

Genomic Testing (Secondary Findings) ACT Sheet *MLH1, MSH2, MSH6, PMS2, EPCAM* Pathogenic Variants Lynch Syndrome (Hereditary Non-polyposis Colon Cancer [HNPCC])

Pathogenic or likely pathogenic variants (mutations) in the *MLH1, MSH2, MSH6, and PMS2* mismatch repair (MMR) genes and *EPCAM*, a gene that can silence the *MSH2* gene, may result in Lynch Syndrome (LS) or Hereditary Non-Polyposis Colon Cancer (HNPCC), a condition predisposing to colorectal cancer (CRC), endometrial cancer, and other cancers.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Inform the individual (or parent/guardian) of the genomic screening result and that there is a high lifetime risk of developing cancer.
- Obtain and review family and medical history. Evaluate the patient.
- Refer to gastroenterologist and gynecologist or gynecological oncologist for surveillance or and risk-reducing surgery discussion for endometrial and ovarian cancers.
- Refer for genetic consultation and counseling.

Clinical Considerations: Cumulative lifetime risk of development of CRC is 30-80%, endometrial cancer is 30-70%, gastric cancer is 1-9%, ovarian cancer is 6-14%, and prostate cancer is 9-30%. Other cancers associated with Lynch syndrome include biliary tract, urinary tract, sebaceous adenocarcinoma, glioblastoma, and possibly breast cancer ((*MSH6* and *PMS2*). Incidence of cancer varies by the gene involved and the sex of the individual. Unless contraindicated, colonoscopy is the recommended intervention for surveillance of colorectal cancer since it can both identify and remove pre-cancerous polyps. Ongoing management includes frequent colonoscopy (every 1-2 years), which reduces mortality due to CRC. Screening for other associated cancers will be guided by the gene involved. Carriers of an *EPCAM* deletion have a lower risk of endometrial cancer than carriers of MMR gene variants.

Prevalence: About 1 in 400 in the general U.S. population.

Mode of Inheritance: Lynch Syndrome has an autosomal dominant pattern of inheritance. As Lynch Syndrome cancers may develop early in adult life, it is imperative that immediate and extended family members be offered genetic testing. Carriers are at risk for having a child with constitutional mismatch repair deficiency syndrome if their partner is also a carrier.

Additional Information:

[GeneReviews](#)

[Genetics Home Reference](#)

[ClinGen Actionability Report](#)

Referral (local, state, regional and national):

[Testing](#)

[Find Genetic Services](#)

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

LOCAL RESOURCES: Insert local website links

State Resource site *(insert website information)*

Name

URL

Comments

Local Resource Site *(insert local and regional website information)*

Name

URL

Comments

APPENDIX: Resources with Full URL Addresses

Additional Information:

Gene Reviews

<https://www.ncbi.nlm.nih.gov/books/NBK1211/>

Genetics Home Reference

<https://ghr.nlm.nih.gov/condition/lynch-syndrome>

ClinGen Actionability Report

<https://actionability.clinicalgenome.org/ac/Adult/ui/stg2SummaryRpt?doc=AC069>

Referral (local, state, regional and national):

Testing

<https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=MLH1>

Find Genetic Services

<https://clinics.acmg.net>

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