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 yndrome 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 ofcolorectal 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

Medline Plus
ClinGen Actionability Report

Referral (local, state, regional and national):

Testing
Find Genetic Services

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

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/

Medline Plus
https://medlineplus.gov/genetics/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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