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Genetic Testing for Colon Cancer

Benefits of genetic testing for patients with colon cancer: which test to order and why

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ARUP is an enterprise of the University of Utah and its Department of Pathology.

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INTRODUCTION

In the United States, colorectal cancer is second only to lung cancer as a cause of cancer-related deaths; individuals have a 6 percent lifetime risk of developing the disease. Colorectal cancer can be roughly divided into sporadic, hereditary/familial forms.

Sporadic, the most common form (~80 percent), does not have a strong genetic or hereditary component. Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome accounts for 2 to 3 percent of colon cancer cases in the United States. Familial adenomatous polyposis (FAP) occurs in 1 in 20,000 live birth and accounts for fewer than 1 percent of colon cancer cases.

FORMS OF COLORECTAL CANCER

Sporadic

Approximately 80 percent of people are diagnosed with colorectal cancer each year for no obvious reason. Individuals with sporadic colorectal cancer do not have a significant family history of the disorder. Industrialized nations appear to have the greatest risk of colorectal cancer, while most developing nations have lower rates. The development of cancer in the colon and rectum is influenced by a diet high in animal fats, age, weight, smoking history, and physical activity.

Hereditary

Colon cancer exhibits familial clustering in >10 percent of patients. The best-known hereditary colon cancer syndrome is Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC), which accounts for approximately 2 percent of colorectal and endometrial cancers. HNPCC and Lynch syndrome were formerly synonymous; however, Lynch syndrome has recently been redefined as the subclass of individuals with germline mismatch repair gene mutations.

Individuals with Lynch syndrome have an increased risk of colorectal cancer and extra-colonic cancers, including those of the stomach, endometrium, renal pelvis, ureter, ovary, small intestine, and hepatobiliary tract. Individuals with Lynch syndrome may also have colon polyps, which occur at an earlier age than in the general population and are more likely to become cancerous.

Lynch syndrome is caused by pathogenic germline mutations in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes. Mutations in *MLH1* and *MSH2* account for 90 percent of Lynch syndrome, while mutations in *MSH6* and *PMS2* are responsible for approximately 10 percent. Mutations in any of these genes prevent the proper repair of DNA-replication errors and predispose individuals to cancer; however, not all individuals who carry these mutations develop cancerous tumors.

Lynch syndrome-associated tumors commonly exhibit microsatellite instability (MSI), a contraction or expansion of short nucleotide repeats due to defective DNA mismatch repair. Approximately 90 percent of HNPCC-associated colorectal cancers show a high level of MSI (MSI-H), and both inherited and sporadic tumors with MSI are associated with a better prognosis than stable colon cancers. Fluorouracil-based adjuvant chemotherapy appears to be effective only in individuals with microsatellite-stable colon cancers and may be harmful to those exhibiting MSI.

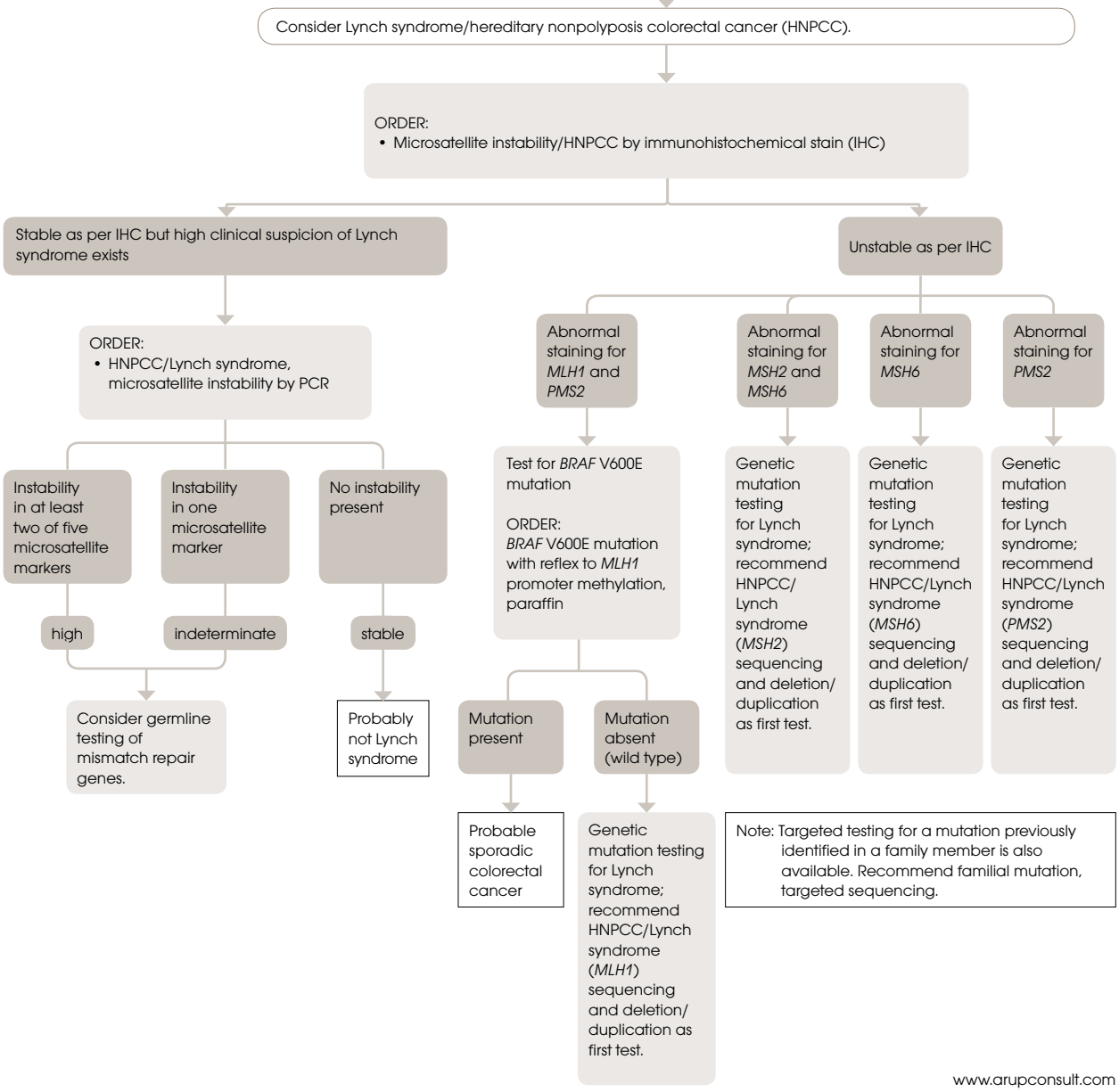
LYNCH SYNDROME TESTING (HNPCC)

INDICATIONS FOR TESTING

- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors (colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), regardless of age.
- Colorectal cancer with MSI-H histology (presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in an individual <60 years of age.
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one cancer diagnosed before 50 years of age.
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

OR

- Patients diagnosed with Muir-Torre syndrome or Turcot syndrome (especially glioblastoma brain tumor).
- Family members of individuals with a known mismatch repair gene mutation.



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APC is a tumor-suppressor gene; *APC* mutations may cause the following disorders: familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome, all of which predispose individuals to colon cancer.

- FAP is characterized by the development of hundreds to thousands of adenomatous colonic polyps, usually beginning during early adolescence. Without a preventative colectomy, all individuals with FAP will develop colon cancer during their lifetime, with a mean diagnosis age of 39.

- Additional characteristics of FAP may include dental anomalies, polyps of the gastric fundus and duodenum, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).

- Attenuated FAP differs from FAP in that affected individuals typically have 10–100 (average of 30) more proximally located polyps, and cancer generally occurs at a later age than for individuals with FAP.

- Gardner syndrome occurs in 20 percent of families with classic FAP and is associated with benign osteomas, desmoid tumors, and soft-tissue tumors.

- Turcot syndrome consists of colon polyps and central nervous system (CNS) tumors. Turcot syndrome associated with medulloblastoma is often caused by APC mutations, while Turcot with glioblastoma multiforme is usually caused by mismatch repair gene mutations.

- *MUTYH*-associated polyposis (MAP) is associated with 10–100 polyps, with an age of onset in the third decade or later.

Juvenile polyposis (JPS) is characterized by multiple hamartomatous polyps in the stomach, small intestine, colon, and rectum. Affected individuals can have a few to hundreds of polyps, and onset varies from childhood to middle age. By age 20, most affected individuals have some polyps. The risk of colon cancer with JPS is about 20 percent by age 35 and approaches 70 percent by age 60.The risk for other cancers (e.g., stomach, upper GI tract, and pancreas) is also increased.

Germline mutations in either the *SMAD4* or *BMPR1A* genes may result in JPS. Approximately 28 percent of individuals with JPS have *SMAD4* gene mutations, while 24 percent of individuals with JPS have *BMPR1A* mutations.

Germline mutations in the *PTEN* gene can also be associated with hamartomatous polyposis, resulting in several distinct conditions collectively referred to as *PTEN* hamartoma tumor syndrome (PHTS)

SCREENING

Several tests are available for colorectal cancer screening. The American Cancer Society recommends annual fecal blood stool testing, a sigmoidoscopy every five years, and a colonoscopy every 10 years.

Septin 9 is a biomarker for the presence of colorectal cancer indicated for individuals over the age of 50 who have an average risk and no family history of colorectal cancer.

LABORATORY TESTING

Molecular Testing

- MSI testing with reflex to additional tests for suspected Lynch syndrome.

- *KRAS* and *NRAS* mutation testing (if *KRAS* or *NRAS* mutation is positive in codons 12, 13, or 61, patients may have an inhibited response to anti-EGFR therapy).

Genetic

- *APC* sequencing and deletion/duplication, and targeted *MUTYH* mutation analysis for FAP/polyposis.

- Sequencing and deletion/duplication of *MSH2*, *MLH1*, *MSH6*, and *PMS2* for Lynch syndrome.

- Juvenile polyposis (*SMAD4*) sequencing and deletion/duplication.

- Juvenile polyposis (*BMR1A*) sequencing and deletion/duplication.

- *PTEN*-related disorders sequencing and deletion/duplication.

Histology

- Tissue is gold standard for tumor type diagnosis and further testing *(MSI, KRAS, NRAS,* and *BRAF)*.

- Immunohistochemistry—potential stains for further diagnosis include CDX2, CEA monoclonal, CEA polyclonal, CK 20, Muc-2, Muc-4, and p21 (Waf1/Cip 1).

REFERENCES

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NOTES

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