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Lynch Syndrome
Updated NCCN Guidelines

Lynch syndrome was formerly known as hereditary nonpolyposis colorectal cancer (HNPCC). It is the most common cause of inherited colorectal cancer (CRC), accounting for about 3% of all CRC cases.[1] It also increases a person's chances of getting some other types of cancer (see Sidebar). It is passed down in an autosomal dominant fashion. A parent carrying a mutated gene has a 50% chance of passing it to his/her child. A child who inherits a mutated gene inherits the syndrome and is at increased risk for cancer.

Updated Screening Guidelines

The National Comprehensive Cancer Network (NCCN) updated the screening guidelines for hereditary CRC in May 2014.[2] Screening for Lynch syndrome used to be recommended only for those at high risk. Now screening can be considered for all patients with CRC. Another change is the addition of mutation testing as a screening option. Before, it was only recommended to confirm the screening tests. This change means that people who don't have available cancer tissue can now be screened. They include at-risk family members and some people with cancer.

Whom to screen

The NCCN guidelines recommend screening[2]:

- All patients with CRC, *or*
- All patients with CRC who were either diagnosed at <70 years of age or are ≥70 and meet any of the revised Bethesda guidelines
- People without CRC who:
  - Have a family history of Lynch syndrome
  - Meet revised Bethesda or Amsterdam criteria
  - Had endometrial cancer diagnosed at <50 years of age
  - Have a ≥5% risk of Lynch syndrome based on a computer model

How to screen

Cancer tissue available

The NCCN guidelines recommend using immunohistochemistry (IHC) and/or microsatellite instability (MSI) testing for screening.[2] Sensitivity can be maximized by using both MSI and IHC.[3]

Cancers caused by Lynch syndrome

People with Lynch syndrome have an increased risk of getting several types of cancer. The cancer often occurs at a younger age than it does in people without the syndrome.

Cancer Type	Cancer Risk (%)[4]
Colorectal	52-82
Endometrial	25-60
Stomach	6-13
Ovarian	4-12
Small bowel	3-6
Sebaceous neoplasm	1-9
Hepatobiliary	1-4
Urinary tract	1-4
Brain/CNS	1-3

CNS, central nervous system

An IHC test can detect lack of protein expression of one or more of the nucleotide mismatch repair (MMR) genes. It uses antibodies to test a sample of tumor tissue for the presence of MMR proteins. If IHC detects loss of an MMR protein (no expression), a test to sequence the related gene is recommended.

The MSI test examines 5 microsatellite regions for changes (instability) in DNA. If DNA from a tumor sample has instability at ≥2 of the 5 regions, the result is MSI-high (MSI-H). In most cases, MSI-H is associated with lack of expression of one or more of the MMR genes. An MSI-H test result should be followed up with mutation testing.

Cancer tissue not available

When there is no tumor tissue, the NCCN recommends mutation testing.[2] Testing all 4 MMR genes and the *EPCAM* gene can be done at once. Or they can be tested one at a time, starting with the one that is mutated most often (see Sidebar). Or if the familial mutation is known, familial mutation testing (see below) can be done.

How the laboratory can help

The laboratory plays a critical role in screening and diagnosing Lynch syndrome. Quest Diagnostics offers:

- MSI testing of cancer tissue
- IHC testing of cancer tissue
- MMR gene mutation testing of blood samples

The presence of a mutation, deletion, or duplication in an MMR gene confirms a diagnosis of Lynch syndrome. A diagnosis puts a patient at increased risk for cancers linked to the syndrome.

Quest Diagnostics offers 2 types of mutation testing:

- Broad sequencing and deletion/duplication testing: used for screening when there is no cancer tissue and used to follow-up abnormal MSI or IHC tests.
- Familial mutation testing: targets only the relevant part of the gene; used when there is a history of Lynch syndrome and the familial mutation is known.

Both types of mutation testing are available for the *MLH1, MSH2* (including *EPCAM*), *MSH6*, and *PMS2* genes.

Contribution of MMR genes to Lynch syndrome

MMR genes include *MLH1, MSH2, MSH6,* and *PMS2*. The percentage of cases of Lynch syndrome due to mutation in these genes is[4]:

- *MLH1:* 50%
- *MSH2:* 40%
- *MSH6:* 7% to 10%
- *PMS2:* <5%

References

1. American Cancer Society. Colorectal cancer facts and figures 2014-2016. cancer.org/acs/groups/content/documents/document/acspc-042280.pdf. Accessed January 27, 2015.
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3. Pino MS, Chung DC. Application of molecular diagnostics for the detection of Lynch syndrome. *Expert Rev Mol Diagn*. 2010;10:651-665.
4. Kohlmann W, Gruber SB. Lynch syndrome. In: Pagan RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews® [Internet]*. Seattle, WA: University of Washington, Seattle; 1993-2015. ncbi.nlm.nih.gov/books/NBK1211/. Accessed January 27, 2015.