

Hereditary **Colorectal** **Cancer**

Referral Guide
for Cancer Genetic Evaluation

The field of cancer genetics continues to expand as hereditary cancer conditions are further characterized, both molecularly and clinically. Additionally, patients are increasingly seeking information regarding their own cancer risk and using genetic information to facilitate decisions about treatment and cancer risk management.

The purpose of this booklet is to provide physicians with information on the currently known genetic conditions associated with susceptibility for colorectal cancer and to assist in identifying when a cancer genetic evaluation may be appropriate.

The following indications for a cancer genetic evaluation are meant to be used as general guidelines in order to identify a majority of patients who are at-risk for hereditary colorectal cancer. As a result, there are patients who may benefit from a cancer genetic evaluation that do not fit the criteria presented in this booklet. *Please contact us if you have questions regarding a specific patient.*

Background Information:

Hereditary Cancer: Cancer due to a heritable germline mutation that leads to an increased susceptibility for particular types of cancers; accounts for approximately 5-10% of colorectal cancer cases.

Familial Cancer: A clustering of cancers in a family that is not due to a hereditary condition; most likely due to a combination of genetic and environmental factors; increases cancer risks for close relatives; accounts for approximately 10-20% of colorectal cancer cases.

Sporadic Cancer: An occurrence of cancer that has no obvious hereditary or familial basis; usually occurs later in life; the majority of colorectal cancer cases are sporadic.

General Characteristics of Hereditary Colorectal Cancer:

- ☉ Early age of onset compared to the general population.
- ☉ Multiple family members in more than one generation affected with colorectal cancer or other associated cancers.
- ☉ Synchronous or metachronous colorectal cancers.
- ☉ Multiple primary cancers.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Also known as *Lynch syndrome*.

Accounts for approximately 5% of colorectal cancer cases.

Germline mutations in: *MLH1, MSH2, MSH6, PMS1, PMS2*

Main Clinical Features:

- ☞ Characterized by early onset colorectal cancer and/or endometrial cancer.
- ☞ Average age of colorectal cancer: 45 years.
- ☞ Average age of endometrial cancer: mid-forties.
- ☞ Colorectal cancers are predominantly right-sided tumors.
- ☞ Risk for other cancers, such as endometrial adenocarcinoma, epithelial ovarian, gastric, pancreatic, biliary tract, small bowel adenocarcinoma, and transitional cell carcinoma of the ureter and renal pelvis.

Clinical Variants:

- ☞ Turcot syndrome- presence of brain tumors in addition to HNPCC-related malignancies.
- ☞ Muir-Torre syndrome- presence of sebaceous adenomas or adenocarcinomas, keratocanthomas, or squamous and basal cell carcinomas in addition to HNPCC-related malignancies.
- ☞ Familial endometrial cancer-clustering of endometrial cancer in families without the presence of colorectal cancer.

Inheritance: Autosomal dominant condition with a 70-80% lifetime risk for colorectal cancer and a 20-40% lifetime risk of endometrial cancer.

Diagnosis: Based upon family history information and/or genetic testing.

Familial Adenomatous Polyposis (FAP)

Accounts for ~1% of colorectal cancer cases.

Germline mutations in: *APC*

Main Clinical Features:

- Characterized by multiple adenomatous polyps (hundreds to thousands) in the colon and rectum, which usually develop in the 2nd to 3rd decades of life.
- Associated with nearly a 100% lifetime risk for colon cancer if prophylactic colectomy is not performed.
- Average age of colorectal cancer: 39 years.
- Polyps may develop throughout the GI tract.
- Risk for other cancers, such as duodenal, pancreatic, and thyroid.
- Other variable features include osteomas, epidermoid cysts, desmoid tumors, childhood hepatoblastoma, and congenital hypertrophy of retinal pigment epithelium (CHRPE).

Clinical Variants:

- Attenuated FAP (AFAP) - characterized by the presence of fewer polyps (usually less than 100) and later age of onset of polyp formation and colorectal cancer than in classic FAP.
- Turcot syndrome - presence of brain tumors, usually medulloblastomas, in addition to polyposis and FAP-related malignancies.
- Gardner syndrome - older term referring to the presence of any of the extracolonic manifestations listed above in addition to polyposis and FAP-related malignancies.

Inheritance: Autosomal dominant condition with nearly 100% risk for colorectal cancer.

Diagnosis: Usually diagnosed when there are greater than 100 polyps present; however, individuals with greater than 20 polyps should be evaluated for other features of FAP. Family history is not present in approximately 30% of cases due to a new germline mutation.

MYH Polyposis Syndrome

Prevalence is unknown. First described in 2002.

Germline mutations in: *MYH*

Main Clinical Features:

- Characterized by multiple adenomatous polyps (typically less than 100) in the colon and rectum.
- Probably associated with a high lifetime risk for colorectal cancer; risk estimates have not yet been established due to recent identification of the condition.
- Average age of polyps and colorectal cancer: late 40s.
- Unknown whether there are other features associated with this condition.
- Clinically resembles AFAP and occasionally FAP.

Inheritance: Autosomal recessive condition; not clear whether or not an increased cancer risk exists for heterozygous carriers.

Diagnosis: Usually based upon genetic testing. Family history is typically not present due to recessive inheritance pattern.

Peutz-Jeghers Syndrome (PJS)

Germline mutations in: *STK11*

Main Clinical Features:

- Characterized by multiple hamartomatous polyps that can occur throughout the GI tract, most commonly in the small intestine.
- The hamartomatous polyps are characterized by glandular epithelium with a central core of arborizing smooth muscle bands (Peutz-Jeghers polyps).
- Polyps usually develop before age 20.
- Characteristic mucocutaneous pigmented macules on the lips, perioral region, buccal mucosa, hands, and feet; present in infancy or early childhood but disappear by adulthood.
- Associated with a high risk for malignancy, with approximately a 35-40% lifetime risk for colon cancer.
- Risk for sex cord tumors, melanoma, and pancreatic, lung, breast, uterine, gallbladder, biliary, and GI cancers.

Inheritance: Autosomal dominant condition that may show clinical variability among family members. Family history is not present in approximately 40% of cases.

Diagnosis: Based upon diagnosis criteria, which include the presence of a Peutz-Jeghers polyp and other features or family history of PJS, and/or genetic testing.

Juvenile Polyposis Syndrome (JPS)

Germline mutations in: *MADH4, BMPR1A*

Main Clinical Features:

- Characterized by multiple hamartomatous polyps located in the gastrointestinal tract.
- The hamartomatous polyps are characterized by a prominent lamina propria compartment with dilated cystic glands (juvenile polyps).
- Polyps usually present in childhood.
- Associated with a 10-50% lifetime risk for colon cancer.
- Average age of colon cancer: 34 years.
- Lifetime risk of 15-20% for gastric and duodenal cancers due to polyps in upper GI tract.

Inheritance: Autosomal dominant condition; however, an associated family history may be absent.

Diagnosis: Based upon diagnostic criteria, which includes the presence of juvenile polyps, and/or genetic testing.

Cowden Syndrome (CS)

Germline mutations in: *PTEN*

Main Clinical Features:

- Multiple hamartomatous polyps in the GI tract (most are juvenile type polyps).
- Skin manifestations, including facial trichilemmomas, acral keratoses, papillomatous papules, fibromas, and lipomas usually present by the late 20s.
- Elevated risk for malignancies, including those of the breast, thyroid, and uterus.
- Risk for colorectal cancer does not appear to be elevated.

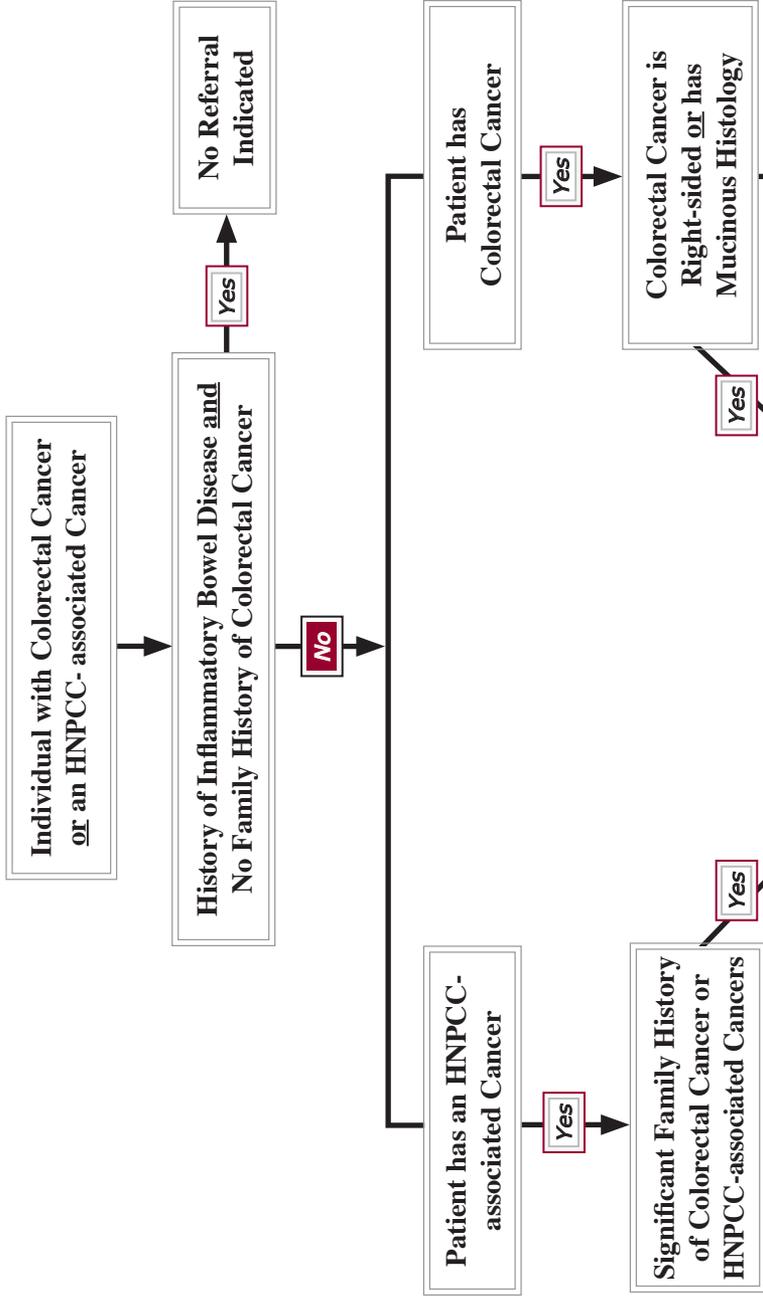
Clinical Variants:

- Bannayan-Riley-Ruvalcaba syndrome- individuals or families with macrocephaly, lipomas, pigmentation of the glans penis, polyposis, and/or other diagnostic criteria.

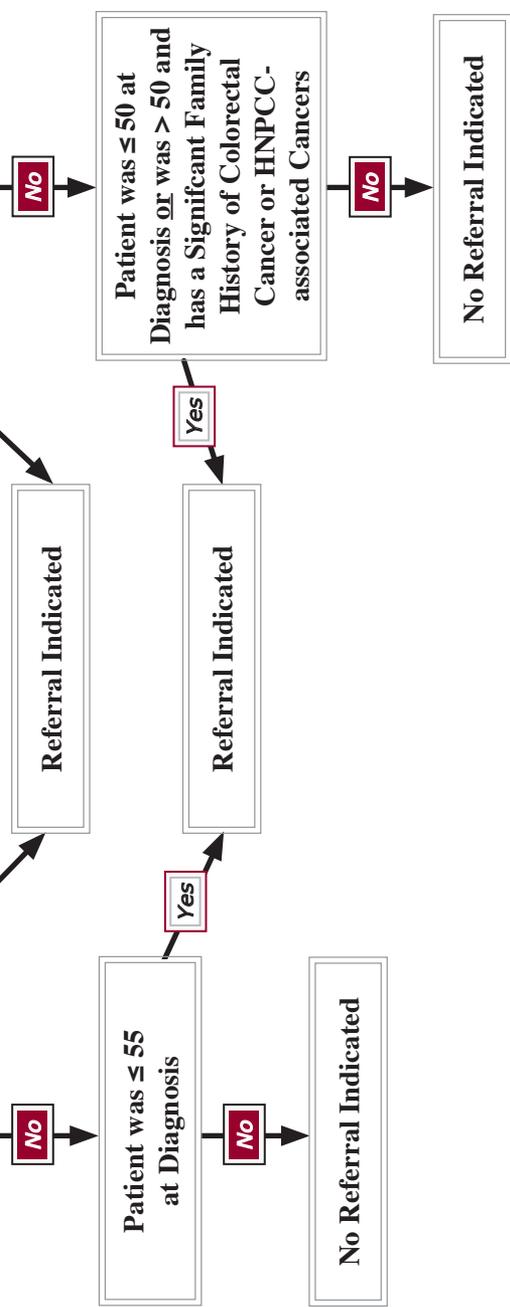
Inheritance: Autosomal dominant condition; however, an associated family history may be absent.

Diagnosis: Based upon diagnostic criteria and/or genetic testing.

HEREDITARY COLORECTAL CANCER ALGORITHM



Evaluation/Genetic Testing

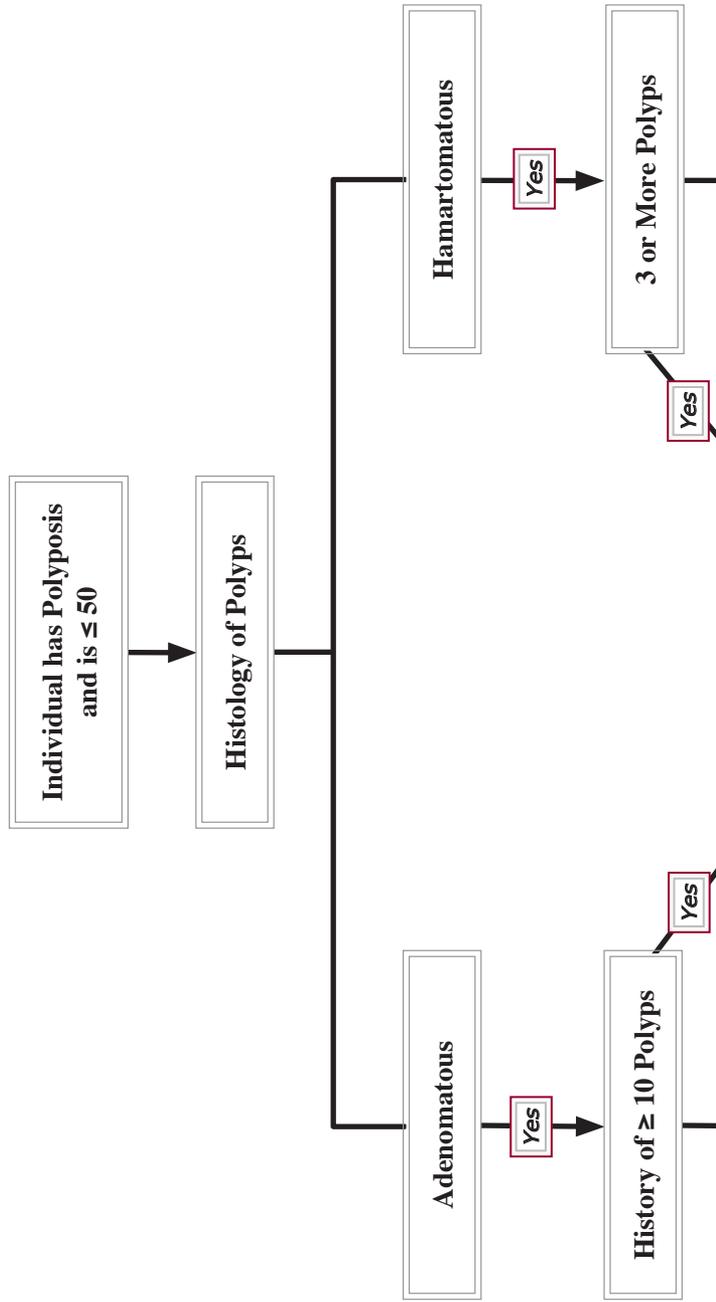


NOTE: A referral is indicated if a mutation associated with hereditary colorectal cancer or polyposis syndrome has been identified in the family or if there is a family history of HNPCC, FAP, or other hereditary polyposis syndrome.

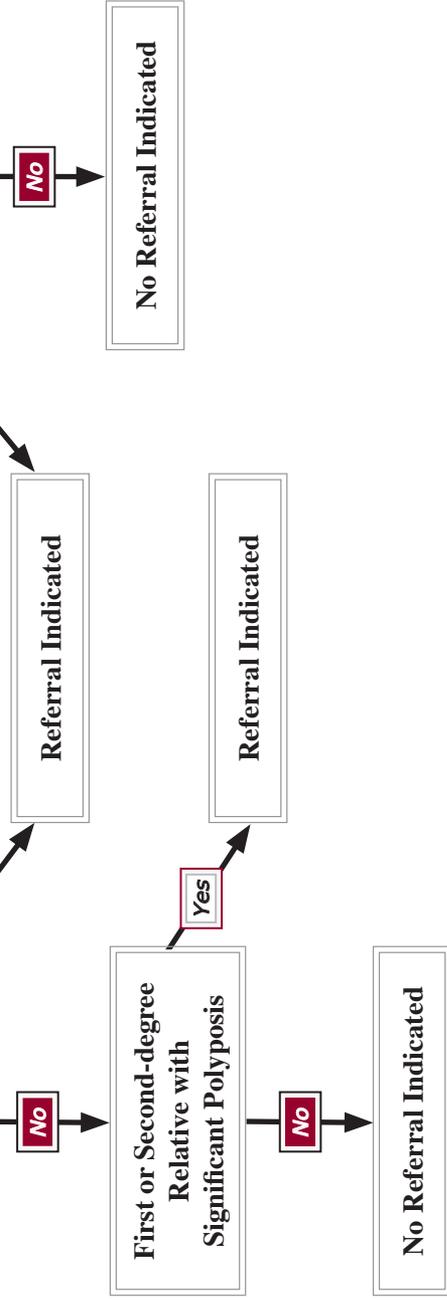
- HNPCC-ASSOCIATED CANCERS:**
- Endometrial Adenocarcinoma, Gastric, Epithelial Ovarian, Pancreatic, Biliary Tract, Small Bowel Adenocarcinoma, and Transitional Cell Carcinoma of the Ureter and Renal Pelvis

HNPCC: *Hereditary Non-Polyposis Colorectal Cancer*

POLYPOSIS ALGORITHM



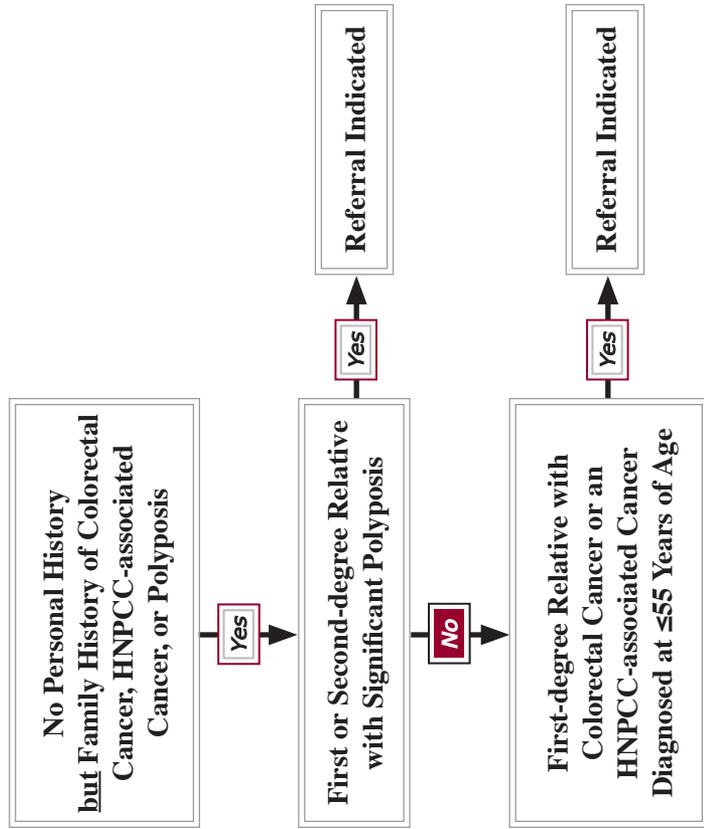
Evaluation/Genetic Testing



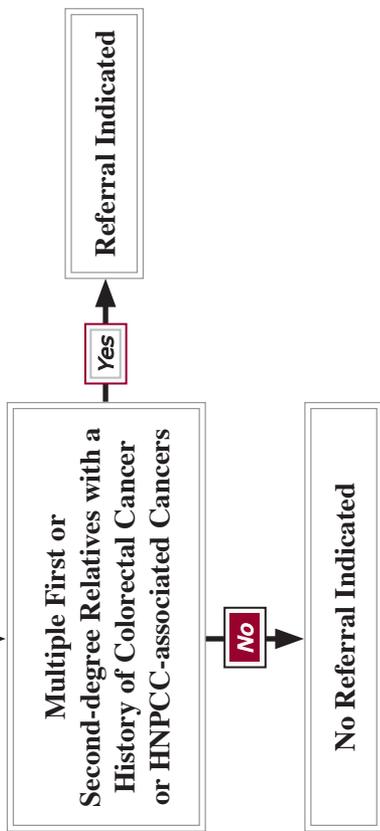
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- FAP: Familial Adenomatous Polyposis
- AFAP: Attenuated Familial Adenomatous Polyposis
- PJS: Peutz-Jeghers Syndrome
- JPS: Juvenile Polyposis Syndrome

FAMILY HISTORY OF COLORECTAL CANCER OR POLYPOSIS ALGORITHM



Evaluation/Genetic Testing



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HNPCC-ASSOCIATED CANCERS:

Endometrial Adenocarcinoma, Gastric, Epithelial Ovarian, Pancreatic, Biliary Tract, Small Bowel Adenocarcinoma, and Transitional Cell Carcinoma of the Ureter and Renal Pelvis

HNPCC: *Hereditary Non-Polyposis Colorectal Cancer*

FAP: *Familial Adenomatous Polyposis*

AFAP: *Attenuated Familial Adenomatous Polyposis*

PJS: *Peutz-Jeghers Syndrome*

JPS: *Juvenile Polyposis Syndrome*

Referring for a Cancer Genetic Evaluation

An evaluation includes:

- Discussion and review of the patient's medical history.
- Analysis of the personal and family history.
- Risk assessment based upon medical and family history information.
- Explanation of cancer genetics and how predisposition to cancer can be inherited.
- Screening recommendations.
- Genetic testing information including the risks, benefits, and limitations of testing.
- Genetic testing, if appropriate and desired by patient.
- Letter sent to patient and physician documenting and reviewing information provided during the evaluation.

Additional appointments are required if patient elects genetic testing.

Appointments:

Contact Cindy Hunter, MS, CGC
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For Questions or Additional Information:

Contact Cindy Hunter, MS, CGC

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