Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

# General

## Guideline Title

Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline.

## Bibliographic Source(s)

Weissman SM, Burt R, Church J, Erdman S, Hampel H, Holter S, Jasperson K, Kalady MF, Haidle JL, Lynch HT, Palaniappan S, Wise PE, Senter L. Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. J Genet Couns. 2012 Aug;21(4):484-93. [56 references] PubMed

## Guideline Status

This is the current release of the guideline.

# Recommendations

## Major Recommendations

- Microsatellite instability (MSI) and immunohistochemistry (IHC) tumor analyses should be performed on cancer of the colon and/or rectum (CRC) or endometrial cancers as the first-line testing strategy for any patient being evaluated for Lynch syndrome (LS) (this includes individuals with CRC or endometrial cancer who meet Amsterdam I or II criteria or Bethesda guidelines).
    - MSI and IHC tumor analyses are highly sensitive and specific approaches to identify patients and families with LS (Palomaki et al., 2009). Figure 1 in the original guideline document outlines the testing schema for individuals where LS is suspected based on personal and/or family history.
    - MLH1 promoter methylation and BRAF V600E mutation testing may help to reduce the number of germline genetic tests needed when IHC reveals absence of MLH1 and PMS2. However, the National Society of Genetic Counselors (NSGC) and the Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA-ICC) did not find enough data to recommend one test over the other or both concomitantly.
    - IHC may occasionally yield atypical results. If IHC reveals absent MLH1 or MSH2 only, consider genetic testing of those genes individually. If IHC reveals loss of more than two mismatch repair (MMR) proteins, consider repeating the IHC analysis. If the results persist or if repeat testing was not performed, consider following the algorithm based on the most likely true results (i.e., if MSH2, MSH6 and MLH1 or PMS2 are all absent, follow the loss of MSH2/MSH6 pathway; if MLH1, PMS2 and MSH6 or MSH2 are all absent, follow the MLH1 and PMS2 pathway). Further, it is worth noting that there is a mononucleotide microsatellite in MSH6 that may cause loss of MSH6 with another MMR germline mutation leading to aberrant IHC staining patterns (Chang et al., 2001; Shia et al., 2009).
    - When MSI testing is stable, but IHC shows absence of one or more MMR proteins, clinical judgment should be used to determine

whether tumor studies should be repeated or germline genetic testing should be pursued.
- MSI testing should include, at a minimum, the five markers included in the National Cancer Institute (NCI) panel (Boland et al., 1998; Umar et al., 2004).
- MSI and IHC should be performed on pretreated specimens.
    - Some data suggest that MSI and IHC (it is possible to get false positive loss of MSH6 expression) results may be affected by neoadjuvant therapy; therefore, if MSI and/or IHC is performed on a treated specimen, results should be interpreted with caution (Bao et al., 2010; Choi et al., 2007).
- MSI and IHC can be technically challenging assays and should be performed in laboratories that have experience with these tests to minimize the possibility of false positive or false negative results (Müller et al., 2004)
- MSI and IHC should be performed, when possible, on an affected relative's tumor when an unaffected patient is being evaluated for LS.
    - On occasion, obtaining a tumor tissue block will require a patient to involve other family members (e.g., when the patient is not the person who has cancer) or their healthcare providers to request tissue for testing. Ascertainment of the tissue should be possible in most cases as many hospitals store tissue blocks for at least 10 years.
    - While we recognize that some third party payers may not cover MSI and/or IHC analyses on the tumor of a patient's family member(s) (e.g., the family member is deceased), in our expert opinion, we deem testing the family member(s)' tumor is justified because: 1) LS is one of a few hereditary cancer syndromes that has a validated screening test to determine if germline genetic testing is warranted; 2) if an affected family member is living, it is likely that MSI and IHC will be covered by that relative's insurance; 3) a negative germline genetic test for all four MMR genes in an unaffected patient is uninformative; 4) the cost of direct germline genetic testing for each MMR gene ranges from $1000 to $1500, whereas the cost of MSI and IHC together is ~$1000; 5) if IHC is abnormal, additional tumor tests (*BRAF* and *MLH1* promoter methylation) may help determine if germline genetic testing is necessary and if it is warranted, testing can be targeted to one or two genes limiting overall costs; and 6) normal MSI and IHC results on an affected individual would significantly lower the likelihood that LS is the explanation for the cancer in the family and germline genetic testing would most likely not be needed.
- Direct germline genetic testing (refers to both deoxyribonucleic acid (DNA) sequencing and a technology that detects large rearrangements, insertions, deletions and duplications) may be considered on an affected or unaffected patient being evaluated for LS when MSI and IHC testing are not feasible.
    - In the event that a tumor block is not available, a family member(s) is not willing or able to participate in testing, there are financial concerns or there is insufficient tissue to do either MSI or IHC testing, when indicated (e.g., high familial risk is present such as Amsterdam criteria), direct germline genetic testing may be considered. It should be noted, however, that negative germline testing in an affected individual who has not had MMR IHC can also be uninformative because there are some individuals with unidentifiable MMR gene mutations that would be followed as having LS based on abnormal IHC.

## Clinical Algorithm(s)

A clinical algorithm for Lynch syndrome evaluations and testing is provided in the original guideline document.

# Scope

## Disease/Condition(s)

Lynch syndrome

## Guideline Category

Counseling

Diagnosis

Evaluation

Prevention

Risk Assessment

## Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Medical Genetics

Obstetrics and Gynecology

Oncology

Preventive Medicine

Surgery

## Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

## Guideline Objective(s)

To provide guidance and a testing algorithm for Lynch syndrome as well as recommendations on when to offer testing

## Target Population

Individuals who have or may be at risk of developing Lynch syndrome

## Interventions and Practices Considered

1. Tumor analysis on colorectal cancer or endometrial cancers
    - Microsatellite instability (MSI)
    - Immunohistochemistry (IHC)
2. MSI and IHC of affected relative's tumor
3. Direct germ line genetic testing

## Major Outcomes Considered

Sensitivity and specificity of genetic and immunohistochemical testing

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The guideline authors searched via MEDLINE/PubMed for articles from the time period of 1991 to the present. The search terms used were: Lynch syndrome, HNPCC, colon neoplasms, microsatellite instability, immunohistochemistry, MMR genes, endometrial neoplasms, BRAF, MLH1 methylation, MLH1, MSH2, MSH6, and PMS2.

## 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

Review

## Description of the Methods Used to Analyze the Evidence

Expert consensus review of relevant medical literature

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Not stated

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

Published cost analyses were reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Not stated

# Evidence Supporting the Recommendations

## References Supporting the Recommendations


Bao F, Panarelli NC, Rennert H, Sherr DL, Yantiss RK. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. Am J Surg Pathol. 2010 Dec;34(12):1798-804. PubMed

Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57. [119 references] PubMed

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Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009 Jan;11(1):42-65. [133 references] PubMed

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Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004 Feb 18;96(4):261-8. PubMed


## 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

Appropriate use of risk assessment, counseling, and testing for Lynch syndrome

## Potential Harms

- Genetic cancer risk assessment is an important component of a Lynch syndrome evaluation given that testing can be complex, tumor and molecular results may not be straightforward, and psychosocial issues may arise all of which necessitate involvement of a specialized genetics professional.
- False positive and false negative test results

# Qualifying Statements

## Qualifying Statements

- The guidelines outlined herein are intended only to provide guidance for performing a genetic evaluation for Lynch syndrome (LS). The guidelines were not developed to replace a thorough cancer risk assessment by a qualified genetics professional. Genetic cancer risk assessment is an important component of a LS evaluation given that testing can be complex, tumor and molecular results may not be straightforward, and psychosocial issues may arise all of which necessitate involvement of a specialized genetics professional. As the field of genetics is rapidly evolving, it is critical that all healthcare professionals who evaluate patients for LS remain current on advances in this constantly changing field.
- This practice guideline was developed by members of the National Society of Genetic Counselors (NSGC) and Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA-ICC) to assist genetic counselors and other health care providers in making decisions about appropriate management of genetic concerns; including access to and/or delivery of services. This practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable. As such, information and recommendations within this joint NSGC and CGA-ICC practice guideline reflect scientific and clinical knowledge current as of the time of publication, is only current as of its publication date, and is subject to change without notice as advances emerge.
- In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome. Genetic counseling practice guidelines are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient or patient population. This practice guideline is published by NSGC and CGA-ICC for educational and informational purposes only, and neither NSGC nor CGA-ICC "approves" or "endorses" any specific methods, practices, or sources of information contained herein.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Living with Illness

Staying Healthy

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Weissman SM, Burt R, Church J, Erdman S, Hampel H, Holter S, Jasperson K, Kalady MF, Haidle JL, Lynch HT, Palaniappan S, Wise PE, Senter L. Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. J Genet Couns. 2012 Aug;21(4):484-93. [56 references] PubMed

## Adaptation

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

## Date Released

2012 Aug

## Guideline Developer(s)

Collaborative Group of the Americas on Inherited Colorectal Cancer - Disease Specific Society

National Society of Genetic Counselors - Medical Specialty Society

## Source(s) of Funding

National Society of Genetic Counselors

## Guideline Committee

Not stated

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Not stated

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: Available to subscribers from the Journal of Genetic Counseling Web site .

## Availability of Companion Documents

The following is available:

- Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns 2008 Oct;17(5):424-33. Available to subscribers from the Journal of Genetic Counseling Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on June 29, 2012. The information was verified by the guideline developer on July 16, 2012.

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