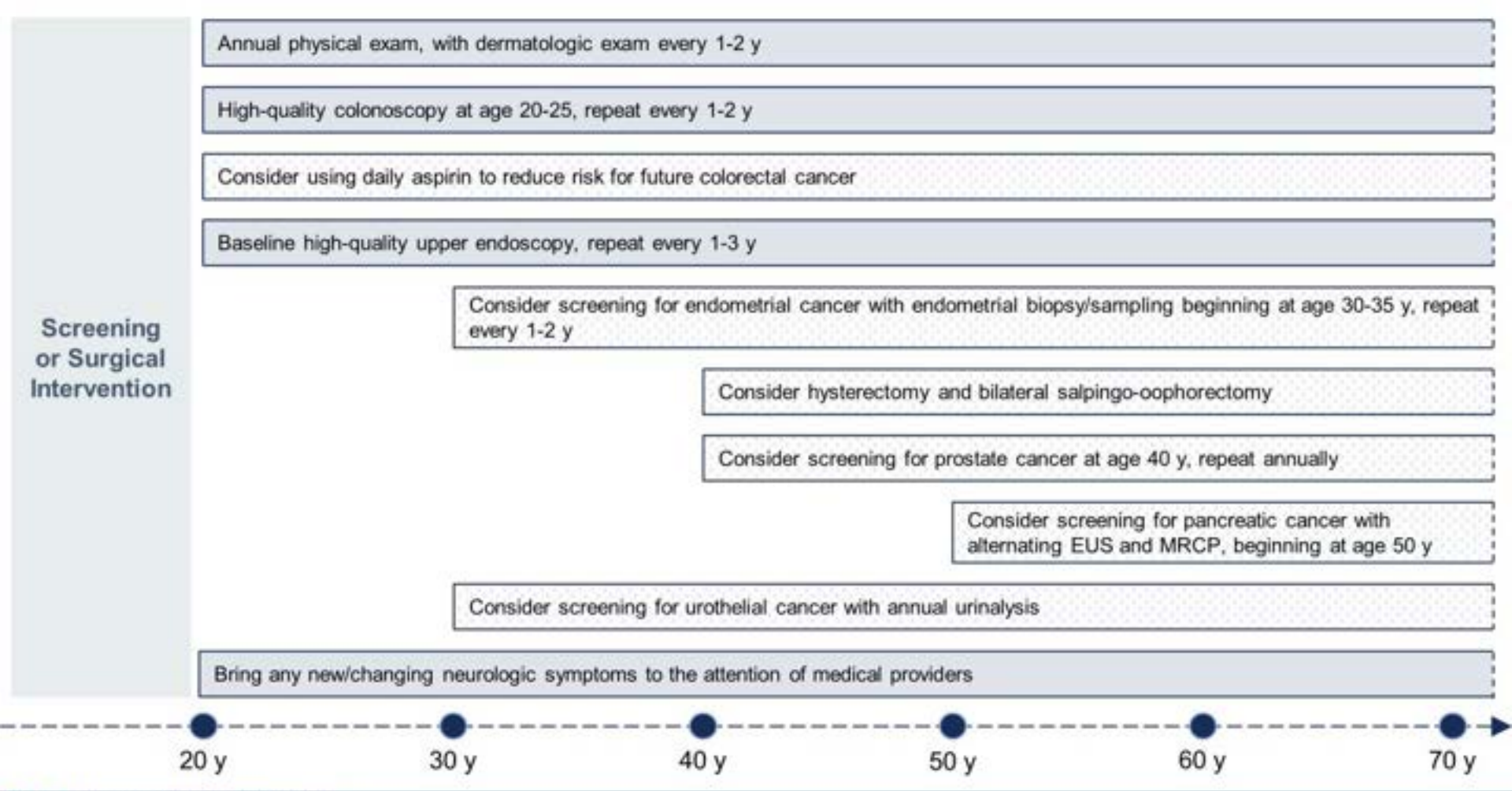
Tumor analysis



Lynch syndrome

Reference updated cancer risks at:
NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Site	General Population	*MLH1*	*MSH2/EPCAM*	*MSH6*	*PMS2*
Colorectal	4.1%	46 - 61%	33 - 52%	10 - 44%	8.7 - 20%
Endometrial	3.1%	34 - 54%	21 - 57%	16 - 49%	13 - 26%
Ovarian	1.1%	4 - 20%	8 - 38%	≤1 - 13%	1.3 - 3%
Renal pelvis	--	0.2 - 5%	2.2 - 28%	0.7 - 5.5%	≤1 - 3.7%
Bladder	2.3%	2 - 7%	4.4 - 12.8%	1.0 - 8.2%	≤1 - 2.4%
Gastric	0.8%	5 - 7%	0.2 - 9%	≤1 - 7.9%	Inadequate data
Small bowel	0.3%	0.4 - 11%	1.1 - 10%	≤1 - 4%	0.1 - 0.3%
Pancreas	1.7%	6.2%	0.5 - 1.6%	1.4 - 1.6%	≤1% - 1.6%
Biliary tract	--	1.9 - 3.7%	0.02 - 1.7%	0.2 - ≤1%	0.2 - ≤1%
Brain	0.5%	0.7 – 1.7%	2.5 - 7.7%	0.8 - 1.8%	0.6 - ≤1%


Screening or Surgical Intervention
Annual physical exam, with dermatologic exam every 1-2 y
High-quality colonoscopy at age 20-25, repeat every 1-2 y
Consider using daily aspirin to reduce risk for future colorectal cancer
Baseline high-quality upper endoscopy, repeat every 1-3 y
Consider screening for endometrial cancer with endometrial biopsy/sampling beginning at age 30-35 y, repeat every 1-2 y
Consider hysterectomy and bilateral salpingo-oophorectomy
Consider screening for prostate cancer at age 40 y, repeat annually
Consider screening for pancreatic cancer with alternating EUS and MRCP, beginning at age 50 y
Consider screening for urothelial cancer with annual urinalysis
Bring any new/changing neurologic symptoms to the attention of medical providers
20 y
30 y
40 y
50 y
60 y
70 y

Family history guidelines

Amsterdam II Criteria

- 3 or more relatives with verified Lynch syndrome-associated cancer in family
- 2 or more generations
- 1 case a first-degree relative of the other two
- 1 CRC diagnosed < 50 y
- FAP excluded

Does not include ovarian, gastric, brain, biliary tract, or pancreatic cancer

Vasen HFA et al. *Gastroenterology*. 116:1453, 1999

Bethesda Guidelines

- CRC diagnosed < 50 y
- Synchronous or metachronous CRC, or other Lynch syndrome-associated tumors regardless of age
- CRC with MSI-High histology diagnosed < 60 y
- CRC with ≥ 1 FDR with Lynch syndrome-associated tumor, with 1 cancer dx < 50 y
- CRC with ≥ 2 FDRs or SDRs with a Lynch syndrome-associated tumor, regardless of age

Umar A et al. JNCI. 2004:96(4):261-268

Indications for Genetic Evaluation

PREMM®
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PREMM 5 Model (harvard.edu)

- Relative with a known Lynch syndrome gene mutation
- Personal history of a tumor with MMR deficiency
- Personal history of a Lynch syndrome (LS)-related cancer*:
  - Diagnosed < 50 y
  - A synchronous or metachronous LS-related cancer
  - 1 FDR or SDR with a LS-related cancer diagnosed <50
  - ≥ 2 FDR or SDR with a LS-related cancer regardless of age

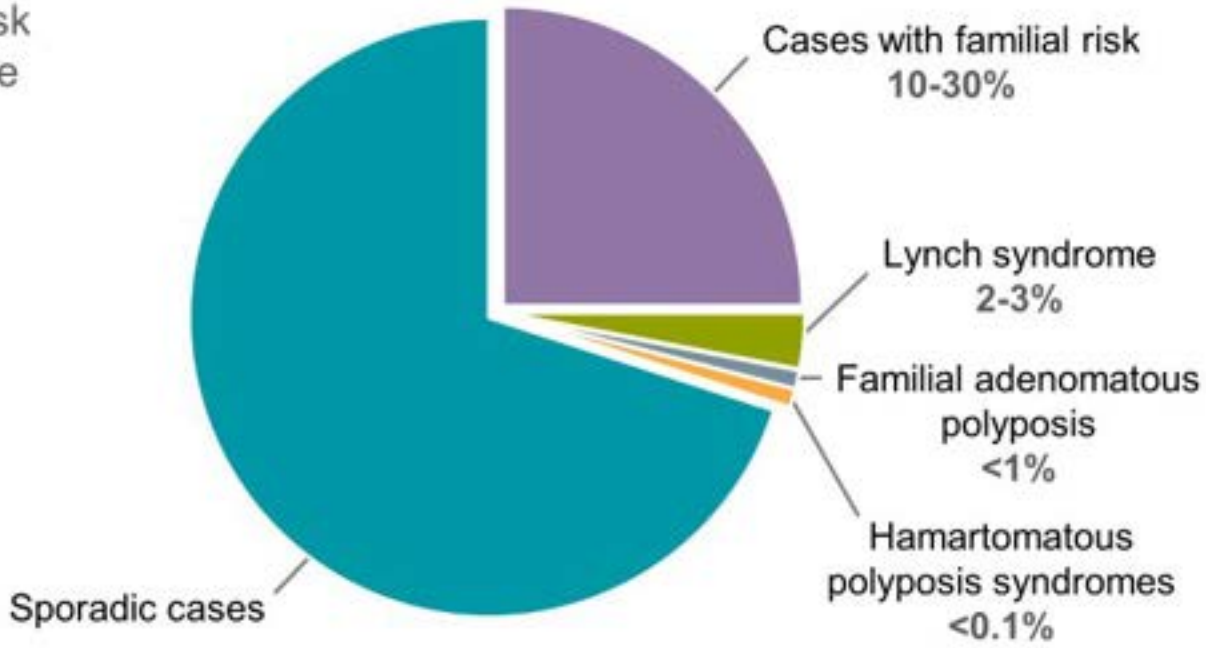
**LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestine, sebaceous tumors*

Hereditary colorectal cancer

Sporadic: Environmental risk factors or unexplained cause

Familial: Combination of environmental and genetic risk factors

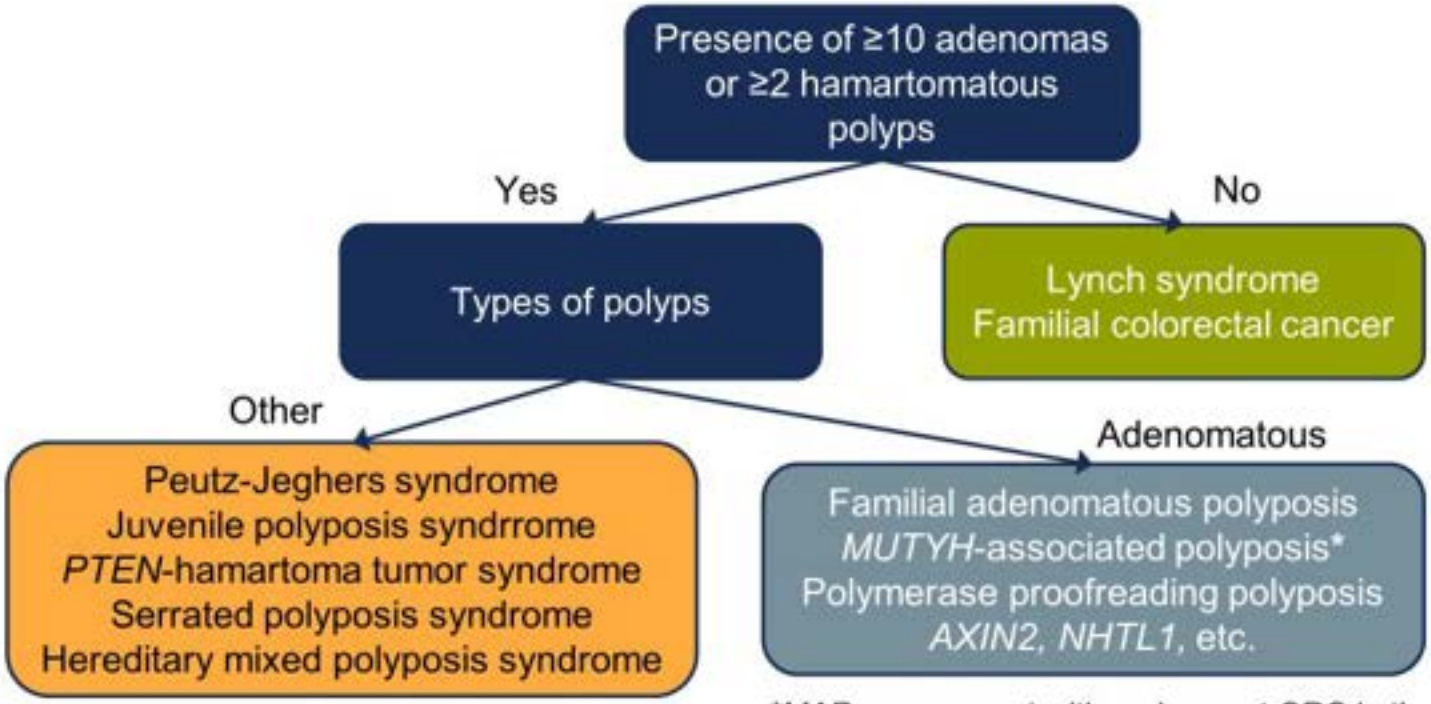
Hereditary: Single major genetic risk factor (Mendelian condition)



Hereditary polyposis syndromes

- Adenomatous polyposis
  - Familial adenomatous polyposis (FAP)
  - *MUTYH*-associated polyposis
  - *POLE*- and *POLD1*-related polyposis
- Hamartomatous polyposis
  - Peutz-Jeghers syndrome
  - Juvenile polyposis
  - *PTEN*-hamartoma tumor syndrome
- Serrated polyposis
- Hereditary mixed polyposis

Hereditary polyposis syndromes



*MAP may present with early-onset CRC in the absence of polyposis

Familial adenomatous polyposis (FAP)

- *APC* gene (tumor suppressor gene, 5q21)
- Autosomal dominant inheritance
- Prevalence is 1 in 10,000 individuals
- 25-30% *de novo* mutations
- Complete penetrance, variable expressivity between family members
- Genotype-phenotype correlations

APC-associated conditions

- Classical FAP
  - Gardner's syndrome - FAP and Osteomas and soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors)
  - Turcot syndrome - FAP and Brain tumor (typically medulloblastoma)
- Attenuated FAP (5' and 3' ends, exon 9)
- Gastric adenocarcinoma and proximal polyposis of the stomach GAPPS (Promoter 1B)
- I1307K - Common mutation in individuals of Ashkenazi Jewish ancestry which does not cause FAP

Classical FAP

- Classical FAP clinical diagnosis:
  - 100+ adenomatous polyps at a young age
  - <100 adenomatous + Family history of FAP
- 100s-1000s of adenomas typically observed throughout the colon
  - Average age of adenoma development is age 16
  - By age 35, 95% of individuals will have polyps
- Average age of colorectal cancer is age 40 without colectomy

Classical FAP

Reference updated cancer risks at:
NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Site	General Population	FAP
Colorectal (without colectomy)	4.1%	Approaches 100%
Rectal/Pouch (post-colectomy)	4.1%	Rectal: 10 - 30% Pouch: <1 - 3%
Duodenal or periampullary	--	<1 - 10%
Gastric	0.8%	0.1 - 7.1%
Small bowel	0.3%	<1%
Desmoid tumors	--	10 - 24%
Thyroid	1.2%	1.2 - 12%
Hepatoblastoma	--	0.4 - 2.5%
Central nervous system	0.6%	1%

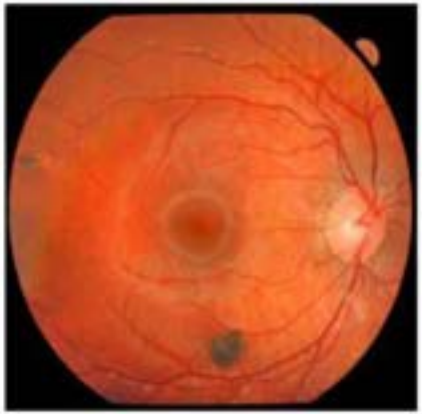
Reference updated maangement recommendations at:
NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Screening or Surgical Intervention

- Liver palpation, serum AFP, abdominal ultrasound, repeat every 6 months through age 5 y
- Colonoscopy at age 10-12 y, repeat annually
- Consider colectomy depending polyp size, number, and pacing of development
- Upper endoscopy with side-viewing scope at age 18 y, repeat every 3-5 years
- Thyroid ultrasound at age 20 y, repeat every 2-5 y
- Bring any new/changing neurologic symptoms to the attention of medical providers

Other FAP Findings

- Duodenal and ampullary adenomas
- Gastric polyps
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE), usually bilateral
- Dental abnormalities (supernumerary teeth, odontomas, unerupted teeth)
- Osteomas
- Desmoid tumors (arises from connective tissue, typically in abdomen)
- Benign skin lesions (epidermoid cysts, fibromas)



Familial Cancer (2006) 5:397–404

Attenuated FAP (aFAP)

- 10-99 adenomas
  - Often right-sided
  - Average of 30 polyps
  - No consensus on clinical diagnosis of aFAP; Diagnosis confirmed by *APC* mutation
- Colorectal cancer often arises at later ages
  - Lifetime risk ~70%
- Upper GI findings, thyroid cancer, and duodenal cancer risks similar to Classical FAP
- Extra-intestinal manifestations are uncommon

MUTYH-associated polyposis (MAP)

- *MUTYH* gene (base excision repair, 1p34.1)
- Autosomal recessive inheritance
- General population carrier frequency is 1-2%
- Typically, fewer than 100 colorectal adenomas (range 0-100s)
    - Primarily adenomas, but multiple serrated polyps (hyperplastic, sessile serrated polyps, serrated adenomas) may be seen
- Risk for CRC is 50% by age 60
- Increased risk for duodenal adenomas and duodenal cancer

Reference updated maangement recommendations at:
NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Screening or Surgical Intervention

High-quality colonoscopy at age 25-30 y, repeat every 1-2 y

Consider colectomy depending polyp size, number, and pacing of development

Upper endoscopy with side-viewing scope at age 30-35 y, repeat every 3-5 years

Indications for Genetic Evaluation

- Relative with a known polyposis gene mutation
- Gene mutation identified on tumor genomic testing that has clinical implications if also identified in the germline (hereditary)
- Personal history of desmoid tumor
- ≥ 10 adenomatous colorectal polyps
- ≥ 2 hamartomatous colorectal polyps

Hereditary colorectal cancer

Sporadic: Environmental risk factors or unexplained cause

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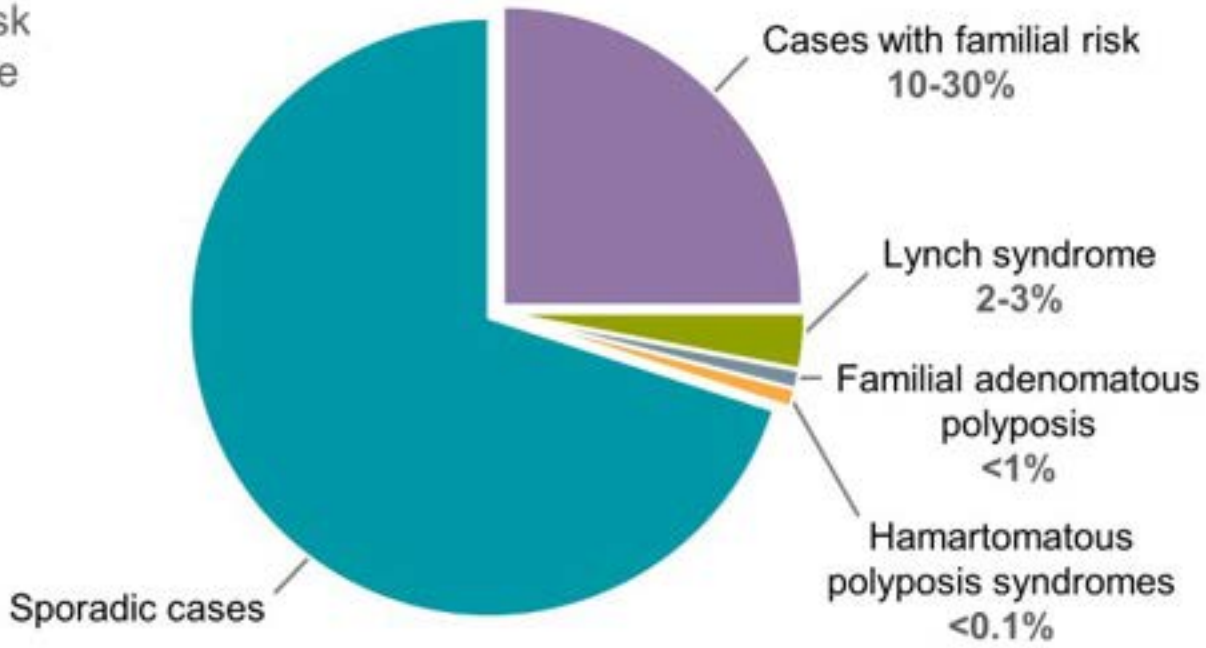


Peutz-Jeghers syndrome

Genetics:

- *STK11* gene (tumor suppressor, 19p)
- Autosomal dominant inheritance
- 50% *de novo* mutations
- Prevalence estimated between 1 in 30,000 - 280,000
- Incomplete penetrance, variable expressivity

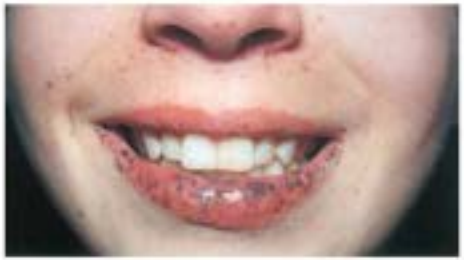
Main features:

- Hamartomatous polyps
- Mucocutaneous pigmentation
- Increased cancer risk:
  - Breast, Colon, Stomach, Small bowel, Pancreas, Lung, Cervix, Ovaries, Testes
- Patients often present in childhood with small bowel intussusception from polyps

Peutz-Jeghers syndrome

Clinical diagnosis:

- 2 or more PJS-type hamartomatous polyps
- Any PJ polyps with mucocutaneous features
- Any PJ polyps or mucocutaneous features with family history of PJS



Mucocutaneous pigmentation

Juvenile polyposis syndrome

Genetics:

- *BMPR1A* gene (25%, 10q)
- *SMAD4* gene (20%, 18q)
- Autosomal dominant inheritance
- 40% *de novo* mutations
- Prevalence 1 in 100,000

Main features:

- Hamartomatous polyposis of small bowel, colon, and stomach
  - "Juvenile" refers to type of polyp, not age of onset
  - GI bleeding, anemia, abdominal pain, prolapsed rectal polyps
- Increased cancer risk
  - Colon, Stomach
- Congenital malformations in some
  - Heart defects, cleft lip/palate, malrotation

Juvenile polyposis syndrome

Clinical diagnosis:

- 3-5 juvenile polyps (JP) of the colon
- Multiple JP throughout the gastrointestinal tract
- Any number of JP with family history of JPS in a FDR

Isolated, solitary JP are common in children (1-2%) and do not carry elevated colorectal cancer risk

Other:

- JPS and Hereditary Hemorrhagic Telangiectasia (HHT) may co-occur with *SMAD4*
  - Nosebleeds, mucocutaneous telangiectasias, arteriovenous malformations (pulmonary, hepatic, cerebral, gastrointestinal)

PTEN-hamartoma tumor syndrome (PHTS)

Genetics:

- *PTEN* gene (tumor suppressor gene)
- Autosomal dominant inheritance
- Prevalence 1 in 200,000 - 250,000
- Includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and *PTEN*-related Proteus syndrome

Main features:

- Hamartomatous polyps
- Increased cancer risk
  - Breast, Thyroid, Endometrial, Kidney, Colorectal, Melanoma
- Mucocutaneous lesions
- Hemangioma
- Arteriovenous malformations
- Macrocephaly
- Lhermitte-Duclos disease

Clinical diagnosis (Cowden syndrome):

- Pathognomonic mucocutaneous lesions; OR
- ≥ 2 Major criteria; OR
- 1 Major and ≥ 3 Minor Criteria; OR
- ≥ 4 Minor Criteria

Cleveland Clinic PTEN Risk Calculator

Lerner Research Institute | Genomic Medicine Institute (ccf.org)

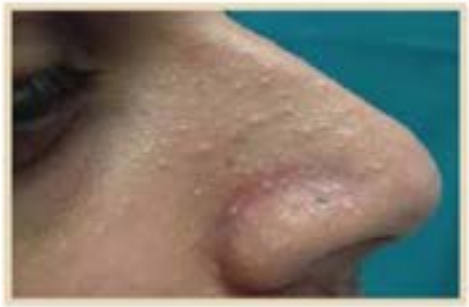
Major Criteria

- Breast cancer
- Epithelial thyroid cancer
- Macrocephaly
- Endometrial cancer

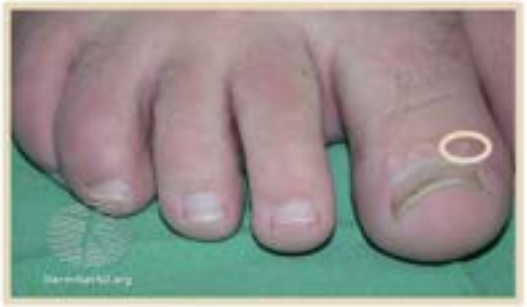
Minor Criteria

- Other thyroid lesions
- Intellectual disability
- Hamartomatous intestinal polyps
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumors
- Genitourinary malformation
- Uterine fibroids

PTEN-hamartoma tumor syndrome (PHTS)



Trichilemmomas - hair follicle hamartomas



Acral keratoses - papules on hands and feet

Facial papules and mucocutaneous papilloma - often form cobblestone appearance

Hereditary cancer syndromes – HBOC/other cancer syndromes

Nicole Cho, MS, CGC

Conflicts of Interest

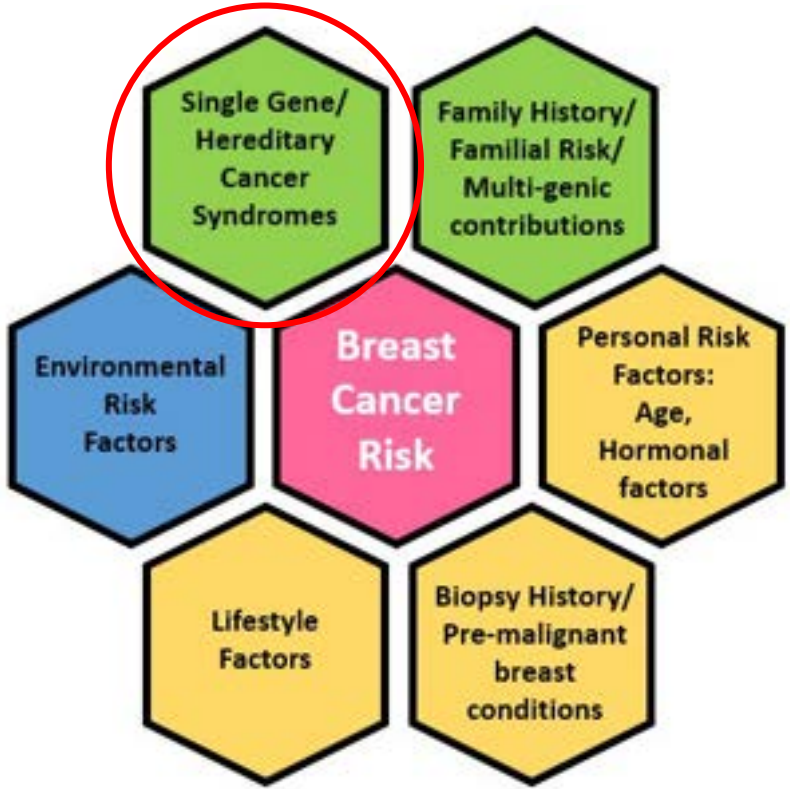
No conflicts of interest to disclose.

Objectives

- Describe risk factors for breast cancer, including genetics
- Overview of hereditary cancer syndromes with susceptibility to breast, ovarian, prostate, and pancreatic cancer
- Discuss considerations of genetics referral
- Describe resources for providing care specific to hereditary cancer syndromes

Breast Cancer and Genetics

- Average risk: 12.5% (1 in 8) of individuals AFAB* will develop breast cancer by age 85
- Risk factors:
  - Personal risk factors
  - Biopsy history/pre-malignant breast conditions
  - Lifestyle factors
  - Environmental risk factors
  - Family history
  - **Genetics**
- 5-10% of breast cancer diagnoses are due to a genetic predisposition
- A genetic diagnosis can impact treatment, management recommendations, and family members



*AFAB: Assigned female at birth

High penetrance breast cancer susceptibility genes

- Hereditary breast and ovarian cancer syndrome: *BRCA1, BRCA2*
- *PALB2*
- Hereditary diffuse gastric cancer: *CDH1*
- PTEN hamartoma syndrome: *PTEN*
- Peutz Jeghers Syndrome: *STK11*
- Li Fraumeni Syndrome: *TP53*

High penetrance breast cancer susceptibility genes

- **Hereditary breast and ovarian cancer syndrome: *BRCA1, BRCA2***
- *PALB2*
- Hereditary diffuse gastric cancer: *CDH1*
- PTEN hamartoma syndrome: *PTEN*
- Peutz Jeghers Syndrome: *STK11*
- Li Fraumeni Syndrome: *TP53*

Hereditary breast and ovarian cancer syndrome (HBOC)

- Accounts for up to **5 to 10% of breast cancers** in persons AFAB and around **15% of ovarian cancers** in the U.S. every year
- Prevalence: ~1 in 400 individuals
- Frequency in Ashkenazi Jewish Population: 1 in 40
  - 3 Founder mutations
- Due to pathogenic variants in the ***BRCA1*** and ***BRCA2*** genes
  - Tumor suppressor genes, involved in double-stranded DNA break repair
  - **Autosomal dominant** inheritance
- **High penetrance, highly actionable**

HBOC Cancer Risks

Table 2.

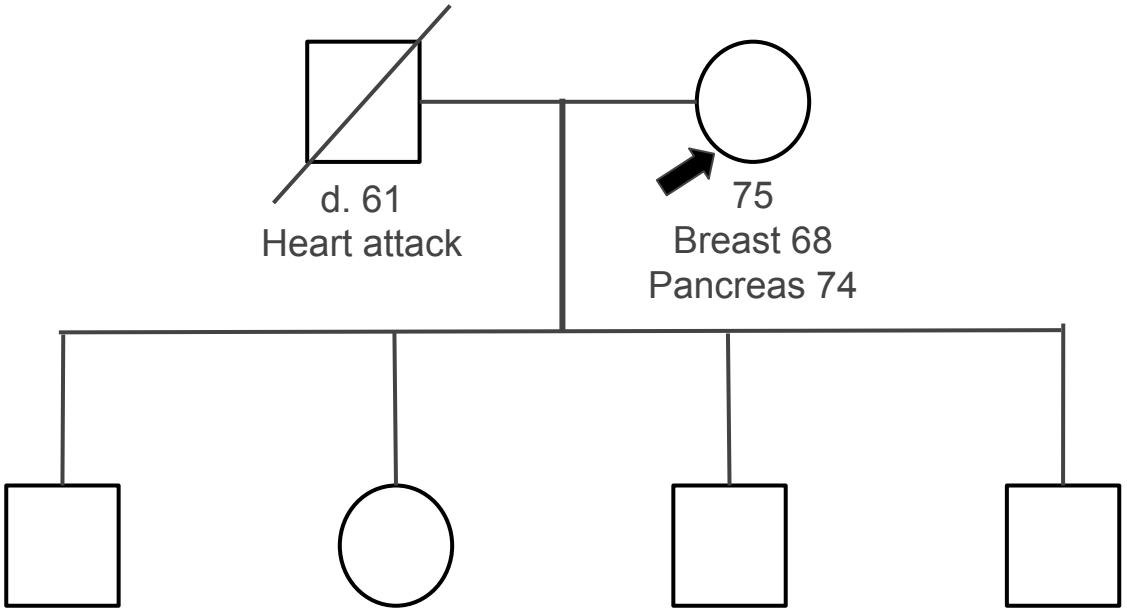
Risk of Malignancy in Individuals with a Germline *BRCA1* or *BRCA2* Pathogenic Variant

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	*BRCA2*
Breast	12%	55%-72% by age 70	45%-69%
Contralateral breast cancer	2% w/in 5 yrs	20%-30% w/in 10 yrs; 40%-50% w/in 20 yrs	
Ovarian	1%-2%	39%-44%	11%-17%
Male breast	0.1%	1%-2%	6%-8%
Prostate	6% by age 69 yrs	21% by age 75 yrs; 29% by age 85 yrs	27% by age 75 yrs; 60% by age 85 yrs
Pancreatic	0.5%	1%-3%	3%-5% by age 70 yrs
Melanoma (cutaneous & ocular)	1.6%		Elevated risk

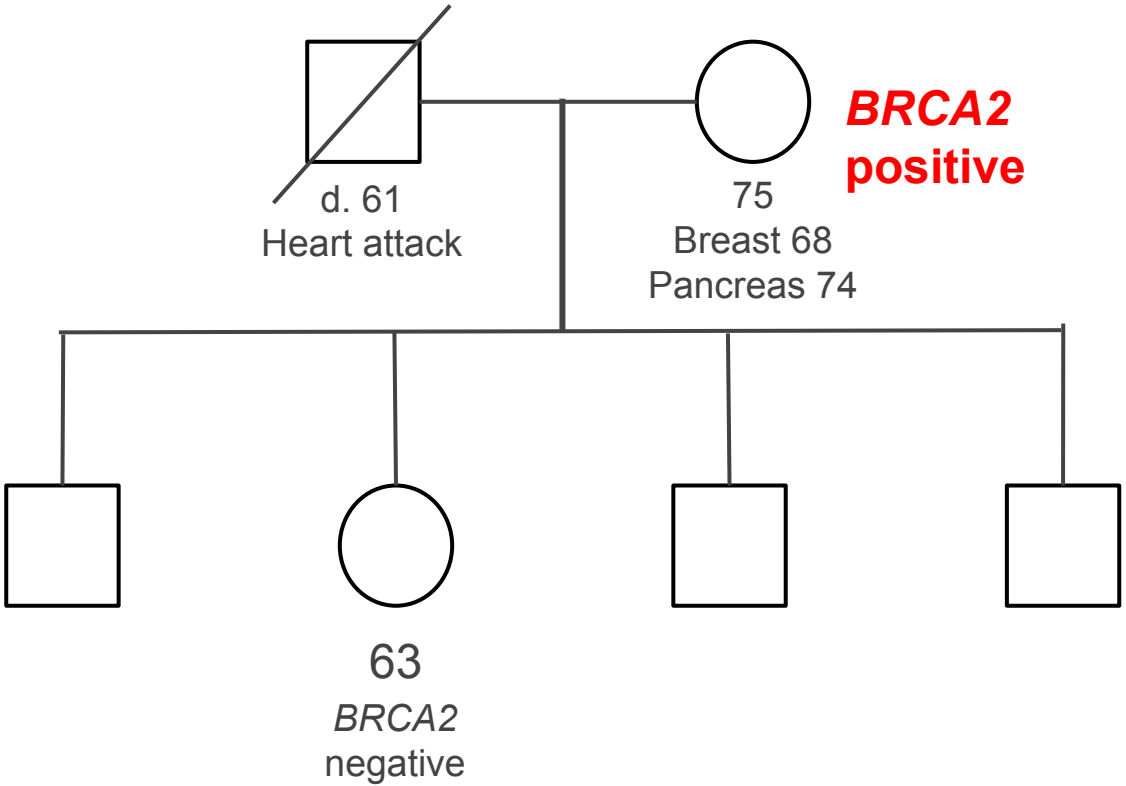
HBOC Management Recommendations

- **High risk screening**
  - Annual breast MRI at age 25-29, annual breast MRI + mammogram at age 30-75
  - Consideration of annual mammogram for AMAB with *BRCA2* pathogenic variant
  - Prostate cancer screening starting at age 40
  - Consideration of MRCP/EUS for pancreatic cancer risk
  - Annual full-body skin examination
- **Chemoprevention**
  - Tamoxifen: 40% reduction of breast cancer risk
- **Surgical intervention**
  - Risk-reducing mastectomy: 90-95% risk reduction
  - Risk-reducing salpingo-oophorectomy: 90%+ risk reduction
- **Treatment Impact**
  - Surgical planning
  - PARP inhibitors

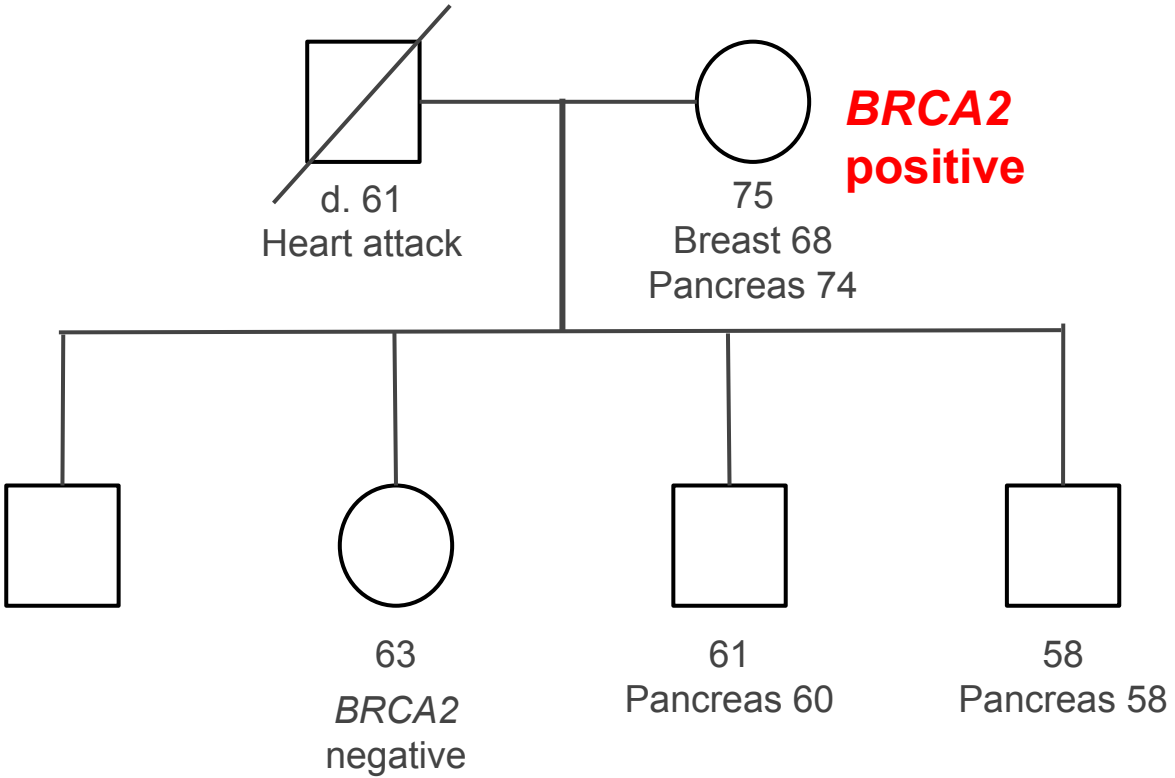
Case Example:



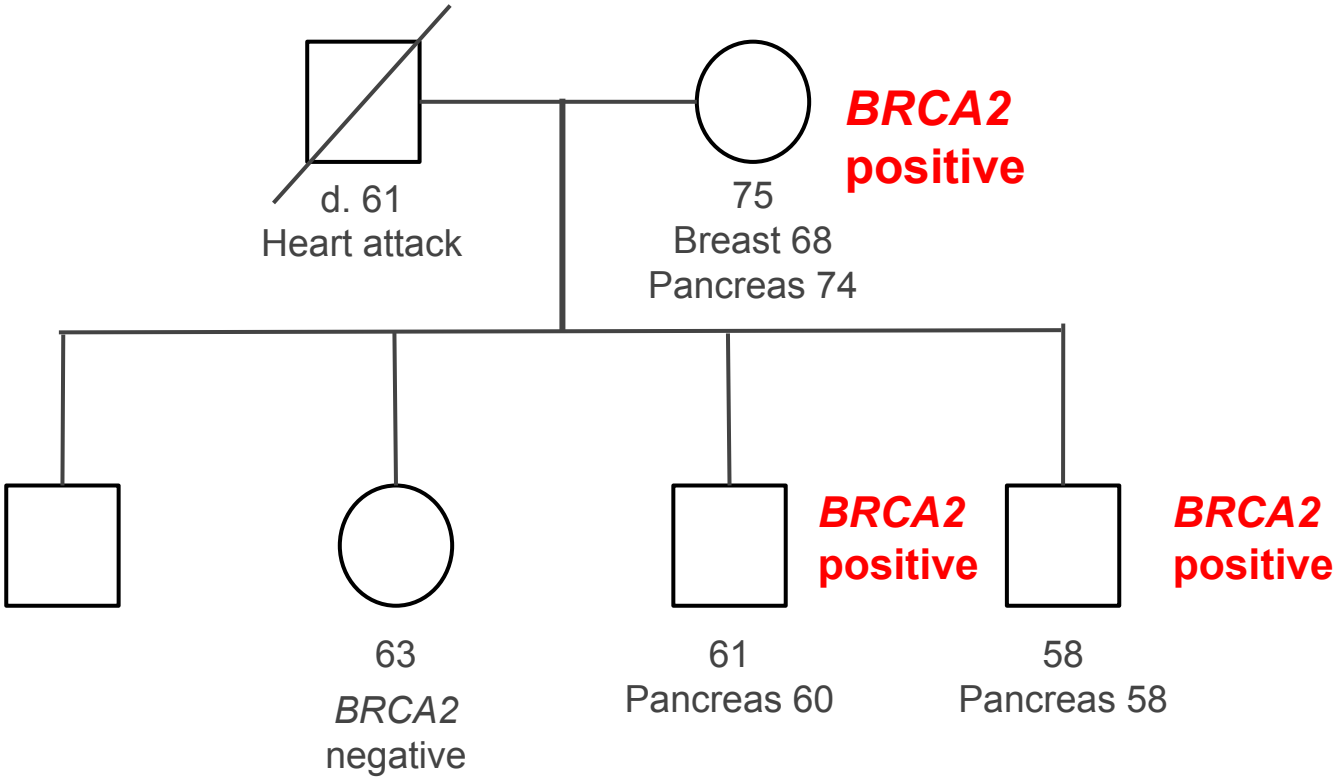
Case Example:



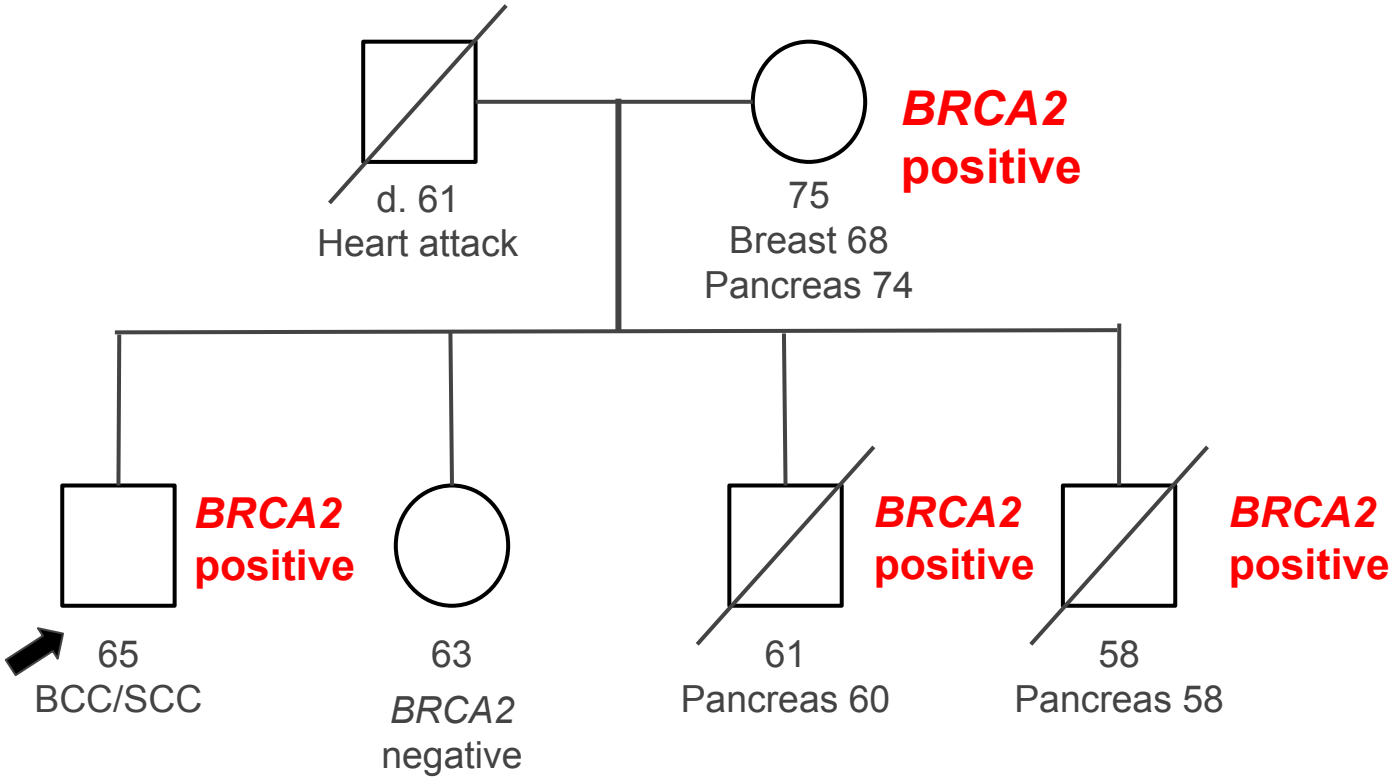
Case Example:



Case Example:



Case Example:

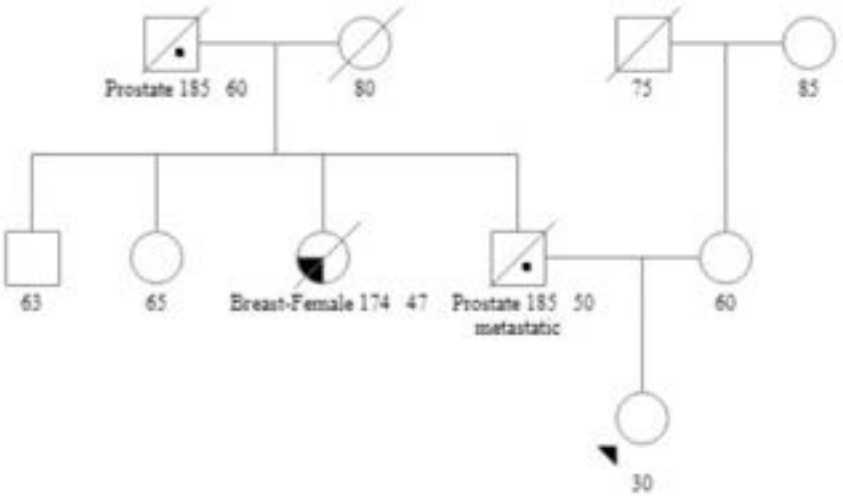


Consideration of genetics referral for breast cancer patients:

- **Personal history of breast cancer with the following features:**
  - Diagnosed at or younger than age 50
  - At any age if deciding systemic treatment decisions using PARP inhibitors, to aid in adjuvant treatment decisions with HER2-negative breast cancer
  - At any age if pathology/histology is consistent with triple negative breast cancer, multiple primary breast cancers, lobular breast cancer w/ personal or family history of diffuse gastric cancer,
  - At any age if diagnosed with AMAB breast cancer
  - At any age if Ashkenazi Jewish ancestry
  - At any age if there is family history of breast cancer diagnosed at or younger than age 50, male breast cancer, ovarian cancer, pancreatic cancer, or metastatic prostate cancer
  - At any age if there is family history of over three diagnoses of breast and/or prostate cancer on the same side of the family, including the patient with breast cancer

What if my patient does not have breast cancer but there is extensive family history of cancer?

- Family history criteria: Individuals not affected with breast cancer **has a first-or second-degree blood relative meeting criteria described on the previous slide**



High penetrance breast cancer susceptibility genes

- Hereditary breast and ovarian cancer syndrome: *BRCA1, BRCA2*
- ***PALB2***
- **Hereditary diffuse gastric cancer: *CDH1***
- **PTEN hamartoma syndrome: *PTEN***
- **Peutz Jeghers Syndrome: *STK11***
- **Li Fraumeni Syndrome: *TP53***

Other hereditary breast cancer syndromes

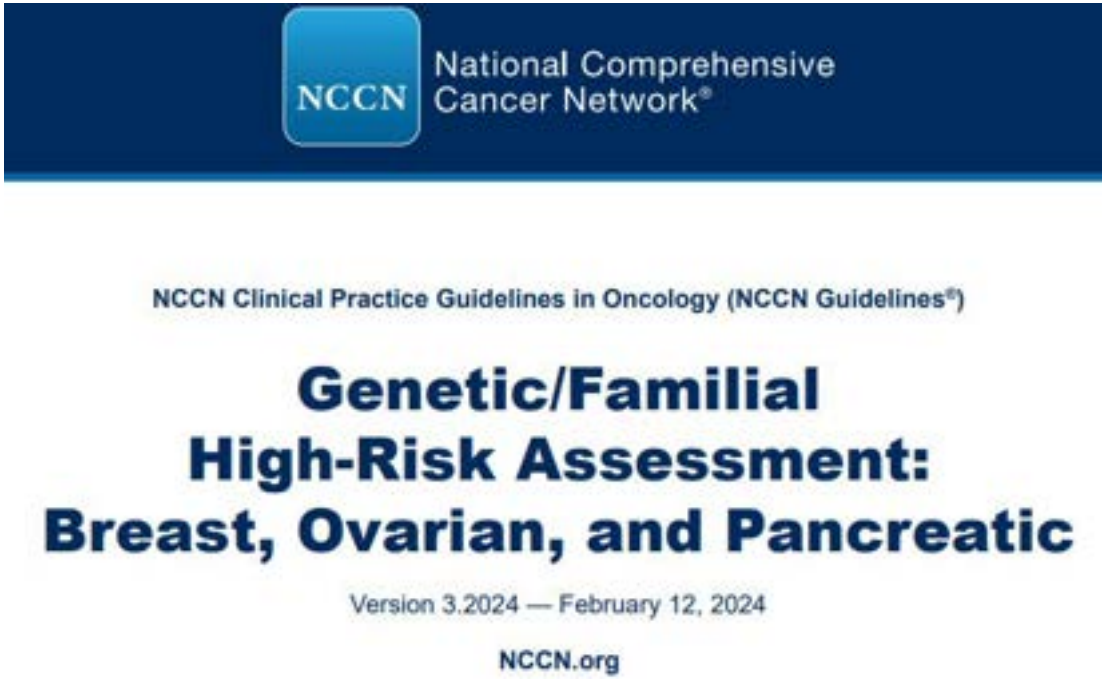
Condition	Gene	Cancer Risks and Key Features
PALB2	*PALB2*	Breast, Ovarian, and Pancreatic cancer
Hereditary diffuse gastric cancer	*CDH1*	Lobular breast and diffuse gastric cancer
PTEN Hamartoma Tumor syndrome	*PTEN*	Breast, uterine, and thyroid cancer; large head size; skin findings
Peutz Jeghers Syndrome	*STK11*	Breast, colon, pancreatic, and gastric cancer; hamartomas in GI tract; freckling of lips in childhood
Li Fraumeni Syndrome	*TP53*	Breast, brain, and lung cancers, sarcomas, adrenocortical carcinoma; young age of onset
ATM	*ATM*	Breast (moderate risk), ovarian, pancreatic cancer
BARD1	*BARD1*	Breast (moderate risk)
CHEK2	*CHEK2*	Breast (moderate risk), prostate, thyroid cancer

Other hereditary cancer syndromes: Ovarian, Pancreatic, and Prostate Cancer

Condition	Gene	Cancer Risks and Key Features
BRIP1	*BRIP1*	Ovarian cancer
Familial multiple mole melanoma syndrome	*CDKN2A*	Pancreatic cancer, melanoma
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	Colon, uterine, ovarian, pancreatic, prostate
RAD51C	*RAD51C*	Breast (moderate penetrance), ovarian cancer
RAD51D	*RAD51D*	Breast (moderate penetrance, ovarian cancer

Resources

- NCCN
- GeneReviews



Genetic Testing in Oncology

Michelle Jacobs, MS, CGC

Who are genetic counselors?

Patients may be referred to a genetic counselor by a doctor to discuss their personal and family history and genetic risks. This can occur before or after having genetic testing. Genetic counselors are not medical doctors. They are part of the healthcare team and work with patients and providers to help them understand:

- Patient's genetic risks based on personal and/or family history
- Patient's genetic risks for certain diseases or cancer
- Whether genetic testing might be right for patients
- What the results of genetic tests may mean for patients and family members

Genetic counselors can also provide emotional support as patients make decisions and empower them with information for their overall healthcare.

Adapted from National Society of Genetic Counselors
https://www.aboutgeneticcounselors.com/Who-Are-Genetic-Counselors/Who-Are-Genetic-Counselors

What happens in a cancer genetic counseling session?

- Collection of cancer-focused personal and family history (three generations)
- Review of genetic testing options and details
- Discussion of risks, benefits, and limitations of genetic testing
- Order genetic testing (most common sample types: blood, saliva)

  Results are typically available 3 weeks after patient's sample received at lab (may vary based on test ordered and other factors).

For patients with prior genetic testing and/or a known genetic diagnosis, a genetic counselor can review the testing completed, explain what the results mean for patients and their families, and discuss next steps..

Provider-ordered genetic testing

- Most common method of patients undergoing genetic testing
- May be ordered be genetic counselor, other genetics provider (geneticist, genetics nurse, etc), or other providers such as oncologist or OBGYN

Direct-to-consumer (patient-initiated) genetic testing

- Customers purchase a genetic test directly from a company, send a DNA sample via mail, and receive results online, often without healthcare provider involvement
- Different options: recreational versus clinical

https://www.health.harvard.edu/medical-tests-and-procedures/should-you-try-a-home-genetic-test-kit

Direct-to-consumer (patient-initiated) genetic testing

Early option: genotyping

- Analysis of common variants to predict ancestry, traits, and certain health risks
- Positive health results may need confirmation with clinical testing
- Negative health results may not be “true negative” results

More recently: clinical-grade sequencing and interpretation by reputable labs

Benefits:

✓ Accessibility
✓ Relatively low cost
✓ VUS typically not reported
✓ Privacy

Limitations:

x Limited genes/variants analyzed
x “One size fits all” testing/interpretation
x VUS typically not reported
x Follow up care/management

Direct-to-consumer (patient-initiated) genetic testing

Even more recently: sequencing/raw data analysis offered by other companies

- May not be clinical grade sequencing/interpretation
- Many false positives (and likely negatives); inaccuracies in sequencing/reporting
- Often, types of results not useful for clinical management; research at best (at current time)

Resources for patients:

MedLine Plus → Direct-to-Consumer Genetic Testing
https://medlineplus.gov/genetics/understanding/dtcgenetictesting/

NIH → National Human Genome Research Institute
https://www.genome.gov/dna-day/15-ways/direct-to-consumer-genomic-testing

Watershed DNA → Frequently Asked Questions https://www.watersheddna.com/faqs

Genetic testing in oncology

Tumor profiling

Tumor DNA sequencing

Somatic testing

Cancer sequencing

Cancer genome sequencing

Personalized medicine

Precision medicine

Targeted treatment

NGS cancer sequencing

Genetic profiling

Genetic sequencing

Genetic testing

Genetic testing in oncology

	WHAT IS TESTED?	INHERITANCE	RISKS
INHERITED (GERMLINE)	Blood or saliva Genes that are identical in all cells of your body	Can be inherited and passed on to family members	Linked to an increased risk for other cancer(s)
TUMOR (SOMATIC)	Your tumor tissue for cancer-specific changes	Not inherited and only present in your tumor cells. Cannot be passed to family members	Does not increase your risk for other cancers Can impact your treatment

Typically ordered by genetic counselors/ providers

Typically ordered by oncologists/ oncology providers

Adapted from Ambry Genetics

Genetic testing in oncology

Tumor only	Paired tumor-germline
Pros: ● Only requires tumor tissue ● Appropriate for limited testing	Pros: ● Accurately classify variant as germline or somatic ● Incidental identification of hereditary cancer syndromes ● In rare cases, may eliminate need to order separate germline testing
Cons: ● Does not eliminate need for germline testing ● Possible miscalls between somatic vs. germline ● Possible germline findings require additional test to confirm	Cons: ● Does not eliminate need for germline testing (usually) ● Need two sample types ● Incidental identification of hereditary cancer syndromes

Tumor sequencing follow-up

- Many tumor sequencing labs flag incidental or possible germline findings on their reports → check with your preferred lab(s) for more information

Resources:

- Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations. Kuzbari *et al*. 2023; 34(3), 215-227. *Annals of Oncology* https://doi.org/10.1016/j.annonc.2022.12.003
    - Recommendations for follow-up of potential germline variants detected on tumor-only sequencing
- Check for publications and/or guidelines specific to your disease group

Placing referrals

Cancer Genetics

Breast and ovarian cancer only → Cancer Center Breast & Ovarian Risk Evaluation (REF398)

All others cancer types → Cancer Genetics Clinic (REF320)

Non-Cancer Indications

Cardiology (early/familial arrhythmia, cardiomyopathy → Cardiology Genetic Counseling (REF424)

Ophthalmology (retinal dystrophies) → Ophthy Retinal Dystrophy (REF153)

All other indications → Medical Genetics Clinic (REF26)

FAQ

Do patients have to meet with someone before getting genetic testing?

- Meeting with a genetic counselor or specialist before testing is encouraged to help review benefits, risks, and options for testing and make sure the appropriate test is ordered. While some direct-to-consumer testing is available, it is important to confirm that the genetic test ordered adequately assess for hereditary cancer risk. Companies that include genetic counseling and/or require a physician to order the testing may address this issue.

Who can order genetic testing?

- A doctor or genetics specialist. A genetic counselor can help ensure the correct testing is ordered.

FAQ

How can I find a local genetic counselor?

- NSGC find a genetic counselor tool: https://findageneticcounselor.nsgc.org
- Most academic medical centers have genetic counseling services
- Directory of Cancer Genetic Services Providers: https://migrc.org/providers/michigan-cancer-genetics-alliance/mcga-directory-of-cancer-genetic-services-providers/

Do patients need to meet with someone in-person?

- No, many genetics clinics have options for telehealth/phone visits.

Other considerations

Cost:

- Cost of genetic testing has decreased significantly in the last few years
- Generally patients do not pay more than $250 out-of-pocket
- Financial assistance may be available
- Genetic counselor can answer questions about cost during appointment

Insurance discrimination:

- Federal law, Genetic Information Nondiscrimination Act (GINA), prevents health insurance and employers from discriminating based on predictive genetic testing results → some exclusions
- Life insurance, long term care, and disability insurance are not covered by GINA
- Resource: http://ginahelp.org/

Common questions/misconceptions (GINA, cost of testing/insurance coverage, limitations of GT)

Vedika Ramesh, MS, CGC

Is Genetic Testing Covered by Insurance?

- Genetic testing for cancer predisposition is often covered by health insurance
  - Coverage may involve meeting certain criteria related to personal or family medical history
  - Contacting your insurance company is helpful to learn about your policy's specific coverage
- Self-pay and/or financial assistance options may be available
- Genetic counselors can answer questions about cost for genetic testing during an appointment

<u>Patients with Medicare Insurance</u>

Covers genetic testing for people with a cancer diagnosis who meet certain criteria

Important to check with Medicare provider to verify coverage for genetic testing

<u>Patients with Medicaid Insurance</u>

Many state Medicaid programs cover *BRCA* genetic counseling and testing for individuals who qualify (e.g., known mutation in the family, specific personal and/or family history of cancer)

Eligibility and coverage policies vary by state

How can Genetic Testing impact Health &/or Life Insurance?

Under the Genetic Information Nondiscrimination Act (GINA):

- Health insurers cannot use genetic information to determine eligibility, set premiums, or make coverage decisions
  - Health insurers are still able to make these decisions based on an existing health condition (e.g., current cancer diagnosis)
- Employers cannot use genetic information in making employment decisions

Exceptions:

- Does not apply to life, disability, or long-term care insurances
- Does not apply to certain employers:
  - Members of the US Military
  - Veterans obtaining healthcare through Veterans Administration
  - Individuals using Indian Health Service
  - Federal Government Employees
  - Employers with less than 15 employees

Who could have access to my genetic test data?

If genetic test ordered through your doctor:

- Results are added to your medical record
  - Only your doctor and care team would have access to these results
- The Health Insurance Portability and Accountability Act (HIPAA) ensures that your doctor cannot share test results without permission

If genetic test ordered through a private genetic testing company:

- Many companies with certifications that uphold strict data privacy standards
- Some companies may combine your results with other customers and use or sell it for other purposes (but your individual result remains private)

What limitations are there with genetic testing?

- May not identify all mutations
- Possibility for an uncertain or inconclusive result
  - Not all variants have known health impacts
  - May not have enough information to influence clinical management and/or treatment decisions