# Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3

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**A panel of members of the 2009 International Myeloma Workshop developed guidelines for standard investigative workup of patients with suspected multiple myeloma. Both serum and urine should be assessed for monoclonal protein. Measurement of monoclonal protein both by densitometer tracing and/by nephelometric quantitation is recommended, and immunofixation is required for confirmation. The serum-free light chain assay is recommended in all newly diagnosed patients with plasma cell dyscrasias. Bone marrow aspiration and/or biopsy along with demonstration of clonality of plasma cells are necessary. Serum $\beta_2$-microglobulin, albumin, and lactate dehydrogenase are necessary for prognostic purposes. Standard metaphase cytogenetics and fluorescent in situ hybridization for 17p, t(4;14), and t(14;16) are recommended. The skeletal survey remains the standard method for imaging screening, but magnetic resonance imaging frequently provides valuable diagnostic and prognostic information. Most of these tests are repeated during follow-up or at relapse. (*Blood*. 2011; 117(18):4701-4705)**

## Introduction

The plasma cell proliferative disorders are characterized by the proliferation of a single clone of plasma cells in the bone marrow and by the production of monoclonal immunoglobulins. These disorders may range from a phenotypically benign entity, monoclonal gammopathy of undetermined significance, to symptomatic myeloma with bone destruction, suppression of bone marrow function, and renal damage. The International Myeloma Working Group has established criteria for the diagnosis of plasma cell proliferative disorders. These test criteria have been adopted and/or slightly modified by other groups and are shown in Table 1.[1-3] In everyday practice, there is still some confusion regarding the use of standard laboratory tests that evaluate serum and urine monoclonal proteins. Furthermore, a new test, serum-free light measurement, has emerged. Over the last decade, newer imaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT), are increasingly used in the assessment of patients with multiple myeloma. In this paper, we report International Myeloma Working Group Consensus Panel recommendations for the minimal diagnostic and prognostic tests, the follow-up investigation after therapy, and the tests to be performed at relapse for patients with multiple myeloma. The Consensus Panel consisted of several physicians with a research interest in plasma cell dyscrasias who held several teleconferences, and their recommendations were presented during the 2009 International Myeloma Workshop.

## Minimal diagnostic and prognostic tests

Initial investigation of a patient with suspected multiple myeloma should include the tests shown in Table 2. Family history should focus on first-degree relatives with the diagnosis of hematologic malignancies, especially lymphoma, chronic lymphocytic leukemia, and plasma cell dyscrasias. Past medical history should focus on comorbid conditions that may affect treatment decisions, such as coronary artery disease, congestive heart failure, hypertension, renal disorders, liver disorders, and lung diseases. A complete blood count with differential should be ordered, and a peripheral blood smear should be evaluated in search of specific findings, such as rouleaux formation and circulating plasma cells. A complete biochemistry screen should be ordered, which includes liver function tests, renal function tests, electrolytes, calcium, and albumin.

Both serum and urine should be assessed for monoclonal protein. Agarose gel electrophoresis or capillary zone electrophoresis of serum and urine is preferred to screen for the presence of monoclonal protein. However, quantitation of serum immunoglobulins by nephelometry should also be performed. Measurement of monoclonal protein both by densitometer tracing and by nephelometric quantitation is recommended. These 2 tests are complementary, and nephelometric quantitation may be particularly useful for low levels of uninvolved immunoglobulins.[4] However, it should be

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**Table 1. Diagnostic criteria for plasma cell disorders**

| Disorder/criteria | Comment |
|---|---|
| **Monoclonal gammopathy of undetermined significance** | All 3 criteria must be met |
| Serum monoclonal protein < 3 g/dL | |
| Clonal bone marrow plasma cells < 10% | |
| Absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and bone lesions, which can be attributed to the plasma cell proliferative disorder | |
| **Smoldering multiple myeloma (asymptomatic multiple myeloma)** | Both criteria must be met |
| Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or clonal bone marrow plasma cells ≥ 10% | |
| Absence of end-organ damage, such as lytic bone lesions, anemia, hypercalcemia, or renal failure, which can be attributed to a plasma cell proliferative disorder | |
| **Symptomatic multiple myeloma** | All 3 criteria must be met except as noted |
| Clonal bone marrow plasma cells ≥ 10% | |
| Presence of serum and/or urinary monoclonal protein (except in patients with nonsecretory multiple myeloma)* | |
| Evidence of end-organ damage, which can be attributed to the underlying plasma cell proliferative disorder, specifically | |
| Hypercalcemia: serum calcium ≥ 11.5 mg/dL | |
| Renal insufficiency: serum creatinine > 2 mg/dL | |
| Anemia: normochromic, normocytic with a hemoglobin value of > 2 g/dL below the lower limit of normal, or a hemoglobin value < 10 g/dL | |
| Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures | |

*More than 10% clonal plasma cells are required for the diagnosis of nonsecretory myeloma.

noted that nephelometric quantitation may overestimate the monoclonal protein concentration when its value is high.[5] Serum immunofixation is the "gold standard" method to confirm the presence of a monoclonal protein and to distinguish its heavy and light chain type. Serum immunofixation should also be performed when there is hypogammaglobulinemia (a frequent finding in light chain only myeloma) or even when the serum electrophoretic pattern appears normal if there is a suspicion of multiple myeloma or a related disorder. Low levels of monoclonal proteins may be associated with a normal serum electrophoresis. When a patient has only monoclonal light chain or has a monoclonal serum protein but the immunofixation is negative for IgG, IgA, or IgM, the possibility of IgD or IgE monoclonal immunoglobulin must be considered. If only a monoclonal light chain is found, immunofixation for IgD and IgE should be performed; and if positive for IgD or IgE, then quantitation of these immunoglobulins follows. This approach eliminates the need for quantitation of IgD or IgE in many instances. Immunosubtraction has been used in place of immunofixation electrophoresis but is less sensitive and is being supplanted by immunofixation electrophoresis.

The quantitation of serum albumin is important because albumin is a key component of the currently used International Staging System for multiple myeloma.[6] The most accurate method to measure serum albumin is by nephelometry, but this approach is not widely used. Serum albumin can be measured by densitometry from the electrophoretic strip. However, its value can be affected by the level of the monoclonal protein: high concentrations of monoclonal protein tend to overestimate the concentration of serum albumin.[7] Serum albumin can also be measured with bromcresol, which is the method used in some laboratories when serum albumin is ordered in a chemistry panel. This assay shows good correlation with the "gold standard" nephelometric quantitation and is independent of the monoclonal protein levels. A recent study indicated that all albumin methods perform similarly in predicting survival and may be used in prognostication by the International Staging System.[8]

**Table 2. Laboratory tests for multiple myeloma**

| |
|---|
| History and physical examination |
| Complete blood count and differential; peripheral blood smear |
| Chemistry screen, including calcium and creatinine |
| Serum protein electrophoresis, immunofixation |
| Nephelometric quantification of serum immunoglobulins |
| Routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation |
| Bone marrow aspirate and/or biopsy |
| Cytogenetics (metaphase karyotype and FISH) |
| Radiologic skeletal bone survey, including spine, pelvis, skull, humeri, and femurs; magnetic resonance imaging in certain circumstances |
| Serum $\beta_2$-microglobulin and lactate dehydrogenase |
| Measurement of serum-free light chains |

Routine urinalysis is important in suspected myeloma. For screening, a random urine protein electrophoresis and urine immunofixation may be performed. Once a diagnosis of myeloma is suspected or established, all patients should undergo 24-hour urine collection to calculate the amount of proteinuria. An aliquot from an adequately concentrated 24-hour specimen should be sent for electrophoresis. A monoclonal protein appears as a homogeneous peak in the densitometer tracing. Its concentration can be calculated on the basis of the size of the peak and the amount of total protein in the 24-hour urine specimen. Immunofixation of an aliquot from a concentrated 24-hour urine collection is required to confirm the presence and type of heavy and light chain.[4] Immunofixation should be performed even if there is no measurable protein and even if there is no peak on urine electrophoresis. A 24-hour urine collection cannot be replaced by a morning urine sample. The use of random urine samples with analytes corrected relative to creatinine concentration requires further evaluation but cannot be recommended at this point. Measurement of urine-free light chain levels or urine total κ and total λ levels is not recommended.

Serum-free light chain assay, as it becomes widely available, is recommended in all newly diagnosed patients with plasma cell dyscrasias.[9,10] Measurement of serum-free light chain is very important in patients with nonsecretory multiple myeloma (ie, with negative serum and urine immunofixation) and in patients who secrete small amounts of monoclonal protein in the serum and/or urine (oligosecretory myeloma), as well as in light chain only myeloma.[11] Serum-free light chain estimation does not obviate the need for 24-hour urine studies. Serum-free light chains may be useful in patients with solitary plasmacytoma or with smoldering (asymptomatic) myeloma because an abnormal value may be

associated with a higher risk of progression to symptomatic myeloma.[12,13] Testing for serum-free light chains is also recommended for patients with monoclonal gammopathy of undetermined significance.[14] Urine-free light chain assay should not be performed.

A patient with suspected multiple myeloma should undergo a unilateral bone marrow aspirate and/or biopsy, and the diagnosis is confirmed when more than 10% clonal plasma cells are detected. Whenever possible, CD 138 stains should be used to accurately determine the percentage of plasma cells in bone marrow biopsies. Clonality of plasma cells should be established by identification of a monoclonal immunoglobulin in the cytoplasm of plasma cells by immunoperoxidase staining or by immunofluorescence.[15] Immunophenotyping by flow cytometry is performed by some centers, but this technique may not be widely available and standardized for general use. Furthermore, plasma cell percentage cannot be determined by flow cytometry of the bone marrow aspirate. Although bone marrow aspirate alone may be sufficient to confirm the diagnosis, a trephine biopsy should be considered during the same procedure for the following reasons: (1) it may provide a more reliable assessment of plasma cell infiltration; and (2) it may obviate the need for a repeat procedure should the bone marrow aspirate prove to be inadequate. When both procedures are performed, the highest number of plasma cells obtained by either procedure is recorded for the purpose of diagnosis.[16]

Standard metaphase cytogenetics should be included in the initial assessment of a patient with high suspicion of multiple myeloma. Despite the low yield of this method ($\leq$ 20%), it can provide useful prognostic information by separating hyperdiploid from nonhyperdiploid patients and can capture uncommon additions, deletions, and translocations. Furthermore, patients should undergo fluorescent in situ hybridization (FISH), preferably after sorting of plasma cells with probes that include chromosome 17p13, t(4;14), and t(14;16).[17]

Although some tests are not required for the diagnosis of myeloma, they are important for prognosis or staging. As such, the following tests are recommended: serum $\beta_2$-microglobulin, which reflects tumor burden and forms the basis for the International Staging System; and serum lactate dehydrogenase, which has an independent prognostic significance in several studies.[6,18] Assessment of erythrocyte sedimentation rate does not provide additional information and is not required. Although C-reactive protein is not useful for the risk assessment of myeloma, it may be helpful when an infection is suspected.

The skeletal survey remains the standard method for imaging screening at diagnosis, is readily available at modest cost, allows large areas of the skeleton to be assessed, and may detect long bone lesions at risk of impending fracture. Plain radiographs should include a posteroanterior view of the chest, anteroposterior and lateral views of the cervical, thoracic, and lumbar spine, humeri, and femora, anteroposterior and lateral views of the skull, and anteroposterior view of the pelvis.[15]

Magnetic resonance imaging is a noninvasive technique that provides detailed information about bone marrow involvement, and its pattern (focal, diffuse, or variegated) is useful for the assessment of the extent and nature of soft tissue disease arising from bone lesions, and can detect unsuspected, asymptomatic lesions.[19] An MRI of the spine and pelvis is mandatory in all patients with a presumed diagnosis of solitary plasmacytoma.[20] An MRI should also be considered in patients with smoldering (asymptomatic) myeloma because it can detect occult lesions and, if positive, can predict for more rapid progression to symptomatic myeloma.[21,22] MRI can be considered in patients with symptomatic myeloma as routine evaluation because (1) unsuspected focal lesion and soft tissue plasmacytomas involving the spine and pelvis can be visualized; and (2) patterns of MRI abnormality (ie, diffuse pattern or a high number of focal lesions) may have prognostic significance.[23-25] However, MRI is mandatory in symptomatic patients for a detailed evaluation of a painful area of the skeleton to look for a soft tissue mass arising from a bone lesion or for the investigation of patients with a suspicion of cord compression, providing an accurate assessment of the level and extent of cord or nerve root compression, size of the tumor mass, and degree to which it may affect the epidural space. An MRI of the spine is valuable in defining the etiology of new, painful collapsed vertebra (ie, because of osteoporosis or myelomatous involvement). Osteoporosis with compression fracture requires thorough evaluation with an MRI. If a focal myelomatous lesion is detected, then the patient has symptomatic myeloma, which requires treatment. However, if the fracture is the result of osteoporosis (especially in certain populations, such as elderly white women), then other criteria, such as degree of marrow infiltration and anemia, should be considered to diagnose symptomatic myeloma. Occasionally, an MRI-assisted CT-guided biopsy of the collapsed vertebra is needed to make the diagnosis. Furthermore, an MRI is strongly indicated in patients with nonsecretory myeloma for their initial assessment and follow-up of response to treatment.

The role of PET-CT is yet to be clearly defined in multiple myeloma. It is helpful for detection of extraosseous soft tissue masses and evaluation of rib and appendicular bone lesions. PET-CT is especially useful in patients with elevated lactate dehydrogenase, Bence Jones protein escape, and otherwise rapidly recurrent disease or with suspected extramedullary plasmacytoma. Unlike MRI, PET-CT obviates the need for a skeletal survey.[25,26] A recent study showed an independent predictive value of baseline fluorodeoxyglucose-PET/CT and of fluorodeoxyglucose suppression before high-dose therapy.[27] There is recent evidence that the combination of PET-CT and MRI may improve the diagnostic accuracy of solitary plasmacytoma but is not recommended.[28,29]

Finally, specific tests may be required during the initial assessment of a patient with suspected myeloma. When the degree of anemia is out of proportion of the myeloma tumor load, other coexistent causes need to be looked for, such as iron deficiency and vitamin deficiency. When mild or moderate hypercalcemia is detected and no typical myeloma bone lesions are seen, the possibility of primary hyperparathyroidism should be ruled out with measurement of serum parathyroid hormone. When a patient presents with lytic bone lesions, low levels of monoclonal protein, and less than 10% plasma cells in the bone marrow, the presence of monoclonal gammopathy of undetermined significance, and metastatic carcinoma should be considered, and biopsy of a bone lesion may be indicated. Finally, when there is nonselective proteinuria, unexplained weight loss, low electrocardiogram voltages, and left ventricular hypertrophy on echocardiogram, congestive heart failure, unexplained hepatomegaly, elevated alkaline phosphatase or $\gamma$-glutamyltransferase, symptoms and signs of peripheral or autonomic neuropathy or carpal tunnel syndrome, and the possibility of primary systemic amyloidosis should be considered by specific staining of subcutaneous fat aspirate and bone marrow. Biopsy of a suspected organ may be necessary. In some myeloma patients with diabetes or hypertension who present with nonselective proteinuria associated with mild to moderate but stable renal impairment, a renal biopsy may be indicated to rule out renal lesions related to a plasma cell disorder. Furthermore, nonselective proteinuria without

evidence of amyloidosis in a patient with plasma cell dyscrasia may be secondary to immunoglobulin deposition disease. In such a case, a renal biopsy with appropriate studies is necessary. Routine testing for hyperviscosity is not recommended. The plasma hyperviscosity, as determined by testing, correlates poorly with clinical manifestations of hyperviscosity. Funduscopic examination is more helpful in defining clinically significant hyperviscosity. Hyperviscosity in IgG myeloma is rare unless it is IgG subclass 3. Simple numerical values of test results for hyperviscosity do not warrant clinical intervention with plasmapheresis.

## Follow-up treatment

For patients with measurable monoclonal protein in serum, both electrophoretic studies and quantitative immunoglobulins are recommended to assess response, although electrophoretic measurements to follow monoclonal protein are preferred. For several patients, especially with IgA or IgD myeloma, nephelometric quantitation of serum immunoglobulin is necessary. It is however important for a particular patient to use the same method for the follow-up of his disease. For patients with light chain myeloma, 24-hour urine collection with total protein and urine electrophoresis to quantify Bence Jones proteinuria is recommended. For patients with nonsecretory or oligosecretory myeloma, the free light chains should be serially assessed. For most patients, there is no necessity for bone marrow examination to assess response, provided that the myeloma can be monitored with serum and urine studies and there is no indication to change the patient's treatment. Bone marrow aspiration and/or biopsy are indicated to establish complete response. Complete response has prognostic implications because several studies have indicated that it may predict for longer duration of response and survival. Furthermore, there is no indication to repeat the metaphase karyotype, FISH studies, or flow cytometric studies as a routine follow-up. There is no need to repeat the skeletal survey in a patient who is responding to treatment unless he develops bone symptoms.

## Test to be performed at relapse

Most of the workup recommended at diagnosis is also pertinent at relapse. The prognostic significance of $\beta_2$-microglobulin or International Staging System at relapse is not clear. Elevated serum lactate dehydrogenase is predictive of poor prognosis. A bone marrow aspirate and/or biopsy should be performed if clinically indicated (ie, suspicion of hyposecretory myeloma progression) or when a myelodysplastic syndrome is considered (presence of cytopenias). For patients who had normal results or who did not have cytogenetic or FISH analyses at baseline, these tests should be performed at relapse. However, if a patient already had an identified high-risk feature on cytogenetic or FISH analyses, there is no need to look for it again at relapse. There is evidence that some novel agent-based treatments may be more effective than others in patients with adverse cytogenetic features. A skeletal survey may be indicated to detect possible lesions at risk for fracture. Other imaging studies (CT, MRI, and PET-CT) to detect soft tissue masses arising from bone lesions, or extramedullary disease may be indicated according to clinical circumstances.

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