ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Lynch Syndrome Panel: Information for Ordering Providers

In general, the lifetime risk to develop colon cancer in Canada is 1 in 16 (6.1%) for men and 1 in 19 (5.3%) for women[1]. Most colon cancers occur sporadically. Approximately 5-10% of colon cancers are related to a hereditary cancer syndrome. Lynch syndrome is a hereditary cancer syndrome which is associated with an increased risk for multiple cancers including colon, ovarian, and uterine. Approximately 2-4%[2] of colon cancers and 2.5% of uterine cancers[2] are due to Lynch syndrome.

Alberta has a universal Lynch syndrome screening program for all patients with a new diagnosis of colorectal cancer, endometrioid or undifferentiated tumor of endometrium and ovary using immunohistochemistry (IHC) analysis of DNA mismatch repair proteins in tumour tissue.

Lynch syndrome can also be diagnosed using the Amsterdam criteria. All the following must be met:

- three or more relatives with a histologically verified Lynch Syndrome-associated cancer, one of whom is a first-degree relative of the other two
- affecting at least two successive generations
- one or more cases diagnosed before the age of 50

Indications for Testing

Testing should be considered in affected individuals who

- meet Amsterdam criteria OR
- have abnormal tumour IHC suggestive of Lynch syndrome
    - When *MLH1* or *MLH1* and *PMS2* are absent:
        - For endometrial cancers, *MLH1* promoter hypermethylation results are required.
        - For colon cancer, *BRAF* and/or *MLH1* promoter hypermethylation results are required.
        - If the *BRAF* V600E mutation or *MLH1* promoter hypermethylation are detected, the cancer is likely sporadic, and germline genetic testing is not indicated. If there is a young age of onset or significant family history, consider a referral to Genetics.

Ordering Privileges

Please refer to the APL Test Directory (http://ahsweb.ca/lab/apl-td-lab-test-directory) for specific ordering restrictions.

Lynch Syndrome NGS Panel

This panel includes five genes known to cause Lynch Syndrome: *MLH1*, *MSH2, MSH6*, *PMS2* and *EPCAM*. Analysis of the *EPCAM* gene is limited to large deletions in the 3' end of the gene.

Reflex testing by *MSH2* Multiplex Ligation-dependent Probe Amplification (MLPA) will only be performed if no pathogenic variant is detected and both *MSH2* and *MSH6* was absent by IHC.

Reflex testing for *PMS2* (MLPA for exons 11-15) will only be performed if no pathogenic variant is detected and *PMS2* was absent by IHC. If *PMS2* and *MLH1* were both absent, reflex MLPA will not be performed.

IHC results *must* be noted on the requisition form to ensure appropriate reflex testing is performed.

Associated Disorders[3]

Hereditary cancer predispositions are typically inherited in an autosomal dominant fashion. Some of the genes on these panels are associated with other rare disorders including:

Constitutional mismatch repair deficiency syndrome is a rare autosomal recessive condition that occurs in individuals who have two pathogenic variants in one of the following genes: *EPCAM, MLH1, MSH2, MSH6 or PMS2.* Affected individuals often have onset of colon/intestinal cancer before the age of 20 years and may have a cutaneous phenotype similar to that seen in neurofibromatosis type I.

When can I expect results?
Results may take up to 4 months.

How are results reported?
Results are sent to the ordering provider and available in Netcare and Connect Care.

Contact Information
Genetic Counsellors, Genetics & Genomics
Edmonton: 780-407-1015
Calgary: 403-955-3097

Requisition forms, contact information and other resources can be found at:
http://ahsweb.ca/lab/if-lab-genetics-and-genomics

References

1. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2021. Toronto, ON: Canadian Cancer Society; 2021. Available at: cancer.ca/Canadian-Cancer-Statistics-2021-EN (accessed [2022 September])
2. Bhattacharya P, McHugh TW. Lynch Syndrome. 2022 Jul 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28613748.
3. Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1211/ (accessed [2022 September])