Medicare Local Coverage Determination Policy

Mass Spectrometry (MS) Testing in Monoclonal Gammopathy (MG)

CPT: 0077U

CMS Policy for Illinois, Minnesota, and Wisconsin

Local policies are determined by the performing test location. This is determined by the state in which your performing laboratory resides and where your testing is commonly performed.

Medically Supportive ICD Codes are listed on subsequent page(s) of this document.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Indications of Coverage

The use of serum mass spectrometry (MS) in monoclonal gammopathies (MGs), as a potential alternative to serum immunofixation electrophoresis (sIFE), may be considered medically necessary for:

1. 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 (1), or
2. Monitoring:
    1. Discrimination between therapeutic monoclonal antibodies and endogenous M-proteins (2), or
    2. Treatment response assessment per guidelines (3-5)

Limitations of Coverage (not covered)

1. Screening
2. Concurrent sIFE testing
3. Urine MS testing

Summary of Evidence

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 (6). 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 (7). 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 (6).

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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 (1). 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) (1,5). 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) (8). 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 (5).

Other emerging laboratory procedures to detect M-proteins include immunosubtraction (ISUB), mass spectrometry (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 (9). 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 (7). 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 (11). 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 (12). 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 (13). 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 (14). 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 (2). 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 (15). Automation and integrated software may allow implementation of serum MASS-FIX in a high-throughput clinical laboratory (16).