ALBERTA PRECISION LABORATORIES
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Laboratory Bulletin

DATE:	3 October 2023
TO:	All Zones
FROM:	APL Genetics and Genomics, Molecular Genetics (North and South)
RE:	**REVISED - Tumour Testing Results Required for Germline Lynch Syndrome Genetic Testing**

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Key Message

- The bulletin replaces the 12 Dec 2022 bulletin titled "Tumour Testing Results Required for Germline Lynch Syndrome Genetic Testing" and the March 7, 2022, bulletin **"**Lynch Syndrome *MSH2* testing by Multiplex Ligation-dependent Probe Amplification (MLPA)"
- To be eligible for germline genetic testing for Lynch syndrome patients must have tumour testing results suggestive of Lynch syndrome OR meet Amsterdam criteria. Relevant tumour testing results include immunohistochemistry (IHC), MLH1 promoter hypermethylation and BRAF testing. Tumour testing results determine the patient's eligibility for testing and the appropriate testing algorithm. Tumour testing results must be provided on the requisition.

How this will impact you

- Which tumour test results are required?
    - For patients meeting Amsterdam criteria, include tumor testing results if available. If IHC results are not available at the time the test is requested, please provide this information to the laboratory by fax when available. If no IHC results are provided, no MLPA reflex testing will be performed (see below).
    - For patients with ovarian cancer, IHC results are not required.
    - For patients who do not meet Amsterdam criteria and have a personal history of colon cancer or endometrial cancer, IHC results are required.
        - 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.
            - For patients who are <45 years of age with colon or endometrial cancer and normal IHC, consider Microsatellite Instability (MSI) testing. If high microsatellite (MSI-H) instability is detected, the patient is eligible for germline genetic testing. MSI results must be provided on the requisition. Patients with low microsatellite instability (MSI-L) or microsatellite stable (MSS) tumours, are not eligible for germline testing.

- When is reflex testing performed?
- When germline genetic testing does not detect a likely pathogenic or pathogenic variant, IHC results determine whether reflex MLPA testing is indicated.
    - *MSH2* MLPA will be performed when patients have both MSH2 and MSH6 IHC deficiency to rule out the possibility of *MSH2* exon 1-7 inversion, which cannot be detected by our current NGS panel.
    - *PMS2* MLPA will be performed for patients with PMS2 IHC deficiency (**EXCEPTION**: patients with both MLH1 and PMS2 IHC deficiency are not eligible for *PMS2* MLPA).

Action Required

- Include all required clinical information and tumour test results on the requisition as outlined above.
- If above information is not included on the requisition, testing may be cancelled, and sample discarded.
- If tumour testing results are not consistent with Lynch syndrome, testing will be cancelled, and sample discarded.
- For patients with MSH2 IHC deficiency and negative germline testing but without *MSH2* MLPA reflex testing previously done, you may contact the lab to discuss whether *MSH2* MLPA testing is indicated. A new blood sample may be required for this additional testing.

Questions/ Concerns

- Molecular Genetics Laboratory Genetic Counsellors
    - *North* 780-407-1015
    - *South* 403-955-3097

Approved by

- Dr. Dennis Bulman, Medical/Scientific Director, Provincial Genetics and Genomics Program, APL
- Dr. Carolyn O'Hara, Chief Medical Laboratory Officer (Interim), APL

Effective September 1, 2023, APL has become the sole provider of all public lab services in Alberta. As a result, community lab services formally provided by DynaLIFE Medical Labs will become the responsibility of Alberta Precision Labs (APL). This change impacts all zones.