Test Definition: CXCFX

MYD88 Reflex to CXCR4 Mutation Detection, Varies

Overview

Useful For

The prognosis and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Method Name

Only orderable as a reflex. For more information see LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, *MYD88* L265P with Reflex to *CXCR4*, Varies.

Bridged Nucleic Acids (BNA) Clamp Sanger Sequencing/Routine Sanger Sequencing
(BNAClamp is utilized pursuant to a license agreement with BNA Inc.)

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

No additional specimen is required.
Only orderable as a reflex. For more information see LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, *MYD88* L265P with Reflex to *CXCR4*, Varies.

Specimen Minimum Volume

Blood, Bone Marrow: 1 mL
Extracted DNA: 20 mcL with a concentration of at least 10 nanograms per mcL

Reject Due To

Gross hemolysis	OK
B5-fixed tissues Bone marrow biopsies Frozen tissue Methanol	Reject

acetic acid (MAA)-fixed pellets Moderately to severely clotted Paraffin shavings Slides	

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies	10 days	

Clinical & Interpretive

Clinical Information

Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen. It is a B-cell neoplasm that can exhibit excess production of serum IgM symptoms related to hyperviscosity, tissue filtration, and autoimmune-related pathology. *CXCR4* mutations are identified in approximately 30% to 40% of patients with LPL/WM and are almost always in association with *MYD88* L265P, which is highly prevalent in this neoplasm. The status of *CXCR4* muations in the context of *MYD88* L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib. A *MYD88*-L265P/*CXCR4*-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients. A *MYD88*-L265P/*CXCR4*-WT (wildtype) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients. The *MYD88*-WT/*CXCR4*-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a *MYD88*-L265 variant.

Reference Values

Only orderable as a reflex. For more information see LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, *MYD88* L265P with Reflex to *CXCR4*, Varies.

An interpretive report will be provided

Interpretation

Mutation present or not detected; an interpretive report will be issued under LPLFX / Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia, *MYD88* L265P with Reflex to *CXCR4*, Varies.

Cautions

This test is a targeted assay for the C-terminus end of the *CXCR4* gene only. It examines c.898-1059 of the *CXCR4* gene (NCBI NM_003467.2 GRCh37) and does not detect variants outside this region. A 1% analytical sensitivity was established at 50-ng DNA input for the hotspot mutations c.1013C>G/A only, which uses bridged nucleic acids clamped Sanger sequencing, and DNA not meeting established criteria can lead to false-negative results. In the extremely rare event that a rare polymorphism or indel occurs at the Sanger sequencing primer binding sites, in cis with c.1013C>G/A, data can yield a failed result. Routine Sanger sequencing is used to interrogate other mutations in the tested region with a 15% to 20% analytical sensitivity. The analytical sensitivity of the assay can be affected by a variety of factors, including biologic availability (ie, tumor burden), fixation of paraffin-embedded specimens, rare polymorphisms or indels at the primer binding sites, or nonspecific polymerase chain reaction interferences.

Clinical Reference

1. Hunter Z, Xu L, Yang G, et al: The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014 Mar 13;123(11):1637-1646. doi: 10.1182/blood-2013-09-525808
2. Landgren O, Tageja N: MYD88 and beyond: novel opportunities for diagnosis, prognosis and treatment in Waldenstrom's Macroglobulinemia. Leukemia. 2014 Sep;28(9):1799-1803. doi: 10.1038/leu.2014.88
3. Poulain S, Roumier C, Venet-Caillault A, et al: Genomic Landscape of *CXCR4* Mutations in Waldenstrom Macroglobulinemia. Clin Cancer Res. 2016 Mar 15;22(6):1480-1488. doi: 10.1158/1078-0432.CCR-15-0646
4. Roccaro A, Sacco A, Jimenez C, et al: C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood. 2014 Jun 26;123(26):4120-4131. doi: 10.1182/blood-2014-03-564583
5. Schmidt J, Federmann B, Schindler N, et al: MYD88 L265P and CXCR4 mutations in lymphoplasmacytic lymphoma identify cases with high disease activity. Br J Haematol. 2015 Jun;169(6):795-803. doi: 10.1111/bjh.13361
6. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR: Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014 May 1;123(18):2791-2796. doi: 10.1182/blood-2014-01-550905
7. Treon SP, Tripsas CK, Meid K, et al: Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015 Apr 9;372(15):1430-1440. doi: 10.1056/NEJMoa1501548
8. Xu L, Hunter ZR, Tsakmaklis N, et al: Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom Macroglobulinaemia. Br J Haematol. 2016 Mar;172(5):735-744. doi: 10.1111/bjh.13897

Performance

Method Description

The C-terminus end of *CXCR4 (*NM_003467.2, c.898-1059) is amplified from extracted genomic DNA by polymerase chain reaction, followed by Sanger sequencing and capillary electrophoresis analysis. Review of the sequence data is performed using a combination of automated calls and manual inspection.(Unpublished Mayo method)

The hotspot mutations c.1013C>G/A (p.S338X) are examined using bridged nucleic acids clamped Sanger sequencing with an analytic sensitivity of 1%. All other genetic mutations in the test region are examined by routine Sanger sequencing with an analytic sensitivity of 15% to 20%.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
7 to 10 days

Specimen Retention Time
Blood/Bone marrow: 2 weeks; Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81479-Unlisted molecular pathology procedure