Test Specific Guidelines

Lynch Syndrome Tumor Screening - Second-Tier

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Introduction

Lynch syndrome tumor screening with BRAF and MLH1 promoter methylation studies for Lynch syndrome is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
BRAF V600 Targeted Mutation Analysis	81210
MLH1 Promoter Methylation Analysis	81288

What Are BRAF Mutation and MLH1 Promoter Methylation Testing for Lynch Syndrome?

Introduction

Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common known hereditary cause of colon and endometrial cancer.[1-4]

Prevalence

Lynch syndrome affects approximately 1 in 35 individuals with colorectal and endometrial cancer and around 1 in 370 individuals in the general population. Lynch syndrome accounts for 3% of all colorectal and endometrial cancer cases.[1-4]

Symptoms

Lynch syndrome is associated with up to an 80% lifetime risk for colorectal cancer and a 25-60% risk of endometrial cancer, diagnosed at an earlier age than usual age. More recent studies quote the risk for colorectal as up to 61%. The risk

is also increased for small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, bladder, prostate, sebaceous adenoma, and keratoacanthoma tumors.[1,5,6]

Cause

Lynch syndrome is caused by mutations in any one of the following five genes: MLH1, MSH2, MSH6, PMS2, and EPCAM.[5]

Inheritance

Lynch syndrome is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Lynch syndrome mutations inherited in an autosomal recessive manner cause constitutional MMR deficiency syndrome (CMMR-D). Testing for CMMR-D is not addressed in this summary.[5]

Diagnosis

Lynch syndrome is diagnosed with the identification of a pathogenic mutation in MLH1, MSH2, MSH6, PMS2, or EPCAM.[5] To identify individuals in whom genetic testing may be warranted, people suspected to have colorectal or endometrial cancer caused by Lynch syndrome generally have tumor screening studies first.[1,7,8]

Tumors caused by Lynch syndrome often show microsatellite instability (MSI) and absent protein from one or more mismatch repair genes (MLH1, MSH2, MSH6, +/- PMS2) by immunohistochemistry (IHC).[1,5]

If MSI or IHC shows signs of Lynch syndrome, the next step is usually Lynch syndrome genetic testing.[1,2,5]

However, another step may be useful before genetic testing when IHC indicates absent MLH1 protein. Absent MLH1 may be caused by Lynch syndrome, but is also frequently a sporadic finding in colorectal and endometrial cancers. Additional testing can help determine whether MLH1-negative colorectal and endometrial tumors (not other Lynch syndrome-associated tumors) are sporadic or are associated with Lynch syndrome.[1,2,5]

The most common cause of absent MLH1 protein is sporadic methylation of the MLH1 gene, which causes the gene to make no protein.[3]

This MLH1 methylation is often associated with a sporadic mutation in the BRAF gene (in colorectal tumors only; not endometrial).

BRAF is part of a cell signaling pathway that helps control cell growth. About 6-8% of colorectal cancer tumors have a BRAF mutation.[9] A single mutation, called V600E (previously called V599E), accounts for about 90% of these BRAF mutations.[3]

When MLH1 protein is absent and a BRAF mutation is present, the colorectal cancer is rarely caused by Lynch syndrome (i.e., the cancer is usually sporadic).[3]

When MLH1 protein is absent, the tumor is negative for a BRAF V600 codon mutation, and MLH1 promoter methylation is present, the cancer is still generally sporadic. However, other types of mutations (e.g., MLH1 epimutations that cause widespread hypermethylation or MLH1 promoter variants) may cause this result.[1,2]

BRAF gene mutations that are inherited or occur in tumors are relevant to several other diagnoses, including:

Colorectal Cancer Anti-EGFR Therapy Response

Thyroid Cancer Prognosis

Noonan Syndrome

Management

Individuals with Lynch syndrome are managed with more frequent cancer screenings performed at earlier ages. Risk-reducing surgeries are also available.[1]

Test Information

Introduction

Tumor screening for Lynch syndrome may include BRAF mutation analysis +/- MLH1 promoter methylation studies.

BRAF V600 Codon Mutation Analysis or MLH1 Promoter Methylation Status

For Lynch syndrome-related testing, BRAF mutation analysis +/- MLH1 promoter methylation studies are done on colorectal tumor tissue. MLH1 promoter methylation studies (not BRAF) are done on endometrial tumor tissue. Sporadic BRAF mutations do not appear to be responsible for MLH1 methylation in endometrial tumors.[2]

When BRAF is being tested because MLH1 protein was absent on colorectal tumor IHC, most laboratories test only for the BRAF V600 codon mutation. However, some laboratories sequence all or part of the BRAF gene (sometimes for reasons other than Lynch syndrome screening). Targeted mutation analysis is generally less expensive than gene sequencing. Because the V600 codon mutation accounts for most BRAF colorectal cancer mutations, targeted mutation

analysis for this one mutation is sufficient. Results of testing for this single mutation are expected to be reliable.[3]

BRAF mutation analysis and MLH1 promoter methylation studies may be offered as panels or in reflex options. For instance, BRAF mutation analysis may be a reflex test when MLH1 IHC results are abnormal. MLH1 promoter methylation studies may be done as reflex test if BRAF mutation analysis is negative.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to tumor screening with BRAF and MLH1 promoter methylation studies for Lynch syndrome. This section does not address who should have MSI and/or IHC tumor screening for Lynch syndrome at the time of cancer diagnosis.

American Gastroenterology Association

The American Gastroenterology Association (AGA, 2015) suggested “that in patients with colorectal cancer with IHC absent for MLH1, second-stage tumor testing for a BRAF mutation or for hypermethylation of the MLH1 promoter should be performed rather than proceeding directly to germline genetic testing.” [7]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) includes BRAF V600 codon mutation and MLH1 promoter methylation status in their table that outlined “tumor testing results and additional testing strategies.” [1]

For colorectal tumors that show no MLH1 protein by IHC (+/- PMS2 negative), they stated "consider BRAF/methylation studies."

They recommended the following based on the BRAF results:

BRAF V600E Mutation	MLH1 Promoter Methylation	Lynch Syndrome Genetic Testing?
Positive	Not necessary	No

BRAF V600E Mutation	MLH1 Promoter Methylation	Lynch Syndrome Genetic Testing?
Negative	Positive	Most likely a sporadic cancer; genetic testing only if "young age of onset or significant family history; then consider constitutional MLH1 epimutation testing and/or germline MMR [mismatch repair] testing".
Negative	Negative	Pursue MLH1 and/or PMS2 testing.**

Note ** If genetic testing is negative, consider somatic MMR genetic testing.[1] If one somatic mutation only or LOH of one allele only is identified in the tumor, this could mean that the patient has Lynch syndrome due to an unidentifiable germline mutation and these represent the “second hit” in the tumor.

National Society of Genetic Counselors and Collaborative Group of the Americas on Inherited Colorectal Cancer

The National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2012) guidelines stated:[2]

“Both somatic hypermethylation of the MLH1 gene (an epigenetic change) and somatic mutations of the BRAF gene have been described in sporadic CRCs exhibiting MSI and/or loss of expression of MLH1. These somatic events are rarely seen in LS CRCs and therefore may be useful in determining whether a MSI-high CRC is more likely to be sporadic.”

“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, NSGC and the CGAICC did not find enough data to recommend one test over the other or both concomitantly.”

The likelihood of identifying a germline MLH1 with both DNA sequencing and deletion/duplication analysis is approximately 33% when MLH1 +/- PMS2 are absent on IHC and MLH1 promoter hypermethylation is not present.

Criteria

Introduction

Requests for BRAF mutation analysis and MLH1 promoter methylation studies are reviewed using these criteria.

BRAF V600 Codon Mutation Analysis or MLH1 Promoter Methylation Status

Previous Testing:

IHC testing has been performed and indicates a loss of MLH1 protein, AND

Diagnostic Testing for Symptomatic Individuals:

Personal history of colorectal or endometrial** cancer, AND**

Rendering laboratory is a qualified provider of service per the Health Plan policy

**** MLH1 methylation only**

References

Introduction

These references are cited in this guideline.

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