



Complete Summary

GUIDELINE TITLE

American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing.

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001 Jul; 121(1): 195-7. [1 reference]

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SCOPE

DISEASE/CONDITION(S)

Hereditary colorectal cancer, including:

- Familial adenomatous polyposis (FAP)
- Hereditary nonpolyposis colorectal cancer (HNPCC)

GUIDELINE CATEGORY

Diagnosis
Prevention
Risk Assessment
Screening

CLINICAL SPECIALTY

Colon and Rectal Surgery
Family Practice
Gastroenterology

Internal Medicine
Medical Genetics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assist the primary care physician, internist, surgeon, and gastroenterologist with the appropriate provision of genetic testing for hereditary colorectal cancer

TARGET POPULATION

Individuals with a family history and familial aggregation of colorectal cancer consistent with autosomal inheritance and their families

INTERVENTIONS AND PRACTICES CONSIDERED

Genetic testing for familial adenomatous polyposis

1. Pretest genetic counseling and written informed consent of affected and at-risk individuals
2. Germline testing on affected family member to establish detectable adenomatous polyposis coli (APC) gene mutation in the pedigree, usually by protein truncation testing
3. Genetic testing of at-risk family members, using one of the following tests:
 - Linkage analysis
 - Single-strand conformation polymorphism testing (SSCP)
 - Protein truncation testing (PTT)
 - Conversion with protein truncation testing
 - Denaturing gradient gel electrophoresis

Genetic testing for hereditary nonpolyposis colorectal cancer

1. Pretest genetic counseling and written informed consent of affected and at-risk individuals
2. Microsatellite instability testing (MSI) using Bethesda markers on tumor tissues of affected individual
3. Mismatch repair gene testing (MMR) for hMLH1 and hMSH2 genes
4. Germline testing by sequencing, confirmational sensitive gel electrophoresis, or single-strand conformation polymorphism for mutation in the hMSH2 and hMHL1 genes

MAJOR OUTCOMES CONSIDERED

- Sensitivity/accuracy of genetic test
- Risk of developing hereditary colorectal cancer

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A systematic computer-aided search of MEDLINE and Current Contents from January 1966 to December 1999 was performed focusing on the major hereditary colorectal cancer syndromes and associated reports of genetic testing. The search identified all literature under the medical subject headings and text words, "familial adenomatous polyposis", "adenomatous polyposis", "adenomatous polyposis coli", "familial polyposis coli", "hereditary nonpolyposis colorectal syndrome", "HNPCC", "Lynch syndrome", and "gene/genetic testing". In addition, an extensive manual search was conducted using references from all retrieved reports, review articles, and chapters from gastroenterology textbooks. Data concerning availability and costs of genetic tests were collected by a search of GeneTests, and by telephone survey of specific laboratories. Publications and other information were retrieved, and the authors synthesized and assessed the quality of the available data with respect to topicality and currency. Differences among reviewers concerning inclusion were resolved by consensus. Editorials and letters to the editor were excluded from this review.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This document was approved by the Clinical Practice and Practice Economics Committee on March 20, 2001 and by the American Gastroenterological Association Governing Board on April 18, 2001.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Genetic Testing Recommendations

Familial adenomatous polyposis (FAP)

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

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.

Hereditary nonpolyposis colorectal cancer (HNPCC)

Indications: Hereditary nonpolyposis colorectal cancer (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 hereditary nonpolyposis colorectal cancer, including microsatellite instability, is presumed but has not been established. Genetic testing in hereditary nonpolyposis colorectal cancer is indicated for affected individuals in families meeting Amsterdam criteria (see Table 3 of Technical Review), affected individuals meeting Bethesda criteria modified (see Table 4 of Technical Review), and first degree adult relatives of those with known mutation (see Figure 2 in the original guideline document).

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, microsatellite instability testing using the Bethesda markers should be performed on the tumor tissue of individuals putatively affected with hereditary nonpolyposis colorectal cancer. A result of microsatellite instability-high in tumor DNA usually leads to consideration of germline testing by sequencing, confirmational sensitive gel electrophoresis (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 familial adenomatous polyposis. Individuals with microsatellite instability-low or microsatellite stable (MSS) results are unlikely to harbor mismatch repair gene mutations, and further genetic testing is usually not pursued. If microsatellite instability 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.

CLINICAL ALGORITHM(S)

Algorithms are provided for familial adenomatous polyposis gene testing (Figure 1 in the original guideline document) and hereditary nonpolyposis colorectal cancer gene testing (Figure 2 in the original guideline document).

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

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.

POTENTIAL HARMS

When used inappropriately, genetic testing has the potential to misinform affected patients with false-negative results.

Patients testing positive may face anger and denial about the test result, worry about social stigma, have greater trepidation of surgery or death, have more anxiety about interference with work or school, and fear of loss of insurability. Patients testing negative can develop "survivor guilt", – guilt over escaping an illness that has afflicted other family members.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001 Jul; 121(1):195-7. [1 reference]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Apr 18

GUIDELINE DEVELOPER(S)

American Gastroenterological Association - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association

GUIDELINE COMMITTEE

American Gastroenterological Association Clinical Practice and Practice Economics Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

According to the guideline developer, the Clinical Practice Committee meets 3 times a year to review all American Gastroenterological Association guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

This guideline has been reviewed by the developer and is still considered to be current as of Dec 2001.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [American Gastroenterological Association \(AGA\) Gastroenterology journal Web site](#).

Print copies: Available from American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Francis M. Giardiello; Jill D. Brensinger; and Gloria M Petersen. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology*. 2001 Jul; 121(1):198-213 [174 references].

Electronic copies: Available from the [American Gastroenterological Association \(AGA\) Gastroenterology journal Web site](#).

Print copies: Available from American Gastroenterological Association, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2002. The information was verified by the guideline developer on July 12, 2002.

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