Genetic Support Foundation

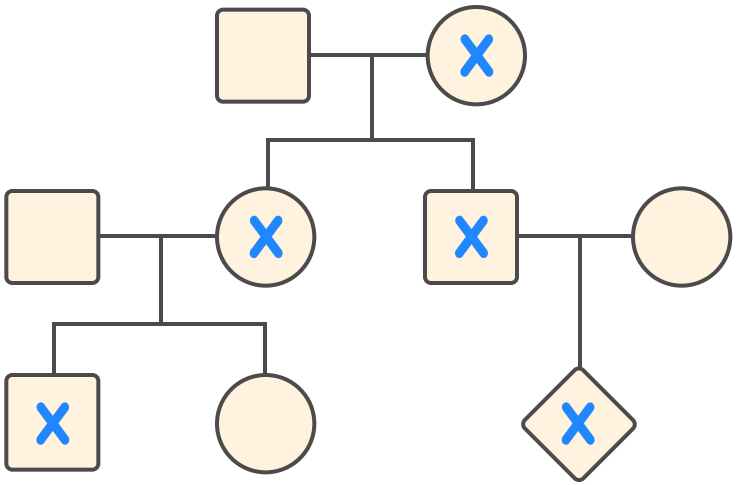
A Provider's Guide to

Hereditary Colorectal Cancer

Hereditary Cancer

Hereditary Cancer

- Most of the time, colorectal and other types of cancer occur sporadically due to random chance and/or risk-increasing environmental factors.
- However, **up to 10%** of cancer cases are hereditary, or caused by an **inherited mutation** in a cancer susceptibility gene that increases the risk of developing specific cancers over a lifetime.
- Most hereditary cancer syndromes are inherited in an **autosomal dominant pattern**, meaning that first-degree family members (parents, siblings, and children) of an affected person each have a 50% chance of having the syndrome.



X related types of cancer

*If a hereditary cancer syndrome is suspected, genetic testing can inform an entire family's screening practices and **save lives**.*

Identifying Hereditary Cancer

Patients should be referred to a genetic counselor if they have a personal or family history of any of the following:

- ≤50 Any cancer with onset at **age 50 or younger**
- ! **Rare** types of cancer (such as ovarian, pancreatic, or metastatic prostate cancer)
- 2+ **Multiple relatives** with the same or related types of cancer (such as colon and endometrial cancer)

Genetic Counseling and Testing

- If a hereditary cancer syndrome is suspected, patients should meet with a **genetic counselor** to discuss their personal and family history in more detail. The genetic counselor will then determine the most appropriate **genetic testing** option.
- Identifying an inherited mutation through genetic testing can allow for **early cancer screening** and diagnosis, and more effective treatment if cancer develops. In some cases, genetic testing can also allow for preventative action that reduces the risk of developing cancer.
- Family members can also be tested to determine whether they should follow these recommendations. Genetic testing can therefore inform an entire family's screening practices and **save lives**.

Lynch Syndrome

- Lynch syndrome (LS) accounts for approximately 2-4% of all colorectal cancer and 2.5% of all endometrial cancer cases.
- LS is caused by mutations in the ***MLH1***, ***MSH2***, ***MSH6***, ***PMS2***, and ***EPCAM*** genes.
- These mutations increase the lifetime risk of **colorectal**, **endometrial**, **ovarian**, **prostate**, **urinary system**, and **other** cancers.

Quick Look: Lynch Syndrome

Red flags: colorectal or endometrial cancer at age 50 or younger, multiple LS-related cancers in a person or family, microsatellite instability (MSI) or lost of mismatch repair (MMR) protein expression on tumor testing

Implications: earlier colonoscopies, upper endoscopies, additional gene and family-specific screening, risk-reducing surgeries

Guidelines: NCCN "Genetic/Familial High-Risk Assessment: Colorectal"

Exact Lynch syndrome cancer risks and screening recommendations depend on which gene is affected, for example:

Cancer	General Population Lifetime Risk	*MLH1*-Associated Risk	*MSH2*-Associated Risk
Colorectal	4%	46-61%	33-52%
Endometrial	3%	34-54%	21-57%
Ovarian	1%	4-20%	8-38%
Prostate	13%	4-14%	4-24%
Gastric	<1%	5-7%	<1-9%
Bladder	2%	2-7%	4-13%
Pancreas	2%	6%	<1-2%
Small Bowel	<1%	<1-11%	1-10%
Renal Pelvis/ Ureter	--	<1-5%	2-28%
Biliary Tract	--	2-4%	<1-2%
Brain	<1%	<1-2%	3-8%
Skin*	--	Increased	Increased

*Increased frequencies of sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas have been reported in people with Lynch syndrome

Polyp-Associated Syndromes

There are a number of hereditary colorectal cancer syndromes that can be identified by the presence and number of certain polyps. For example:

- Classic and attenuated **Familial Adenomatous Polyposis (FAP) syndrome** are caused by mutations in the *APC* gene, and result in ≥10-100s of adenomatous polyps.
- **Peutz-Jeghers syndrome** is caused by mutations in the *STK11* gene, and results in ≥2 Peutz-Jeghers-type hamartomatous polyps.
- **Juvenile Polyposis syndrome (JPS)** is caused by mutations in the *BMPR1A* and *SMAD4* genes, and results in ≥5 juvenile-type hamartomatous polyps.
- **Cowden syndrome** is caused by mutations in the *PTEN* gene, and results in ≥2 hamartomatous polyps.

Quick Look: Polyp-Associated Syndromes

Red flags: ≥10 adenomatous polyps, ≥2 hamartomatous polyps, ≥5 serrated polyps

Implications: earlier colonoscopies, upper endoscopies, syndrome-specific cancer screening, risk-reducing surgeries

Guidelines: NCCN "Genetic/Familial High-Risk Assessment: Colorectal"

	Polyp Features	Cancer Risks	Unique Features
Classic FAP syndrome	≥100 adenomas	Colorectal Duodenal Gastric Thyroid Hepatoblastoma Medulloblastoma	CHRPE Desmoid tumors Osteomas Supernumerary teeth
Attenuated FAP syndrome	10-<100 adenomas	Colorectal Duodenal Thyroid	Desmoid tumors
Peutz-Jeghers syndrome	≥2 Peutz-Jeghers-type hamartomas	Colorectal Breast Stomach Small bowel Pancreas Lung Ovarian sex cord tumors Testicular sertoli cell tumors	Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, and/or fingers
Juvenile Polyposis syndrome	≥5 juvenile-type hamartomas	Colorectal Stomach Small bowel	Hereditary hemorrhagic telangiectasia
Cowden syndrome	≥2 hamartomas	Colorectal Endometrial Breast Thyroid Renal	Mucocutaneous lesions Macrocephaly Autism spectrum disorder Glans penis macular pigmentation

Colorectal Cancer Syndrome Red Flag Checklist

Colon or Endometrial Cancer

Personal history:

- ☐ Diagnosed <50 yrs?
- ☐ MSI or loss of MMR protein expression on tumor testing?
- ☐ Synchronous or metachronous LS-related cancer*?
- ☐ ≥1 first or second-degree relative with LS-related cancer* diagnosed <50 yrs?
- ☐ ≥2 first or second-degree relatives with LS-related cancer*?
- ☐ PREMM5 predictive model score of ≥2.5%?

Family history only:

- ☐ ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 yrs?
- ☐ ≥2 first or second-degree relatives with LS-related cancer*, 1 diagnosed <50 yrs?
- ☐ ≥3 first or second-degree relatives with LS-related cancer*?
- ☐ PREMM5 predictive model score of ≥5%?

Colon Polyps

Personal or family history:

- ☐ ≥10 adenomatous polyps?
- ☐ ≥2 hamartomatous polyps?
- ☐ ≥5 serrated polyps?

Pancreatic Cancer

- ☐ Personal history?
- ☐ First-degree relative?

☑ Yes to ANY

If any boxes are checked, your patient meets criteria for genetic evaluation of a hereditary cancer syndrome and should be referred to a genetic counselor.

Key points to communicate to the patient include:

- **5-10%** of cancer cases are hereditary, or caused by an inherited genetic difference that increases the lifetime risk of developing specific types of cancer.
- When hereditary, **other family members are also at risk** of having a predisposition to cancer.
- **Genetic counseling and testing** can help identify an inherited cancer risk. Knowing about this risk in advance can inform cancer screening and preventative care.

*Lynch syndrome (LS)-related cancers: colorectal, endometrial, ovarian, prostate, small bowel, gastric, pancreatic, bladder, renal pelvis and/or ureter, biliary tract, brain, skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas)