Test Definition: CXCFX

CXCR4, Gene Mutation, Reflex

Overview

Useful For

The prognostication and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

Method Name

Only orderable as a reflex. For more information, see LPLFX / Reflexive Testing of *MYD88* and *CXCR4.*

NY State Available

No

Specimen

Specimen Type

Varies

Specimen Required

Only orderable as a reflex. For more information, see LPLFX / Reflexive Testing of *MYD88* and *CXCR4*

Submit only 1 of the following specimens:

Specimen Type: Peripheral blood

Container/Tube: EDTA (lavender top) or ACD solution B (yellow top

Specimen Volume: 3 mL

Specimen Stability: Ambient (preferred)/Refrigerated

Collection Instructions:

1. Invert several times to mix blood

2. Send specimen in original tube

3. Label specimen as blood

Specimen Type: Bone marrow

Container/Tube: EDTA (lavender top) or ACD solution B (yellow top)

Specimen Volume: 2 mL

Specimen Stability: Ambient (preferred)/Refrigerated

Collection Instructions:

1. Invert several times to mix bone marrow

2. Send specimen in original tube

3. Label specimen as bone marrow

Specimen Type: Extracted DNA

Container/Tube: 1.5- to 2-mL tube with indication of volume and concentration of the DNA

Specimen Volume: Entire specimen

Specimen Stability: Frozen (preferred)/Refrigerated/Ambient

Collection Instructions: Label specimen as extracted DNA and list specimen source. Include indication of volume and concentration of the DNA.

Specimen Type: Paraffin-embedded tissue

Container/Tube: Paraffin block

Specimen Stability: Ambient

Specimen Type: Paraffin-embedded bone marrow aspirate clot

Container/Tube: Paraffin block

Specimen Stability: Ambient

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
Other	B5-fixed tissues Bone marrow biopsies, slides, paraffin shavings Methanol acetic acid (MAA)-fixed pellets Frozen tissue Moderately to severely clotted

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies	10 days	

Clinical and Interpretive

Clinical Information

Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma that is 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 immunoglobulin-M symptoms related to hyper viscosity, tissue filtration, and autoimmune-related pathology. *CXCR4* mutations are identified in approximately 30% to 40% of 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 (wild type) 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, and 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 mutation. This test is used to aid in the prognostication and therapeutic management of LPL/WM.

Reference Values

Only orderable as a reflex. For more information, see LPLFX / Reflexive Testing of *MYD88* and *CXCR4*

An interpretive report will be provided

Interpretation

Mutations detected or not detected. An interpretive report will be issued under the LPLFX / Reflexive Testing of *MYD88* and *CXCR4*.

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 (BNA) clamped Sanger sequencing and DNA that does not meet the established criteria can lead to false-negative results. In the extremely rare event that a rare polymorphism or indel may occur at the Sanger sequencing primer binding sites, in cis, with a 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 PCR 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

2. Landgren O, Tageja N: MYD88 and beyond: novel opportunities for diagnosis, prognosis and treatment in Waldenstromâ€™s Macroglobulinemia. Leukemia 2014 Sep;28(9):1799-1803

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

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

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

6. Treon SP, Cao Y, Xu L, et al: 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

7. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstromâ€™s macroglobulinemia. N Engl J Med 2015 Apr 9;372(15):1430-1440

8. Xu L, Hunter ZR, Tsakmaklis N, et al: 2016. Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom Macroglobulinaemia. Br J Haematol 2016 Mar;172(5):735-744

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 (BNA) clamped Sanger sequencing with an analytic sensitivity of 1%. All other genetic variants in the test region are examined by routine Sanger sequencing with an analytic sensitivity of 15% to 20%.

PDF Report

No

Day(s) and Time(s) Test Performed

Monday through Friday

Analytic Time

7 days

Specimen Retention Time

DNA 3 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81479-Unlisted molecular pathology procedure