MAYO CLINIC LABORATORIES

Test Definition: PCPRO

Plasma Cell Proliferation, Marrow

Overview

Useful For

Establishing a diagnosis of a plasma cell proliferative disorder
Providing prognostic information for newly diagnosed multiple myeloma and other plasma cell proliferative disorders
Assessing response to therapy and detecting disease relapse and progression in treated plasma cell proliferative disorder patients
Determining plasma cell DNA content and proliferation

Additional Tests

Test Id	Reporting Name	Available Separately	Always Performed
FCINT	Flow Cytometry Interp, 2-8 Markers	No	Yes

Testing Algorithm

When this test is ordered, flow cytometry interpretation will always be performed at an additional charge.
The following algorithms are available in Special Instructions:
-Laboratory Approach to the Diagnosis of Amyloidosis
-Laboratory Screening Tests for Suspected Multiple Myeloma

Special Instructions

- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

Method Name

Flow Cytometry/DNA Content/Cell Cycle Analysis

NY State Available

Yes

Specimen

Specimen Type

Bone Marrow

Ordering Guidance

This test can be ordered at diagnosis or follow-up of a plasma cell neoplasm (plasma cell proliferative disorder).
If CSMRT / mSMART Plasma Cell Proliferative Disorder, Pre-Analysis Cell Sorting, Bone Marrow or MPCDS / mSMART, Plasma Cell Proliferative Disorder, FISH, Bone Marrow is desired to be performed at Mayo, order MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report, Bone Marrow.
The Laboratory Screening Tests for Suspected Multiple Myeloma algorithm will allow plasma cell fluorescence in situ hybridization (FISH) testing to be added, based on this test's flow cytometry results.

Necessary Information

1. Include patient's disease state (untreated, treated, monoclonal gammopathy of undetermined significance, stable).

2. Indicate if patient is on anti-CD38 therapy.

Specimen Required

Specimen Type: Redirected bone marrow
Preferred: Yellow top (ACD)
Acceptable: Lavender top (EDTA) or green top (heparin)
Specimen Volume: 4 mL
Specimen Stability Information: <72 hours

Forms

If not ordering electronically, complete, print, and send a Hematopathology/Cytogenetics Test Request (T726) with the specimen.

Reject Due To

Gross hemolysis	Reject
Fully clotted	Reject

Specimen Minimum Volume

2 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Bone Marrow	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Plasma cell proliferative disorders are a group of plasma cell derived clonal hematologic neoplasms that exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma (MM), a disease that is often aggressive with poor long-term survival. Detecting plasma cell clonality through demonstrating immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains), supplemented by the plasma cell immunophenotype and DNA index, is an important element in establishing the diagnosis.

It is important to correctly classify patients with plasma cell proliferative disorders as the various disease entities are treated differently. A number of factors are used for this classification including the proportions of clonal bone marrow plasma cells, the DNA index of the clonal plasma cells, and their proliferative activity. The plasma cell DNA index and proliferation assessment by flow cytometry are rapid and reliable. This information can be used to distinguish patients with overt active MM from less aggressive diseases such as MGUS and smoldering MM.

Furthermore, in combination with other laboratory data, the results of these studies can be used as a measure of disease aggressiveness in newly diagnosed MM and also to determine therapeutic efficacy and detect disease relapse in treated MM patients.

The following algorithms are available in Special Instructions:

-Laboratory Approach to the Diagnosis of Amyloidosis

-Laboratory Screening Tests for Suspected Multiple Myeloma

Reference Values

Plasma Cell Clonality:
Normal bone marrow
No monotypic clonal plasma cells detected
DNA Index:
Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05

Interpretation

Plasma Cell Clonality:
Plasma cell populations with a kappa to lambda ratio of either greater than 3.9 or less than 0.5 will be considered either kappa or lambda immunoglobulin light chain restricted (monotypic), respectively. As, in rare instances, immunoglobulin light chain restricted plasma cell populations may be polyclonal at the genetic level, the term monotypic rather than monoclonal plasma cells will be used.
In addition to immunoglobulin light chain expression, other data collected will be used to supplement the detection of abnormal plasma cell populations. In plasma cells, CD19 expression is associated with the presence of benign, polytypic cell populations. Therefore CD19 expression will be used as a secondary element in detecting clonal plasma cells. While loss of plasma cell CD45 expression is associated with neoplasia, CD45 is expressed by both normal and neoplastic plasma cells. Therefore, absence of plasma cell CD45 expression will be used as an aid in detecting abnormal plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population, therefore inclusion of antibodies to this antigen allows for more sensitive detection of both subtypes. In addition, as DNA content will be simultaneously assessed, the detection of plasma cell aneuploidy will also serve as a tool for identifying abnormal plasma cell populations. These additional immunophenotypic tools for identifying abnormal plasma cells will increase the sensitivity of the method beyond examining light chain expression; particularly in biclonal plasma cell proliferative disorders in which there are both kappa and lambda immunoglobulin light chain expressing subsets.
Plasma Cell Proliferation:
The proportion of plasma cells in S-phase will be determined by measuring the proportion of cells with DNA content between the G0/G1 and G2/M peaks. In some instances, plasma cell proliferation will not be able to be determined by this method, including when there are fewer than 300 abnormal plasma cell events and when there are multiple aneuploid plasma cell populations. In newly diagnosed multiple myeloma, a plasma cell S-phase of greater than 2.0%, is associated with a more aggressive disease course; this value is published standard for identifying plasma cell neoplasms with a high proliferative rate, it will be noted in the report if the estimated S-phase exceeds this value.)
DNA Index:
Processed cells are stained with DAPI (4',6-diamidino-2-phenylindole) to determine the DNA index of the abnormal plasma cells. This will be determined by dividing the measured DNA content of the G0/G1 abnormal plasma cells by the DNA content of the normal G0/G1 plasma cells present. For this determination, normal plasma cells are the optimal control cell population due to similarities in nuclear and overall cell size. Plasma cells with a G0/G1 DNA content index of less than 0.95 will be considered hypodiploid (worst prognosis); those with a G0/G1 DNA content index of greater than 1.05 will be considered hyperdiploid (favorable prognosis). Plasma cells with a DNA index of 1.9 to 2.1 will be considered tetraploid (non-favorable prognosis) if a confirmatory G2/M population with a DNA index of 4 is identified. As noted above, since normal plasma cells are neither hyper- nor hypodiploid, DNA index will be used as a supplemental tool in detecting clonal plasma cells.
Percent Polyclonal Plasma Cells in Total Plasma Cells:
It has been shown that higher percent polyclonal plasma cells in total plasma cells can mean longer progression-free

survival, higher response rates, and lower frequency of high-risk cytogenetics abnormalities. Studies have also shown a higher incidence of polytypic plasma cells in monoclonal gammopathy of uncertain significance and smoldering myeloma in comparison to multiple myeloma.

Cautions

In order to provide an adequate specimen, it is important that the marrow specimen be from a "redirect" marrow aspirate. The marrow needle should be redirected so the marrow can be aspirated from a previously unsampled site.

Clinical Reference

1. Aljama MA, Sidiqi MH, Lakshman A, et al: Plasma cell proliferative index is an independent predictor of progression in smoldering multiple myeloma. Blood Adv. 2018;2(22):3149-3154
2. Mellors PW, Binder M, Ketterling RP, et al: Metaphase cytogenetics and plasma cell proliferation index for risk stratification in newly diagnosed multiple myeloma. Blood Adv. 2020 May 26;4(10):2236-2244
3.Palva B, Vidriales MB, Mateo G, et al. The persistence of immunophenotypically normal residual bone marrow plasma cells at diagnosis identifies a good prognostic subgroup of symptomatic multiple myeloma patients. Blood. 2009 Nov 12;114(20):4369-4372
4. Sidana S, Jevremovic D, Ketterling RP, et al: Rapid assessment of hyperdiploidy in plasma cell disorders using a novel multi-parametric flow cytometry method. Am J Hematol. 2019 Apr;94(4):424-430
5. Ghosh T, Gonsalves WI, Jevremovic D, et al: The prognostic significance of polyclonal bone marrow plasma cells in patients with relapsing multiple myeloma. Am J Hematol. 2017 Sep;92(9):E507-E512
6. Gonsalves WI, Buadi FK, Ailawadhi S, et al: Bone marrow transplant. Utilization of hematopoietic stem cell transplantation for the treatment of multiple myeloma: a mayo stratification of myeloma and risk-adapted therapy (msmart) consensus statement. 2019 Mar;54(3):353-367

Performance

Method Description

Flow cytometric immunophenotyping of bone marrow is performed using the following antibodies; CD19, CD38, CD45, CD138, cytoplasmic kappa and lambda immunoglobulin, and DAPI (4',6-diamidino-2-phenylindole). Plasma cell clonality is detected through demonstrating CD38 and CD138 positivity along with immunoglobulin light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains) and abnormality of CD19 and/or CD45 expression. DNA index of clonal plasma cells and their proliferation activity is determined through staining of double-stranded DNA using DAPI. Plasma cells (monoclonal/monotypic and polyclonal/polytypic) are detected by immunoglobulin light chain restriction, surface immunophenotype, and DNA content. If present, the light chain expressed by the monotypic plasma cells is indicated. The percentage of clonal plasma cells estimated by flow cytometry is affected by specimen processing and antigen loss with specimen aging. Manual differential counting remains the accepted standard for determining the bone marrow plasma cell percentage. The percentage of monotypic plasma cells in S-phase of the cell cycle is determined by quantitative DNA analysis. The DNA index is a calculated value. The presence of more than 1 value indicates the presence of cell populations with differing DNA contents within the monotypic plasma cells.(Sidana S, Jevremovic D, Ketterling RP, et al: Rapid assessment of hyperdiploidy in plasma cell disorders using a novel multi-parametric flow cytometry method. Am J Hematol. 2019 Apr;94(4):424-430)

PDF Report

No

Specimen Retention Time

14 days

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

This test was developed using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

88182-Flow cytometry, cell cycle or DNA analysis
88184-Flow cytometry; first cell surface, cytoplasmic or nuclear marker
88185 x 5-Flow cytometry; additional cell surface, cytoplasmic or nuclear marker (each)
88187-Flow cytometry interpretation, 2 to 8 Markers (added as FCINT)