

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

American Gastroenterological Association Medical Position Statement: Hereditary Colorectal Cancer and Genetic Testing

This document presents the official recommendations of the American Gastroenterological Association (AGA) on Hereditary Colorectal Cancer and Genetic Testing. It was approved by the Clinical Practice and Practice Economics Committee on March 20, 2001, and the AGA Governing Board on April 18, 2001.

The following guidelines were developed to assist the primary care physician, internist, surgeon, and gastroenterologist with the appropriate provision of genetic testing for hereditary colorectal cancer. Hereditary colorectal cancer refers to familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), the 2 best described hereditary syndromes for which genetic testing is clinically available.

The integration of genetic testing into clinical practice provides multiple benefits to individuals in families with histories of colorectal cancer. These benefits include earlier detection of colorectal neoplasm and prevention of cancer, removal of patient uncertainty, greater choice of surgical and other intervention options, elimination of unnecessary screening, and provision of information for planning family and career decisions. In hereditary colorectal cancer, genetic testing has been shown to be cost-effective. Finally, past experience of health care providers in offering genetic testing has shown a need for greater education and guidelines.

Genetic Testing Recommendations

FAP

Indications. FAP is caused by mutation of the adenomatous polyposis coli (APC) gene. Genetic testing for APC gene mutation should be used to screen for FAP. APC gene testing is indicated to confirm the diagnosis of FAP, provide presymptomatic testing for at-risk members (first degree relatives 10 years or older of an affected patient), confirm the diagnosis of attenuated FAP in those with ≥ 20 adenomas, and test those 10 years or older at risk for attenuated FAP (Figure 1).

Appropriate strategy. Genetic testing of both affected and at-risk individuals requires pretest genetic counseling and written informed consent. Germline testing should first be performed on an affected member of the family to establish a detectable mutation in the pedigree, usually by protein truncation testing. If a mutation is found in an affected family member, then

genetic testing of at-risk members will provide true positive or negative results. Appropriate screening strategies can then be undertaken based on the at-risk person's gene test result. If a pedigree mutation is not identified, further testing of at-risk relatives should be suspended because the gene test will not be conclusive: a negative result could be a false negative because the protein truncation testing is not capable of detecting a mutation even if present. When an affected family member is not available for evaluation, starting the test process with at-risk family members can provide only positive or inconclusive results. In this circumstance, a true negative test result for an at-risk individual can only be obtained if another at-risk family member tests positive for a mutation.

HNPCC

Indications. HNPCC is caused by germline mutation of the DNA mismatch repair genes (hMLH1, hMSH2, hPMS1, hPMS2, hMSH6). Microsatellite instability (MSI) is found in the colorectal cancer DNA (but not in the adjacent normal colorectal mucosa) of most individuals with germline mismatch repair gene mutations. Medical benefit of genetic testing in HNPCC, including MSI, is presumed but has not been established. Genetic testing in HNPCC is indicated for affected individuals in families meeting Amsterdam criteria (Table 2 of Technical Review),¹ affected individuals meeting Bethesda criteria modified (Table 3 of Technical Review), and first degree adult relatives of those with known mutation (Figure 2).

Appropriate strategy. Genetic testing of both affected and at-risk individuals requires pretest genetic counseling and written informed consent. In combination with immunohistochemistry for hMSH2 and hMLH1, MSI testing using the Bethesda markers should be performed on the tumor tissue of individuals putatively affected with HNPCC. A result of MSI-high in tumor DNA usually leads to consideration of germline testing by sequencing, confirmational sensitive gel elec-

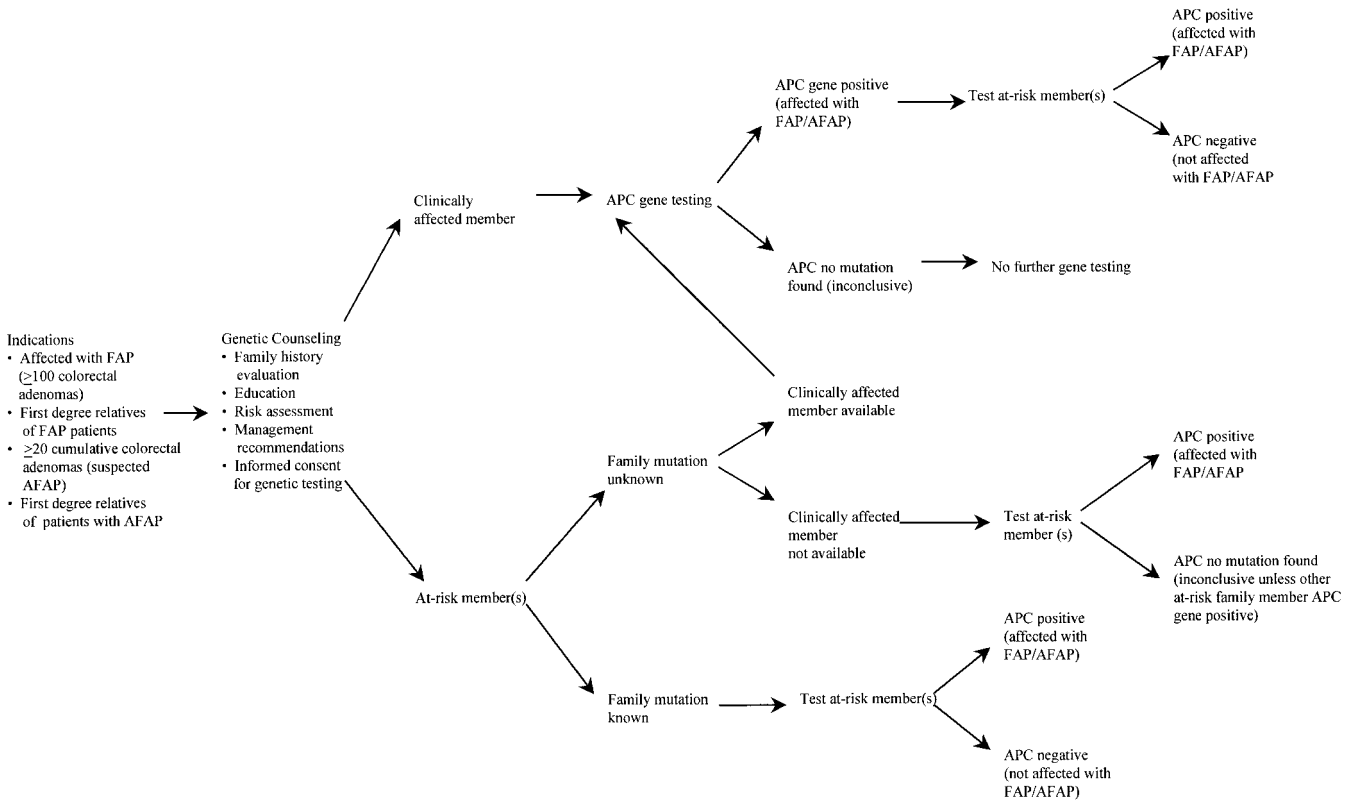
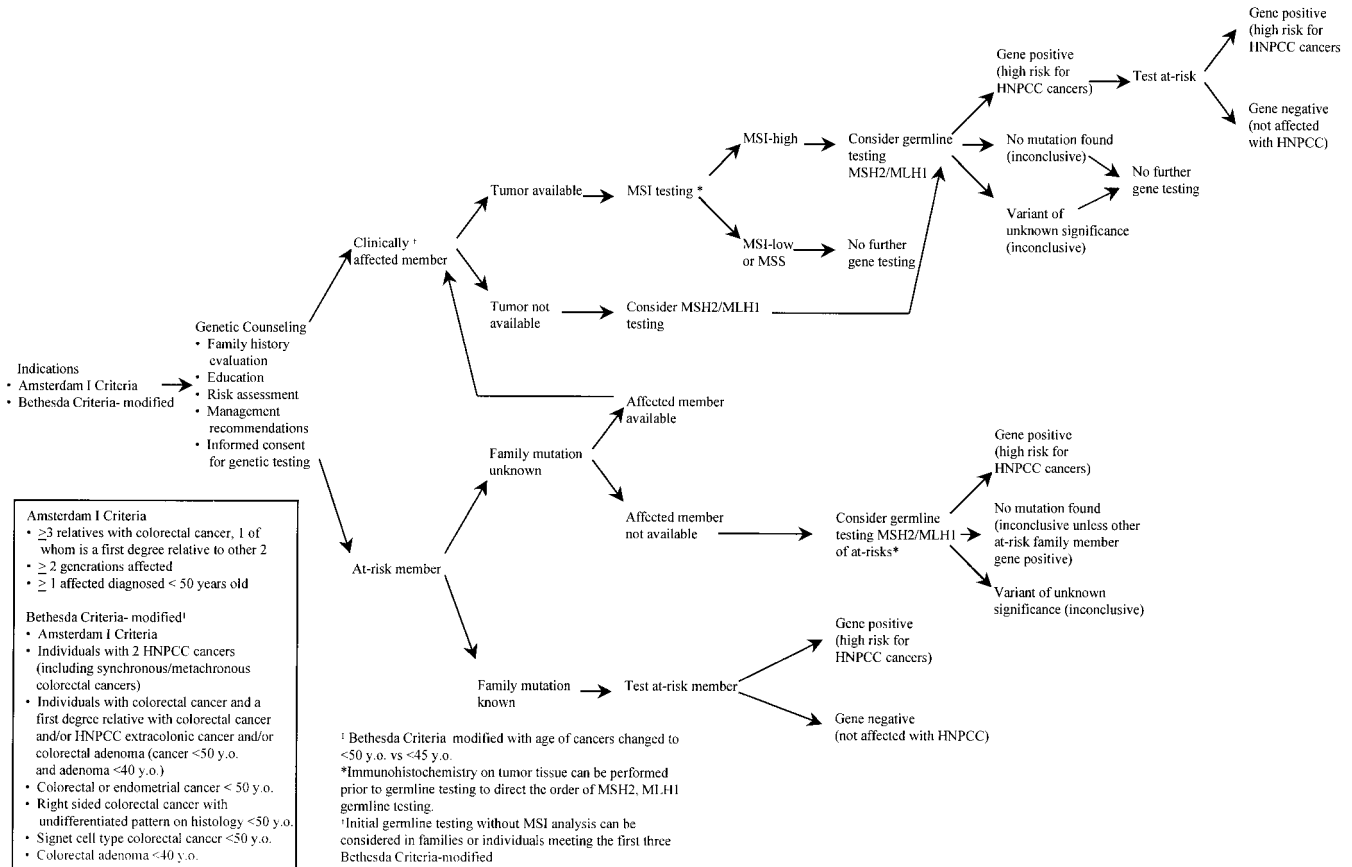


Figure 1. FAP gene testing.



Amsterdam I Criteria

- ≥3 relatives with colorectal cancer, 1 of whom is a first degree relative to other 2
- ≥ 2 generations affected
- ≥ 1 affected diagnosed < 50 years old

Bethesda Criteria- modified†

- Amsterdam I Criteria
- Individuals with 2 HNPCC cancers (including synchronous/metachronous colorectal cancers)
- Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC extracolonic cancer and/or colorectal adenoma (cancer <50 y.o. and adenoma <40 y.o.)
- Colorectal or endometrial cancer < 50 y.o.
- Right sided colorectal cancer with undifferentiated pattern on histology <50 y.o.
- Signet cell type colorectal cancer <50 y.o.
- Colorectal adenoma <40 y.o.

† Bethesda Criteria modified with age of cancers changed to <50 y.o. vs <45 y.o.
 *Immunohistochemistry on tumor tissue can be performed prior to germline testing to direct the order of MSH2, MLH1 germline testing.
 †Initial germline testing without MSI analysis can be considered in families or individuals meeting the first three Bethesda Criteria-modified

Figure 2. HNPCC gene testing.

trophoresis (CSGE), or single-strand conformation polymorphism (SSCP) for mutations in the hMSH2 and hMLH1 genes. Immunohistochemistry may direct which gene (hMSH2 or hMLH1) to target for germline analysis. If a deleterious mutation is found in an affected family member, then genetic testing in at-risk members will provide true positive or negative results. If no deleterious mutation is found in the affected person, only inconclusive results can be given to at-risk members as described above for FAP. Individuals with MSI-low or microsatellite stable (MSS) results are unlikely to harbor mismatch repair gene mutations, and further genetic testing is usually not pursued. If MSI testing is not possible in the affected individual or the family/individual meets any of the first 3 conditions of the Bethesda criteria modified, consideration could be given to initial germline testing in the affected person. Similarly, when an affected family member is not available for evaluation, starting the testing process with at-risk family members can provide only positive or inconclusive results. In this situation, true

negative test results can only be obtained if another at-risk family member tests positive for a mutation. This strategy is not preferred because of the high likelihood of an inconclusive test result.

References

1. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001;121:198-213.

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