MAYO CLINIC LABORATORIES

Test Definition: DMOGA

Monoclonal Gammopathy, Diagnostic, Serum

Overview

Useful For

Screening and diagnosis of monoclonal gammopathies including analysis of free light chains

Assessing the risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
TMAB	Therapeutic Antibody Administered?	No	Yes
TPE	Total Protein	Yes, (Order TP)	Yes
SPE	Protein Electrophoresis	No	Yes
MPTS	M-protein Isotype MALDI-TOF MS, S	Yes, (Order MALD)	Yes
KFLCS	Kappa Free Light Chain, S	Yes, (Order FLCS)	Yes
LFLCS	Lambda Free Light Chain, S	Yes, (Order FLCS)	Yes
KLRS	Kappa/Lambda FLC Ratio	Yes, (Order FLCS)	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
IFXED	Immunofixation Delta and Epsilon, S	Yes	No

Testing Algorithm

This test includes total protein, serum protein electrophoresis, heavy and light chain typing (kappa and lambda), and quantitation of kappa and lambda free light chains.

If a light chain is identified without a corresponding heavy chain during initial testing, immunofixation with IgD and IgE antisera will be performed at an additional charge.

For more information, see Multiple Myeloma: Laboratory Screening

Special Instructions

- Multiple Myeloma: Laboratory Screening

Method Name

TPE: Colorimetric; Biuret

SPE: Agarose Gel Electrophoresis

MPTS: Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS)

KFLCS, LFLCS: Turbidimetry
KLRS: Calculation
IFXED: Immunofixation

NY State Available
Yes

Specimen

Specimen Type
Serum

Ordering Guidance
To monitor a patient with an established diagnosis of a monoclonal gammopathy, order TMOGA / Monoclonal Gammopathy, Monitoring, Serum.

Specimen Required
Patient Preparation: Fasting (12 hour) preferred but not required
Container/Tube:
Preferred: Serum gel
Acceptable: Red top
Specimen Volume: 2 mL

Forms
If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

Renal Diagnostics Test Request (T830)
Hematopathology/Cytogenetics Test Request (T726)

Specimen Minimum Volume
1.5 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	Reject
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	14 days	
	Frozen	14 days	

	Ambient	72 hours	

Clinical & Interpretive

Clinical Information

Monoclonal proteins are markers of plasma cell proliferative disorders. The International Myeloma Working Group guidelines state that to adequately screen for a monoclonal protein, serum protein electrophoresis (SPE), immunofixation electrophoresis, and a serum free light chain (FLC) analysis should all be used. If amyloidosis is suspected, a 24-hour urine monoclonal protein study should be performed.

The detection of M-proteins by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) has shown to be more analytically and clinically sensitive than immunofixation. In addition, the MALDI-TOF method can detect glycosylated light chains that have been demonstrated to be a risk factor for amyloidosis.

This expanded monoclonal protein testing panel provides the highest diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloidosis and light chain deposition disease; disorders that often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by SPE. The FLC assay is specific for free kappa and lambda light chains and does not recognize light chains bound to intact immunoglobulin.

Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other laboratory and clinical assessments.

If a monoclonal protein pattern is detected by MALDI-TOF MS, immunofixation electrophoresis (IFE), or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by SPE or FLC and, in some instances, by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the monoclonal gammopathy screen provides the information (size of M-spike, monoclonal protein isotype, FLC kappa/lambda ratio) needed for a MGUS progression risk assessment (see Interpretation).

Reference Values

TOTAL PROTEIN:
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.

M-PROTEIN ISOTYPE MALDI-TOF MS
No monoclonal protein detected

M-protein Isotype MALDI-TOF MS Flag
Negative

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Interpretation

Monoclonal Gammopathies:
-A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present.
-A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM).
-A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies.
-A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia.
-An abnormal serum free light chain (FLC) kappa/lambda (K/L) ratio in the presence of a normal MALDI-TOF MS suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine.
-The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine.
-The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, a VISCS / Viscosity, Serum should be tested to rule out hyperviscosity syndrome.

After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be a more useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change.

Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value.

Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS or FLC. Accordingly, a normal serum SPE does not rule out the disease and SPE alone should not be used to screen for the disorder if the clinical suspicion is high.

MGUS Prognosis:
-Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%.
-High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%.

Other Abnormal SPE Findings:
-A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease.
-A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome.
-A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine.
-In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent.
-An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Cautions

Serum protein electrophoresis (SPE) alone is not considered an adequate screen for monoclonal gammopathies.

Very large IgG M-spikes (>4 g/dL) may saturate the protein stain. In these situations, quantitative IgG assays more accurately determine M-spike concentrations for monitoring disease progression or response to therapy.

Although the SPE M-spike is the recommended method of monitoring monoclonal gammopathies, IgA and IgM proteins that are contained in the beta fraction may be more accurately monitored by quantitative immunoglobulins.

Fibrinogen will migrate as a distinct band in the beta-gamma fraction but will be negative on immunofixation electrophoresis.

Hemolysis may augment the beta fraction.

Penicillin may split the albumin band.

Radiographic agents may produce an uninterpretable pattern.

Clinical Reference

1. Rajkumar SV, Kyle RA, Therneau TM, et al: Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106:812-817

2. Katzmann JA, Dispenzieri A, Kyle RA, et al: Elimination of the need for urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays. Mayo Clin Proc. 2006;81(12):1575-1578
3. Mills JR, Kohlhagen MC, Dasari S, et al: Comprehensive assessment of M-proteins using nanobody enrichment coupled to MALDI-TOF mass spectrometry. Clin Chem. 2016;62(10):1334-1344
4. Milani P, Murray DL, Barnidge DR, et al: The utility of MASS-FIX to detect and monitor monoclonal proteins in the clinic. Am J Hematol. 2017;92(8):772-779 doi: 10.1002/ajh.24772

Performance

Method Description

Total Protein:
Divalent copper reacts in alkaline solution with protein peptide bonds to form the characteristic purple-colored biuret complex. Sodium potassium tartrate prevents the precipitation of copper hydroxide and potassium iodide prevents autoreduction of copper. The color intensity is directly proportional to the protein concentration which can be determined photometrically.(Package insert: TP2 cobas. Roche Diagnostics; V 12.0, 11/2019)

Electrophoresis:
Serum proteins are separated in an electric field according to their size, shape, and electric charge. The separation is performed on agarose gels. The proteins are visualized by staining with acid blue and the intensity of staining is quantitated by densitometry. Multiplying by the serum total protein converts the percentage of protein in each fraction into serum concentration.(Instruction manual: Helena SPIFE Touch. Helena Laboratories, Corp; 11/2016; package insert: Helena SPIFE Touch SPE Pro 277. Helena Laboratories, Corp; 06/2018)

M-protein isotype:
M-protein isotype by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed with immunoaffinity purification followed by MALDI-TOF MS analysis. For the immunoaffinity purification, patient serum is applied to 5 separate immunoaffinity resins (CaptureSelect, Life Sciences) specific to immunoglobulin G, A, M, K, and L. Unbound protein is washed away and the isolated immunoglobulins are broken down in to their reduced to separate the heavy and light chains subunits to be analyzed via MALDI-TOF mass spectrometry. The 5 separate spectra from each patient immunopurification are overlaid and investigated for the overabundance of an immunoglobulin and/or immunoglobulin light chain.(Kohlhagen M, Dasari S, Willrich M, et al: Automation and validation of a MALDI-TOF MS (Mass-Fix) replacement of immunofixation electrophoresis in the clinical lab. Clin Chem Lab Med. 2020 Aug 3;59(1):155-163. doi: 10.1515/cclm-2020-0581)

Free Light Chains:
The determination of the soluble antigen concentration by turbidimetric methods involves the reaction with specific antiserum to form insoluble complexes. When light is passed through the suspension formed a portion of the light is transmitted and focused onto a photodiode by an optical lens system. The amount of transmitted light is indirectly proportional to the specific protein concentration in the test sample. Concentrations are automatically calculated by reference to a calibrations curve stored within the instrument.(Package inserts: Optilite Freelite Kappa Free Kit. The Binding Site Group, Ltd; 06/2015; Optilite Freelite Lambda Free Kit. The Binding Site Group, Ltd; 06/2015)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
2 to 5 days

Specimen Retention Time
14 days

Performing Laboratory Location
Rochester

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 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 US Food and Drug Administration.

CPT Code Information
83521 x 2
84155
84165
0077U
86334 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
DMOGA	Monoclonal Gammopathy Diagnostic, S	90992-9

Result ID	Test Result Name	Result LOINC® Value
TPE	Total Protein	2885-2
602837	Albumin	2862-1
602838	Alpha-1 Globulin	2865-4
602839	Alpha-2 Globulin	2868-8

602840	Beta-Globulin	2871-2
602841	Gamma-Globulin	2874-6
602842	A/G Ratio	44429-9
602843	M spike	51435-6
602844	M spike	35559-4
602836	Impression	49296-7
65198	M-protein Isotype MALDI-TOF MS	90990-3
606976	Flag, M-protein Isotype	94400-9
LFLCS	Lambda Free Light Chain, S	33944-0
KLRS	Kappa/Lambda FLC Ratio	48378-4
TMAB	Therapeutic Antibody Administered?	98855-0
KFLCS	Kappa Free Light Chain, S	36916-5