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

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

Specimen Minimum Volume

Whole 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	Reject
Bone marrow biopsies	Reject
Frozen tissue	Reject
Methanol acetic acid (MAA)-fixed pellets	Reject

Moderately to severely clotted	Reject
Paraffin shavings	Reject
Slides	Reject

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* mutations 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 biological 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;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;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;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;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;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;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;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;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

Whole 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