DRAFT Medical Coverage Policy | Mass Spectrometry (MS) Testing in Monoclonal Gammopathy

EFFECTIVE DATE: 10|01|2025
POLICY LAST REVIEWED: 06|04|2025

OVERVIEW

Monoclonal gammopathy (MG) is characterized by the proliferation of a single clone of plasma cells which produces monoclonal immunoglobulin protein (M-protein). The M-protein can be an intact immunoglobulin (i.e., containing both heavy and light chains), only light chains (e.g., AL [light chain] amyloidosis), or rarely of heavy chains only. The prevalence of M-protein is relatively high, being detected in approximately 3% of the general adult population over 50 years old, and in up to 7% of those seeking medical evaluation. MGs represent a spectrum of at least 18 distinct entities, ranging from an asymptomatic limited clonal expansion of plasma cells (e.g., monoclonal gammopathy of undetermined significance (MGUS)), to the potentially life-threatening, such as multiple myeloma (MM) and AL amyloidosis. Therefore, timely diagnosis and treatment to prevent irreversible organ damage is critical. A search for M-protein should be considered in any patient with an elevated total serum protein or otherwise unexplained signs and symptoms suggestive of a plasma cell disorder.

The following test(s) are addressed in this policy:

- M-Protein Detection and Isotyping by MALDI-TOF Mass Spectrometry (Mayo Clinic) – CPT code 0077U

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The use of serum mass spectrometry (MS) in monoclonal gammopathies (MGs), as a potential alternative to serum immunofixation electrophoresis (sIFE), is considered medically necessary for the following conditions when filed with a covered indication (See Coding section for details):

- Diagnosis: Initial detection of M-protein in patients with suspected monoclonal gammopathy (MG) to confirm a serum protein electrophoresis (SPEP) or serum free light-chain (sFLC) abnormality, or
- Monitoring:
    - Discrimination between therapeutic monoclonal antibodies and endogenous M-proteins or
    - Treatment response assessment per guidelines

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI

provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products
Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L**. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory testing benefits/coverage.

BACKGROUND

Monoclonal gammopathy (MG) is characterized by the proliferation of a single clone of plasma cells which produces monoclonal immunoglobulin protein (M-protein). The M-protein can be an intact immunoglobulin (i.e., containing both heavy and light chains), only light chains (e.g., AL [light chain] amyloidosis), or rarely of heavy chains only. The prevalence of M-protein is relatively high, being detected in approximately 3% of the general adult population over 50 years old, and in up to 7% of those seeking medical evaluation. MGs represent a spectrum of at least 18 distinct entities, ranging from an asymptomatic limited clonal expansion of plasma cells (e.g., monoclonal gammopathy of undetermined significance (MGUS)), to the potentially life-threatening, such as multiple myeloma (MM) and AL amyloidosis. Therefore, timely diagnosis and treatment to prevent irreversible organ damage is critical. A search for M-protein should be considered in any patient with an elevated total serum protein or otherwise unexplained signs and symptoms suggestive of a plasma cell disorder.

However, the process for identifying patients with MGs is complex and depends on clinical and diagnostic testing information. Laboratories have developed disparate practices for M-protein detection and quantitative measurement, complicating result harmonization, likely resulting in suboptimal detection of treatable MGs. Currently, suspected MGs are initially detected using a combination of three serum-based diagnostic tests: serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (sIFE), and serum measurement of free light-chain (sFLC). SPEP testing for M-protein began in the 1930s and has since steadily improved in resolution. The M-protein usually presents as a single narrow peak; in contrast, a broad-based band usually suggests a polyclonal increase in immunoglobulins (usually an infectious, inflammatory, or reactive process). The initial SPEP should be performed in combination with sIFE (uses antibodies against heavy and light chain components) both to confirm monoclonality and determine isotype (the heavy and light chain class, e.g., IgG kappa). M-protein isotype has significance for prognosis and risk-stratification (e.g., progression of MGUS to MM). The sFLC assay is an antibody-based system that can detect low concentrations of monoclonal free light chains (i.e., kappa or lambda) in the serum. FLC quantification is the most analytically sensitive blood-based method commercially available to diagnose and monitor patients with MGs and is sometimes the only indication of a MG. Assessing changes in M-protein levels helps track disease progression and response to treatment.

Other emerging laboratory procedures to detect M-proteins include immunosubtraction (ISUB), MS, and heavy/light chain (HLC) isotype quantitative measurement. The MS method combines nanobody enrichment of immunoglobulins with matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDITOF- MS) (also termed MASS-FIX, Mayo Medical Laboratories). The idea behind MS is that molecular mass can be used instead of electrophoretic patterns to identify and quantify the M-protein since each light and heavy chain has a unique amino acid sequence, and thus a unique molecular mass whose increased concentration could be distinguished from the normal polyclonal background. In addition to

detection, MS might be able to isotype the M-protein because each immunoglobulin has a constant region with an amino acid sequence unique to each isotype. The multiple charged light and heavy chain ions are converted to their molecular masses, and reconstructed peak area calculations for light chains are used for quantification. Thus, in theory, the MASS-FIX assay uses the unique molecular mass signatures of the different Ig isotypes to generate mass spectra from which M-proteins could be identified, isotyped, and quantified.

A 2016 validation study found comparable analytic sensitivity of MASS-FIX with SPEP and IFE (10). MASS-FIX detected all M-proteins that were detectable by urine or serum protein electrophoresis. In serial dilution studies, MASS-FIX was more analytically sensitive than IFE (identified an M-protein in a higher percentage of samples at every dilution), and where they agreed provided the same primary isotype information for 98% of serum M-proteins (n = 152) and 95% of urine M-proteins (n = 55). A subsequent prospective study of paired serum and urine samples from 257 patients confirmed comparable sensitivity with serum/urine PEP/IFE and sFLC when serum and urine MASS-FIX results were combined. A more recent study of 226 patients diagnosed with MGUS or related gammopathy, considered negative for MGUS by protein electrophoresis and sFLC assay, found that M-protein could be detected at baseline in only 24 patients (10.6%) by IFE compared with 113 patients (50%) by MADLI-TOF mass spectrometry. IFE cannot distinguish if two bands of the same isotype represent biclonal proteins or M-proteins with some other feature. In a study of 81 serum samples with multiple IFE bands of the same isotype, MASS-FIX was able to characterize them as monoclonal or biclonal. In a study of 127 patient sera with abnormal FLC ratios, 43% of monoclonal proteins were confirmed by IFE, 57% by MALDI-TOF MS without FLC enrichment, and 87% with FLC enrichment MALDI-TOF MS. The authors conclude that FLC immunoenrichment coupled to MALDI-TOF MS enables direct detection of mFLCs, significantly increasing the confirmation of abnormal serum FLC ratios (a more indirect methodology), thus improving verification of disease in patients with light chain plasma cell disorders.

Other areas of potential utility include distinguishing endogenous M-proteins from therapeutic monoclonal antibodies; daratumumab, one therapeutic IgG kappa monoclonal antibody, can cause a false positive interference on both SPEP and sIFE, two assays routinely used to monitor a patient's disease status and response to therapy. A study of 31 patients receiving daratumumab with a history of IgG kappa MG found that MASS-FIX could distinguish daratumumab from M-proteins in 26 out of 31 serum samples (84%) versus 14 out of 31 samples (45%) by sIFE. Another study of 311 AL amyloidosis patients showed that MASS-FIX can distinguish a subset with light chain glycosylation, providing a potential path to earlier AL amyloidosis diagnosis. Automation and integrated software may allow implementation of serum MASS-FIX in a high-throughput clinical laboratory.

Combined use of SPEP, sIFE, and sFLC is effective in the initial assessment of MG and is recommended in the International Myeloma Working Group (IMWG) guideline for the evaluation of MM and related disorders. The Myeloma Canada Research Network Consensus Guidelines Consortium and the European Myeloma Network make similar recommendations.

A just released collaborative guideline from the College of American Pathologists (CAP), the American Association for Clinical Chemistry (AACC), and the American Society for Clinical Pathology (ASCP) recommends that clinicians "should order both SPEP and sFLC for the initial detection of M-protein in all patients with suspected MG" (strong strength of recommendation, evidence strength moderate). To confirm a SPEP abnormality, the guideline recommends a "sIFE or alternative method with similar sensitivity" (strong strength of recommendation, evidence strength moderate). To confirm a sFLC ratio abnormality, the guideline identically recommends a "sIFE or alternative method with similar sensitivity" (conditional recommendation, evidence strength low). That an "alternative method" might include MASS-FIX is supported by the statement that "a new technique involving immunoenrichment followed by matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry (MASS-FIX) has been shown to be a highly sensitive, specific, and cost-effective method comparable to sIFE to detect and identify M-proteins". However, the guidelines specifically recommend against MS for screening.

UpToDate refers to MS for analyzing monoclonal proteins as "investigational" and "not a standard part of the evaluation of M-proteins in most centers," but finds utility in the setting of AL amyloidosis, noting that to distinguish AL amyloidosis from other forms of amyloidosis "MS is the preferred method since immunohistochemistry and immunofluorescence have a greater risk of false positive and false negative results." It is not mentioned for other MGs.

NCCN guidelines also recommend amyloid tissue subtyping with MS in the setting of AL amyloidosis "to confirm that the amyloid deposits are composed of light chains." NCCN recommends MS "only if clinically indicated such as in cases where two potential amyloid precursor proteins are present including patients with monoclonal gammopathies who are African-American or elderly men, or who have dominant peripheral or autonomic neuropathy, family histories of amyloidosis, or coexisting inflammatory disorders." Something similar is noted in the NCCN guideline on Waldenstrom Macroglobulinemia. No mention is made of MS in the NCCN MM guideline.

In summary, the use of MALDI-TOF MS to detect and characterize MGs is a novel application of well-established technology for detection of proteins, now applied to a well-established clinical indication (e.g., detection of M-proteins to characterize MGs). The MASS-FIX assay is a well validated, characterized, and published application of this technology in this context. Therefore, NGS considers serum MS use in MG as a possible alternative to sIFE in confirming a SPEP or sFLC abnormality, largely in concordance with the CAP/AACC/ASCP collaborative guideline. Serum MS may also provide advantages in distinguishing between therapeutic and endogenous M-proteins. While published studies and guidelines on MS primarily focus on initial diagnosis, since sIFE also figures prominently in MG monitoring guidelines, it seems logical to also cover serum MS as a sIFE alternative in that setting. MS for screening for MGs is not covered.

CODING

Medicare Advantage Plans and Commercial Products

The following code(s) are considered medically necessary for Medicare Advantage Plans and Commercial Products when filed with the following ICD-10 CM Diagnosis Codes* listed below:

0077U Immunoglobulin paraprotein (M-protein), qualitative, immunoprecipitation and mass spectrometry, blood or urine, including isotype.

The above CPT code is considered medically necessary when filed with one of the ICD-10 CM Diagnosis Codes included in the attached list below:

***Covered Diagnosis Codes List for Mass Spectrometry Testing in Monoclonal Gammopathy (0077U)**

RELATED POLICIES

Biomarker Testing Mandate
Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

PUBLISHED

Provider Update, January/August 2025
Provider Update, November 2023

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