Test Specific Guidelines

Microsatellite Instability and Immunohistochemistry Testing in Cancer

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Introduction

Microsatellite instability and immunohistochemistry testing in cancer 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
Immunohistochemistry Tumor Screening (e.g. MLH1, MSH2, MSH6, PMS2), each additional single antibody stain procedure	88341
Immunohistochemistry Tumor Screening (e.g. MLH1, MSH2, MSH6, PMS2), initial single antibody stain procedure	88342
Microsatellite Instability	81301

What Are Microsatellite Instability and Immunohistochemistry Tests?

Definition

Microsatellite instability (MSI) testing can be accomplished via a number of modalities including: 1) DNA electropherogram which compares normal and tumor tissue to detect size changes within microsatellites (stretches of repetitive DNA), 2) next generation sequencing, which may evaluate microsatellite size distribution using tumor alone (compared to a control population), and 3) immunohistochemistry (IHC), which analyzes whether protein expression of certain genes involved in mismatch repair (MLH1, MSH2, MSH6, and PMS2) is

present or absent via staining of tumor samples.[1] Although these types of changes are identified in many cancer types, they are most commonly seen in tumors associated with Lynch Syndrome.

Lynch Syndrome

Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the most common known hereditary cause of colon and endometrial cancer. It affects approximately 1 in 35 colorectal and endometrial cancer patients and around 1 in 370 individuals in the general population. Lynch syndrome accounts for 3% of all colorectal and endometrial cancer cases.[2-5] Family history alone is unreliable for identifying Lynch syndrome cases.[2,5]

Cancer Risks

Lynch syndrome is associated with a high lifetime risk for colorectal cancer (up to 80%) and endometrial cancer (25-60%), diagnosed at an earlier than usual age. The risk is also increased for small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors.[2,5,6]

Identifying at-risk individuals is necessary for appropriate surveillance and risk reduction.[2,5]

Cause

Lynch syndrome is caused by mutations in the following mismatch repair genes: MLH1, MSH2, MSH6, and PMS2.[5] An additional gene called EPCAM (or TACSTD1) has been found to account for <10% of Lynch syndrome cases.[5]

Inheritance

Lynch syndrome gene mutations are inherited in an autosomal dominant manner. 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).[5,6] If both parents have a mutation in the same Lynch syndrome gene, the risk for a child to have CMMR-D is 1 in 4, or 25%.

Tumor Screening

Individuals with colorectal or endometrial cancer due to Lynch syndrome often have abnormal immunohistochemistry (IHC) and/or microsatellite instability (MSI) results upon tumor testing. These tests have good sensitivity and can identify individuals at sufficient risk for Lynch syndrome to warrant follow-up genetic testing.[2]

Tumor screening is generally offered to those with colorectal or endometrial cancer (see guidelines below).[2,7-9]

Test Information

Introduction

Both IHC and MSI testing evaluate formalin-fixed, paraffin-embedded tumor tissue for evidence of mismatch repair defects. Lynch syndrome is caused by mutations in mismatch repair genes.

No specific tumor screening strategy has been recommended, but studies suggest that both MSI and IHC are cost-effective.[2,3]

MSI and IHC together have better sensitivity for Lynch syndrome than either test alone[5], and may be used simultaneously or sequentially.

Immunohistochemistry

Immunohistochemistry (IHC) can detect the presence or absence of MLH1, MSH2, MSH6, ± PMS2 mismatch repair proteins.[2,6]

Tissue is stained using primary and secondary antibodies. Then a substrate is added. The reaction occurs creating a precipitate that is a visual representation of where the target is bound to the primary antibody.

Most Lynch syndrome-causing mutations result in protein truncation or absent protein expression[8], which leads to abnormal IHC staining. As a result, IHC will detect an estimated 74-94% of underlying Lynch syndrome mutations in colorectal tumors.[3,10] IHC has the distinct benefit of identifying the gene most likely to have a mutation.[5,10] DNA testing can then be targeted to that specific gene.

Microsatellite Instability

Microsatellite Instability (MSI) testing evaluates formalin-fixed, paraffin-embedded tumor tissue for evidence of mismatch repair (MMR) defects. MSI testing can be done on many different cancer types. It is commonly used to screen for Lynch syndrome. Recently, MSI has been identified as a prognostic factor for other cancer types in regards to immune checkpoint inhibitor therapies.[11]

MSI testing may be performed via PCR (polymerase chain reaction) or NGS (next generation sequencing).

PCR: DNA is isolated from the tumor and control tissue followed by amplification of microsatellite sequences. Then capillary electrophoresis is performed and the data is analyzed

NGS: identifies MMR pathway deficiencies by comparing sequencing reads around microsatellite regions in the tumor to a control (or control population)

and/or by counting mutations present in exons that are absent from cancer and population databases.[12,13]

MSI can indicate there is a problem with the mismatch repair (MMR) mechanism. MMR deficiencies can be found through IHC, and abnormal IHC results can be indicative of Lynch syndrome.

Lynch syndrome mutations often cause the size of microsatellites to be unstable.[4] When tumor tissue shows high microsatellite instability (MSI-H), it is indirect evidence of an underlying Lynch syndrome gene mutation. Depending on the panel of MSI markers, 80-91% of MLH1 and MSH2 mutations and 55-77% of MSH6 and PMS2 mutations will be detected by MSI testing.[3]

Guidelines and Evidence

Introduction

This section includes guidelines and evidence pertaining to MSI and IHC testing.

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2015) stated:[14]

"All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency. Analysis may be done by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability (MSI). Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation."

American Gastroenterology Association

The American Gastroenterology Association (AGA, 2015) recommended "testing the tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for microsatellite instability (MSI) to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome".[7]

Evaluation of Genomic Applications in Practice and Prevention Working Group

An evidence-based recommendation from the Centers for Disease Control and Prevention sponsored Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) found sufficient evidence to recommend Lynch syndrome tumor screening to all individuals with newly diagnosed colorectal cancer since morbidity and mortality can be significantly improved for the patient and at-risk relatives through management changes once Lynch syndrome is diagnosed.[3]

Food and Drug Administration

The US Food and Drug Administration (FDA) approved "Keytruda for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs." [15]

MSI and/or IHC testing is also required for prescribing / patient selection per FDA labeling for multiple other cancer types.[16]

Multi-Society Task Force on Colorectal Cancer

The Multi-Society Task Force on Colorectal Cancer (MSTF, 2014) published a consensus statement on genetic evaluation for Lynch syndrome and recommended:[8]

"Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history concerning for LS."

"Analysis can be done by IHC testing for the MLH1 / MSH2 / MSH6 / PMS2 proteins and / or testing for MSI."

"Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation."

The Task Force additionally endorsed utilizing The Colorectal Cancer Risk Assessment Tool to aid in identifying individuals with possible Lynch syndrome.[8,17]

The Multi-Society Task Force on Colorectal Cancer is composed of gastroenterology specialists with a special interest in CRC, representing the following major gastroenterology professional organizations: American College of Gastroenterology, American Gastroenterological Association Institute, and the American Society for Gastrointestinal Endoscopy. Also, experts on LS from academia and private practice were invited authors of this guideline. Representatives of the Collaborative Group of the Americas on Inherited Colorectal Cancer and the American Society of Colon and Rectal Surgeons also reviewed this manuscript. In addition to the Task Force and invited experts, the practice committees and Governing Boards of the American Gastroenterological Association Institute, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy reviewed and approved this document.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2021) published practice guidelines that addressed MSI and IHC tumor screening for Lynch syndrome:[2]

"The panel recommends universal screening of all CRCs and endometrial cancers to maximize sensitivity for identifying individuals with Lynch syndrome (LS) and to simplify care processes."

"The panel also recommends considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis."

"Counseling by an individual with expertise in genetics is not required prior to routine tumor testing. An infrastructure needs to be in place to handle the screening results."

"Abnormal MLH1 IHC should be followed by either germline genetic testing or tumor testing for MLH1 methylation for colorectal or endometrial cancers. Alternatively for colorectal cancers with loss of MLH1 on IHC, the tumor can be tested for a BRAF V600E pathogenic variant. "

"There is a 5%–10% false-negative rate with IHC testing."

“An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.”

“This approach gave a sensitivity of 95.1% (95%CI, 89.8-99.0%) and a specificity of 95.5% (95%CI, 94.7-96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70) recommendations. While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing.”

Individuals meeting revised Bethesda criteria would include:[18]

Colorectal cancer diagnosed before age 50

Presence of synchronous or metachronous colorectal cancer, or colorectal cancer with other Lynch syndrome-associated tumors*, regardless of age

Microsatellite unstable (MSI-H) tumor pathology before age 60 (e.g., tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern, or other reported features)

Colorectal cancer diagnosed in a patient with at least one first-degree relative (parent, sibling, child) with a Lynch syndrome-related tumor*, one of whom was diagnosed before age 50

Colorectal cancer diagnosed in a patient with at least two first- or second-degree relatives with Lynch syndrome-related tumors * at any age

MSI and/or IHC testing is also recommended by NCCN for multiple other cancer types.[19]

Note *** Lynch syndrome-associated tumors include colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain tumors (usually glioblastomas associated with Turcot syndrome variant), sebaceous adenomas, and keratoacanthomas (associated with Muir-Torre syndrome variant).**

National Society of Genetic Counselors

A National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC and CGA-ICC, 2012) Joint Practice Guideline made the following recommendations:[20]

"Microsatellite instability (MSI) and immunohistochemistry (IHC) tumor analyses should be performed on CRC or endometrial cancers as the first-line testing strategy for any patient being evaluated for Lynch syndrome (this includes individuals with CRC or endometrial cancer who meet Amsterdam I or II criteria or Bethesda guidelines)."

"MSI testing should include, at a minimum, the five markers included in the NCI panel."

"MSI and IHC should be performed on pretreated specimens."

"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."

"MSI and IHC should be performed, when possible, on an affected relative's tumor when an unaffected patient is being evaluated for Lynch syndrome."

"Direct germline genetic testing (refers to both 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 Lynch syndrome when MSI and IHC testing are not feasible."

The guideline also noted: "Approximately 25% of individuals with Lynch syndrome are not going to meet Amsterdam or Bethesda criteria so limiting MSI and IHC to individuals who meet these criteria only is inadequate and will miss a large number of individuals with Lynch syndrome."

National Institute for Health Care Excellence

The National Institute for Health Care Excellence (NICE, 2020) published a guideline for individuals with endometrial cancer that stated the following with regard to MSI/IHC testing:[21]

"Offer testing for Lynch syndrome to people who are diagnosed with endometrial cancer. Use immunohistochemistry (IHC) to identify tumours with mismatch repair (MMR) deficiency:

If IHC is abnormal with loss of MLH1, or loss of both MLH1 and PMS2 protein expression, do MLH1 promoter hypermethylation testing of tumour DNA. If MLH1 promoter hypermethylation is not detected, offer germline genetic testing to confirm Lynch syndrome.

If IHC is abnormal with loss of MSH2, MSH6 or isolated PMS2 protein expression, offer germline genetic testing to confirm Lynch syndrome."

Society of Gynecologic Oncology

The Society of Gynecologic Oncology (SGO, 2014) recommended “all women who are diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening. Molecular screening of endometrial cancer for Lynch syndrome is the preferred strategy when resources are available”. Universal molecular tumor testing for either all endometrial cancer or cancers diagnosed at age less than 60, regardless of personal or family cancer history, is a sensitive strategy for identifying women with Lynch syndrome.[22]

Criteria

Introduction

Requests for microsatellite and immunohistochemistry testing in cancer are reviewed using these criteria.

Testing may be considered for individuals who meet ANY of the following criteria:

Member has a tumor type that will benefit from information provided by the requested MSI or IHC test based on at least one of the following:

Member is diagnosed with one of the following cancer types:

colorectal cancer, regardless of age

endometrial cancer, regardless of age

gastric cancer, regardless of age

small bowel adenocarcinoma, regardless of age, OR

Member is diagnosed with another type of cancer, and

NCCN guidelines include MSI testing or IHC testing in the management algorithm for that particular cancer type, and

All other NCCN requirements are met (specific pathology findings, staging, etc.), OR

Treatment with Keytruda is being considered, AND

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

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