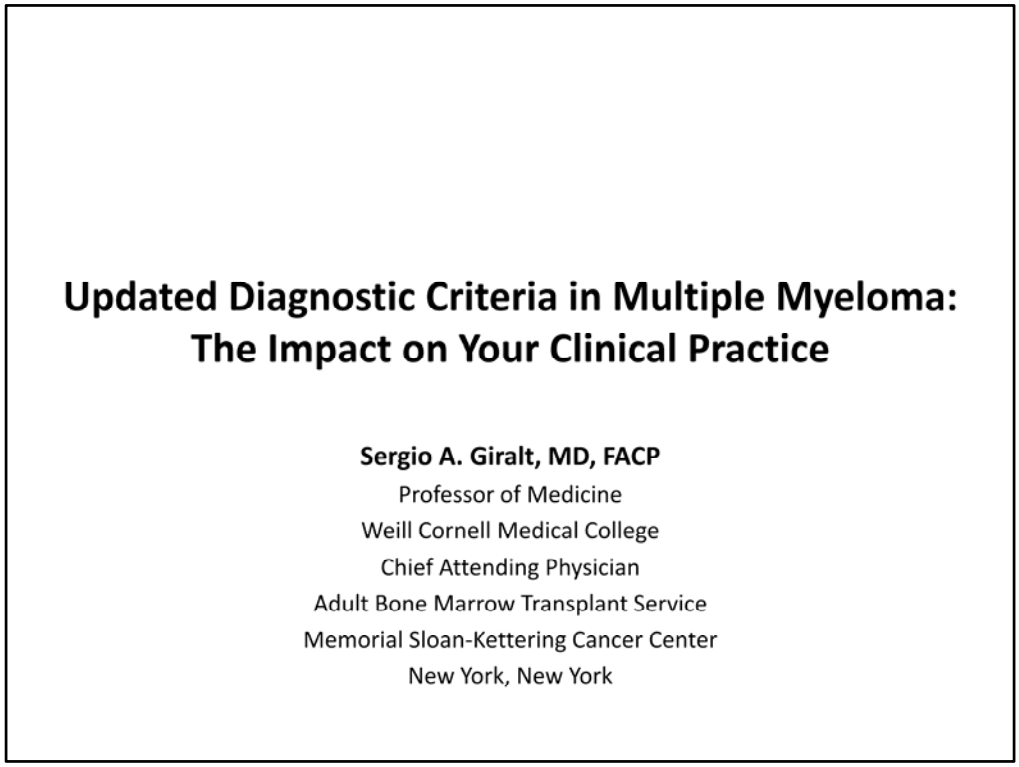
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice



Welcome to *Managing Myeloma*. My name is Sergio Giralt, and I am a professor of medicine at Weill Cornell Medical College. I am the Melvin Berlin Family Chair in Myeloma Research and chief of the Adult BMT Service at Memorial Hospital in New York City. Today, we are going to discuss *Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice.*

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Objectives

- Summarize the recent updates to diagnostic criteria for multiple myeloma
- Compare and contrast updated diagnostic criteria for multiple myeloma with previously utilized standards of diagnosis
- Identify how new diagnostic criteria will impact treatment of patients with active myeloma

Our objectives are to summarize the recent updates to diagnostic criteria for multiple myeloma, compare and contrast updated diagnostic criteria for myeloma with previously utilized standards of diagnosis, and identify how new diagnostic criteria will impact treatment of patients with active myeloma.

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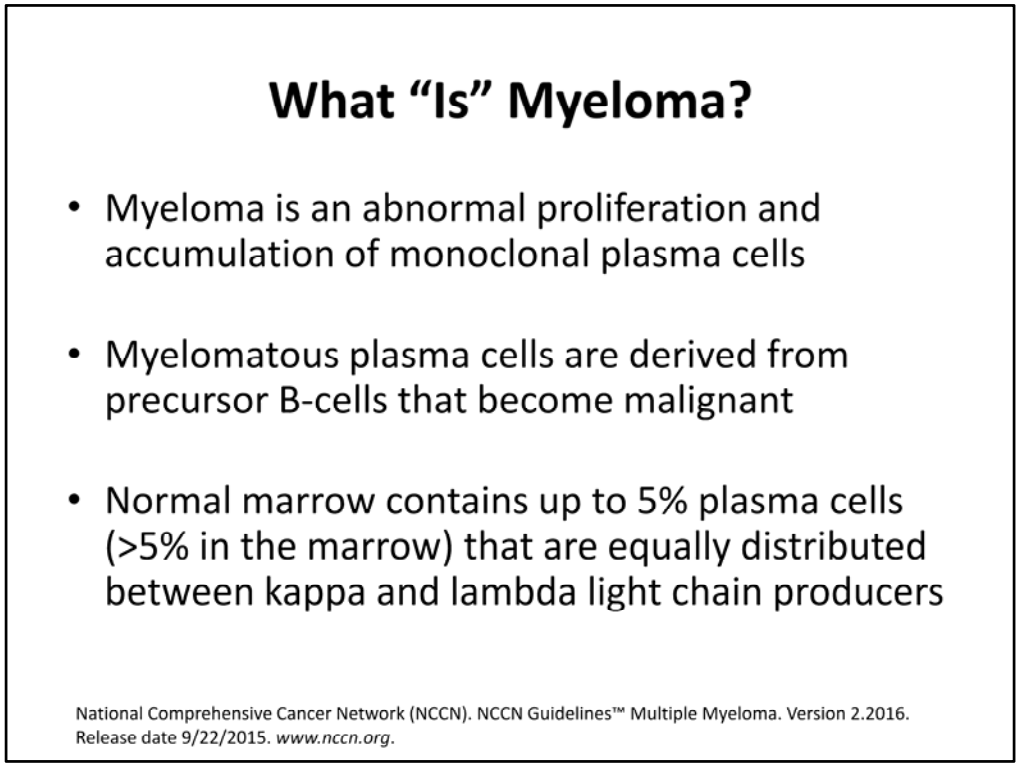

So, what is myeloma? Myeloma is an abnormal proliferation and accumulation of monoclonal plasma cells. Myelomatous plasma cells are derived by precursor B-cells that become malignant. Normal bone marrow should contain up to 5% plasma cells that are equally distributed between kappa light chain and lambda light chain producers.

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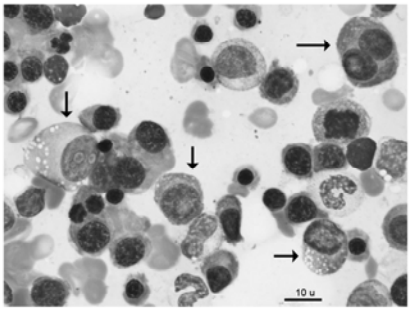
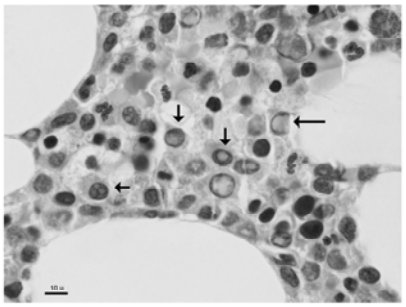
Myeloma Cells



Wright-Giemsa–stained bone marrow aspirate smear



Hematoxylin and eosin stain on the biopsy section

The bone marrow aspiration smear and biopsy are from a patient with multiple myeloma. Tumor cells (arrows) illustrate intranuclear inclusions/bubbles (so-called Dutcher bodies).

Courtesy of Vishnu V. Reddy, MD, Professor Laboratory Medicine, UAB School of Medicine.

Myeloma is an abnormal proliferation of a clonal plasma cell. That means a cell that produces one heavy chain and/or one light chain, so they will be either lambda restricted or kappa restricted. Under the microscope, we can generally imagine that a patient has a malignant plasma cell disorder because instead of having isolated plasma cells, plasma cells will aggregate in clusters, and that will translate into a greater than 5% plasma cell infiltration in the bone marrow.

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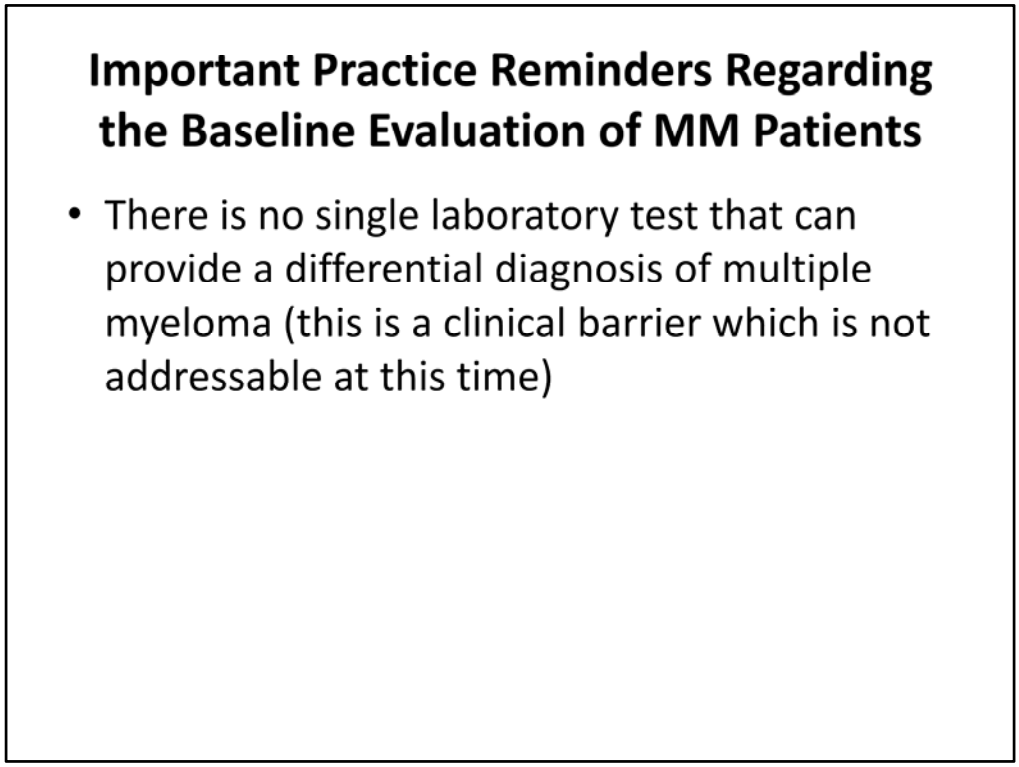

Remember, there is no single laboratory test that can provide the differential diagnosis in multiple myeloma. Myeloma is a clinical diagnosis that is made with a pathologic correlate of a monoclonal proliferation of plasma cells.

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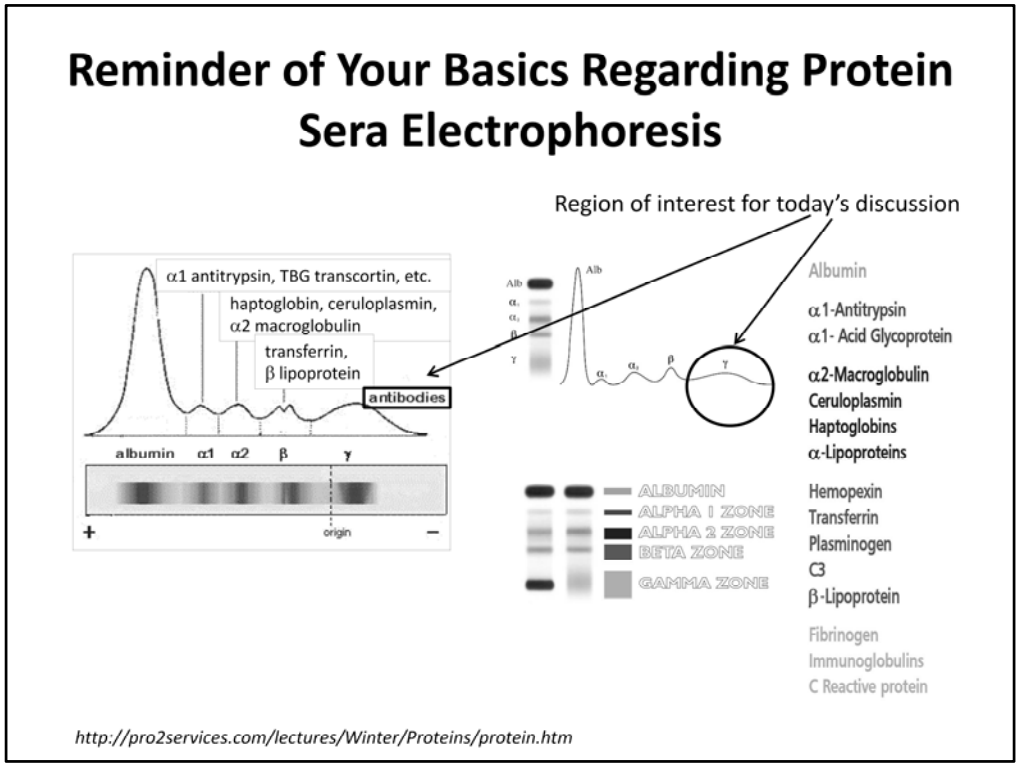

Let's talk a little bit about serum protein electrophoresis. Remember that proteins are separated in a gel according to their weight and the electric charge. When we put serum into a gel, and that is with electric charges, the proteins will separate into different parts. The first peak that we will see will be albumin, then alpha 1, then alpha 2, then beta in a broad band, that we call the gamma band, where all the antibodies produced by normal plasma cells are included. The broad band is due to the fact that you have thousands of plasma cells producing antibodies that all weigh differently and have different electric charges, and therefore migrate on the gel on different speeds.

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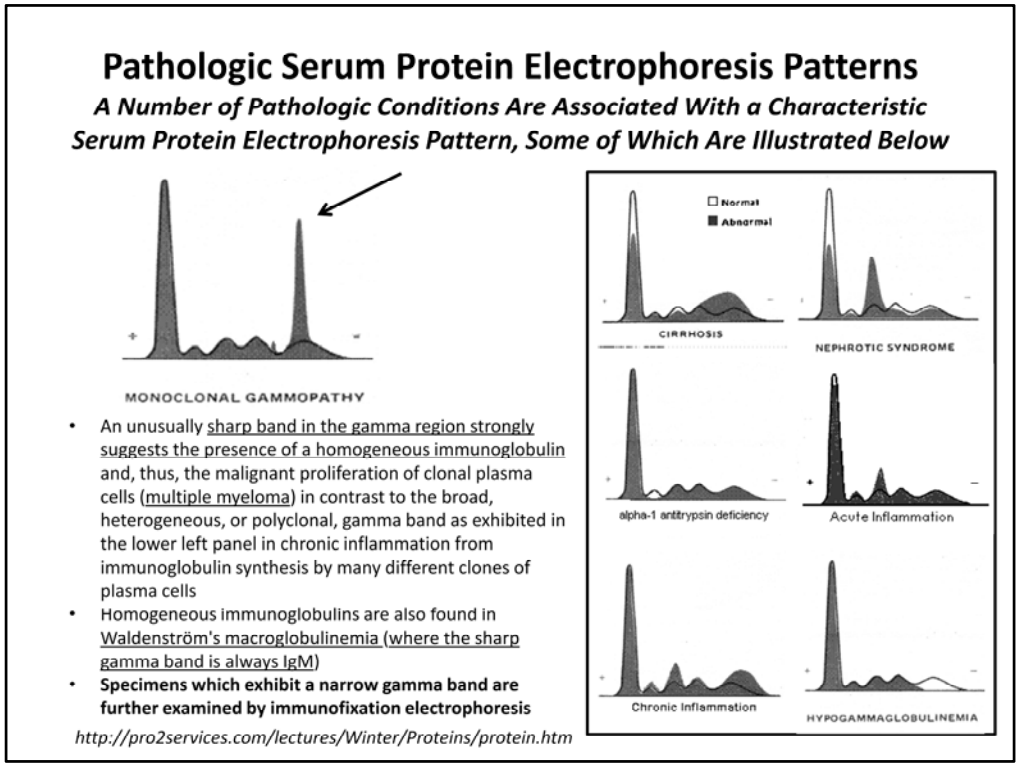

When you have a monoclonal gammopathy, you have essentially a group of plasma cells that are producing a same antibody that weighs the same and has the same electric charge. What will that translate into in a serum protein electrophoresis? It will translate into a paraprotein peak that we recognize as the monoclonal gammopathy. This is a sharp band in the gamma region that suggests the presence of a homogeneous immunoglobulin, and thus, either the overproduction of an antibody by a plasma cell or the production of the same antibody by a clone of malignant plasma cells. It is important to remember that myeloma is not the only tumor that produces immunoglobulins. There are many lymphoproliferative disorders such as CLL, Waldenström macroglobulinemia, and some of the lymphomas that can also have paraproteins present. However, the most common one is multiple myeloma.

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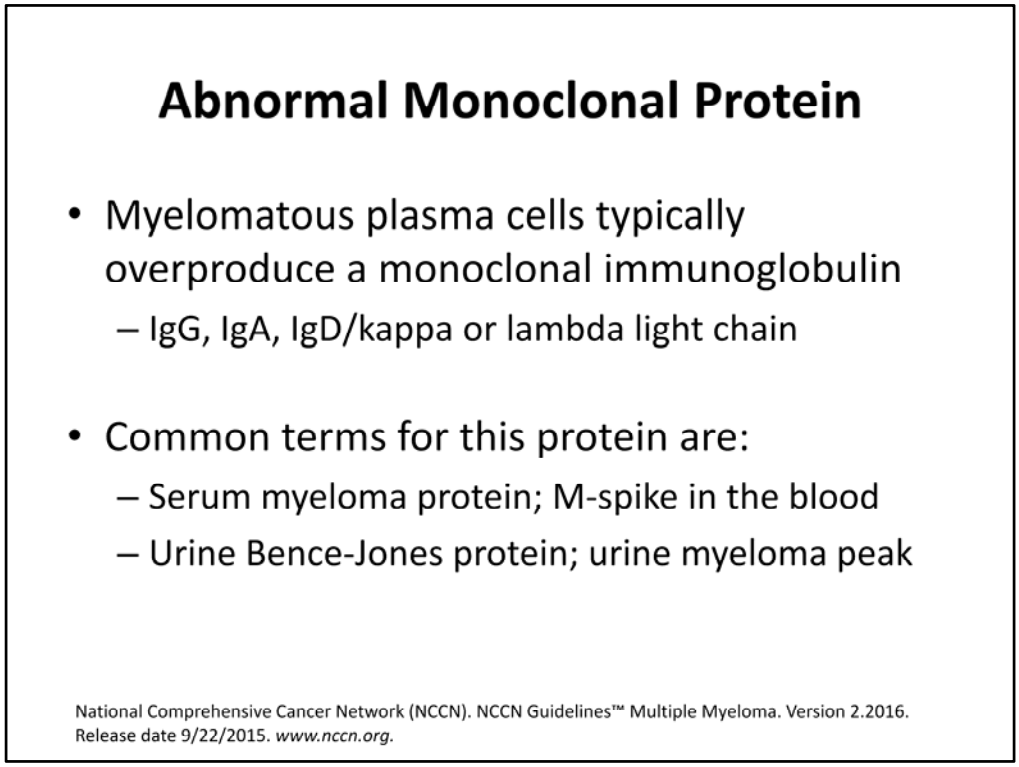

So, what is an abnormal monoclonal protein? As we have stated previously, the plasma cells are clonal. They all produce the same immunoglobulin with the same heavy chain and the same light chain. The most common myeloma protein is an IgG which is either kappa or lambda. The second most common is an IgA. The third most common is actually that the myeloma plasma cells do not produce a heavy chain and it is called light chain-only disease. There are many terms for the myeloma protein, we call it either the M-spike, or in the urine we call it the urine Bence-Jones protein , or the urine myeloma peak.

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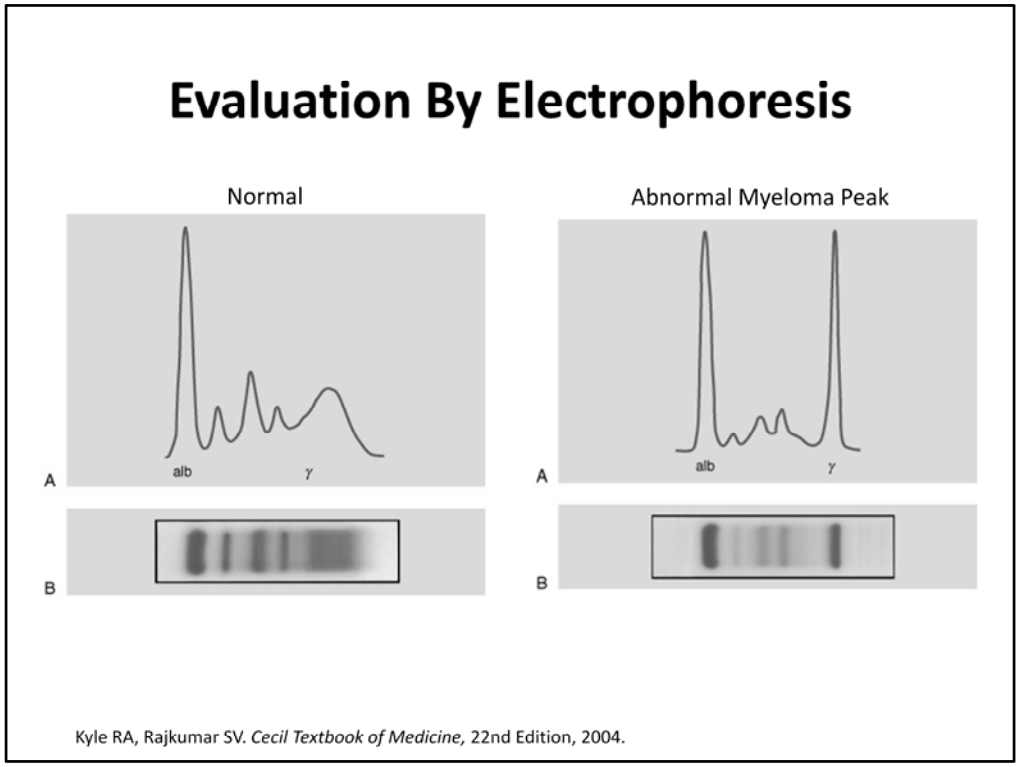

Here is an electrophoretic pattern comparing the normal, and notice that you have a broad gamma peak, versus the abnormal, where you have this sharp peak in the gamma region.

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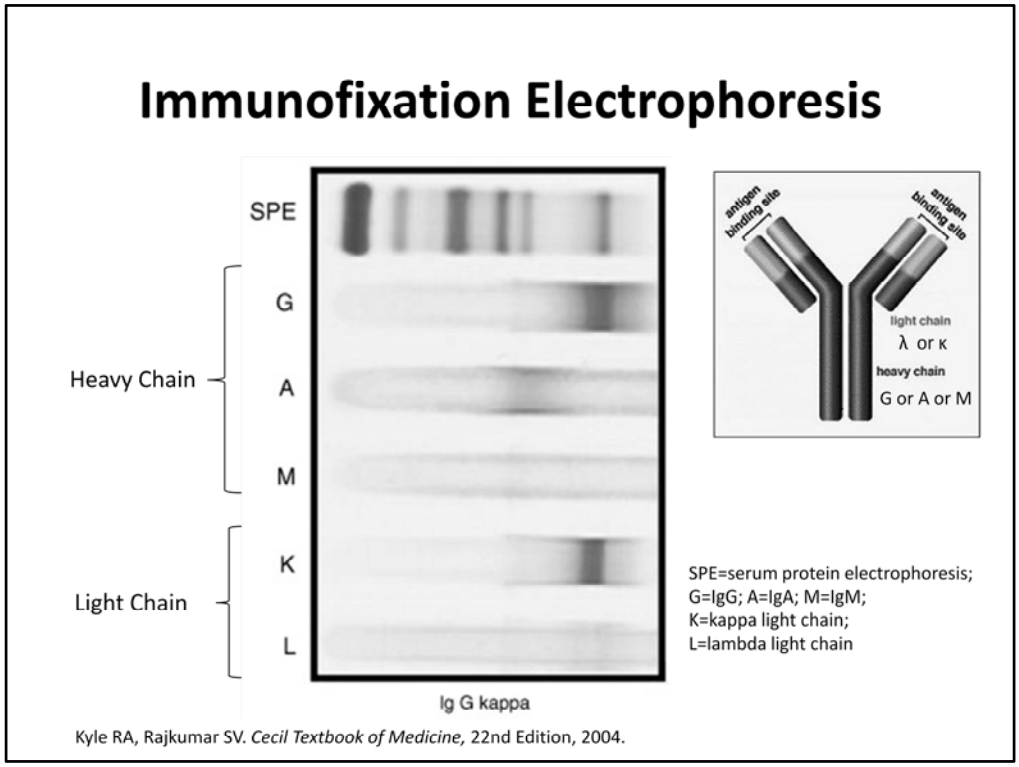

To be able to identify what type of immunoglobulin, we use immunofixation. And as you can see in this slide, immunofixation will identify the heavy chain. In this example, it is IgG – look at the dark band at the IgG level, and a light chain which is kappa – look at the dark band at the kappa row. So, this patient has a paraprotein peak that is IgG kappa.

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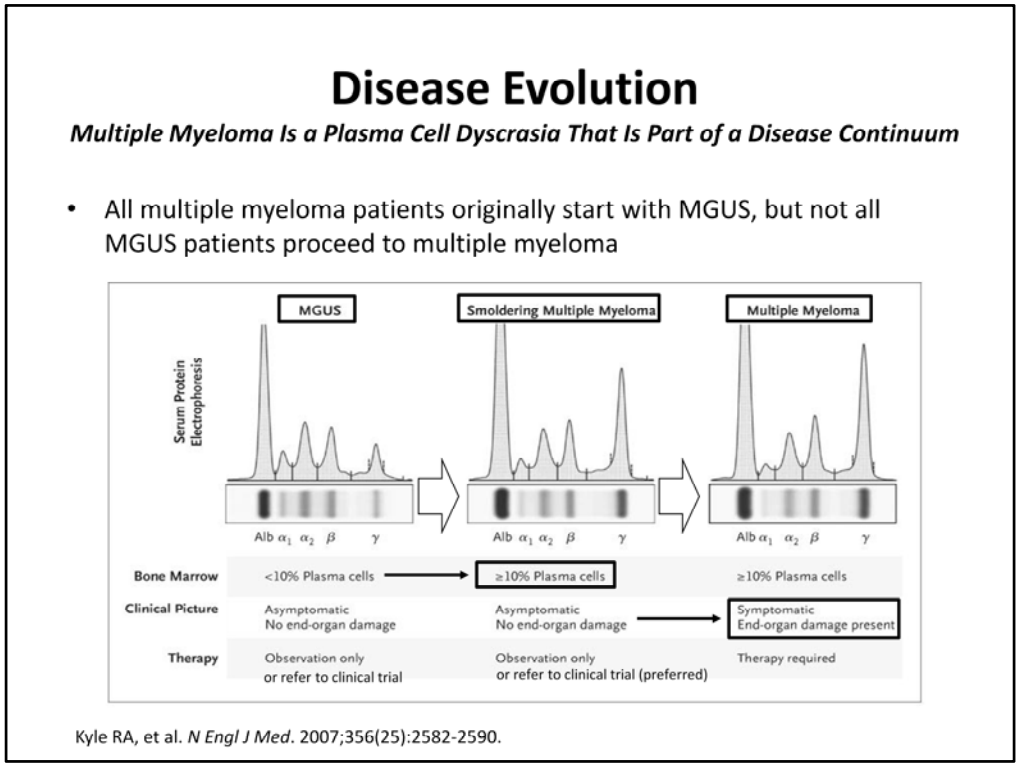

Kyle RA, et al. *N Engl J Med*. 2007;356(25):2582-2590.

Myeloma is a plasma cell dyscrasia that is part of a disease continuum. Work done by Dr. Ola Landgren in the National Cancer Institute demonstrated that all patients with myeloma had a preceding condition called monoclonal gammopathy of undetermined significance. This is a condition that is defined by less than 10% bone marrow plasma cells, no evidence of any end-organ damage, and generally this condition rarely, if ever, transforms to myeloma. The rate of transformation to myeloma is less than 1% a year for all patients with monoclonal gammopathy with undetermined significance. We recognize that there are patients with high-risk MGUS that probably should be followed more carefully because these are patients where the risk of progression to myeloma is actually higher. A second condition that has been identified and described is smoldering myeloma, or asymptomatic myeloma. These are patients who, although they have greater than 10% plasma cells, have no evidence of end-organ damage. They have none of the so-called CRAB criteria. No calcium abnormalities, no renal function abnormalities, no anemia, and no bone disease. These patients will eventually progress to multiple myeloma at different rates. So, we recognize that not all smoldering myelomas will progress to symptomatic myeloma at the same rate. Patients with symptomatic myeloma now have end-organ damage as defined by calcium abnormalities, renal abnormalities, anemia, or bone disease.

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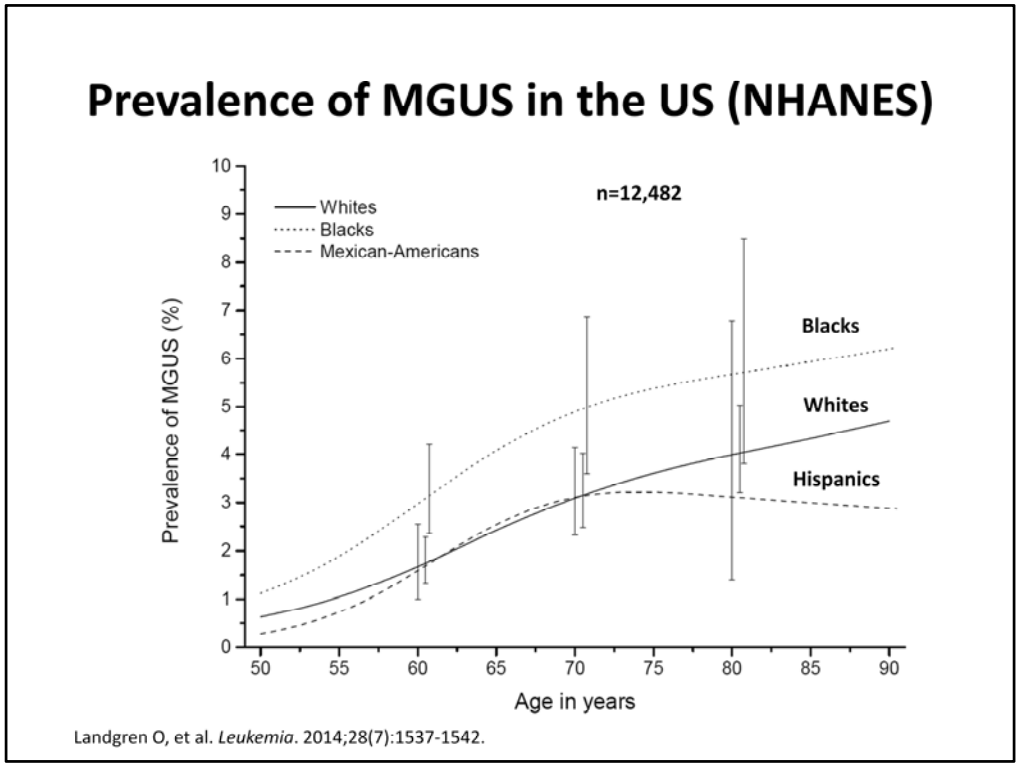

MGUS is a relatively common condition which approximately 7-10% of the patients in different ethnic groups have in any given period of time, with the increased incidence happening in older patients above the age of 70. This is a condition that is commonly seen by the internist, and it is important for us as a community to educate our primary care physicians of which patients with a monoclonal peak should be considered for further evaluation and testing.

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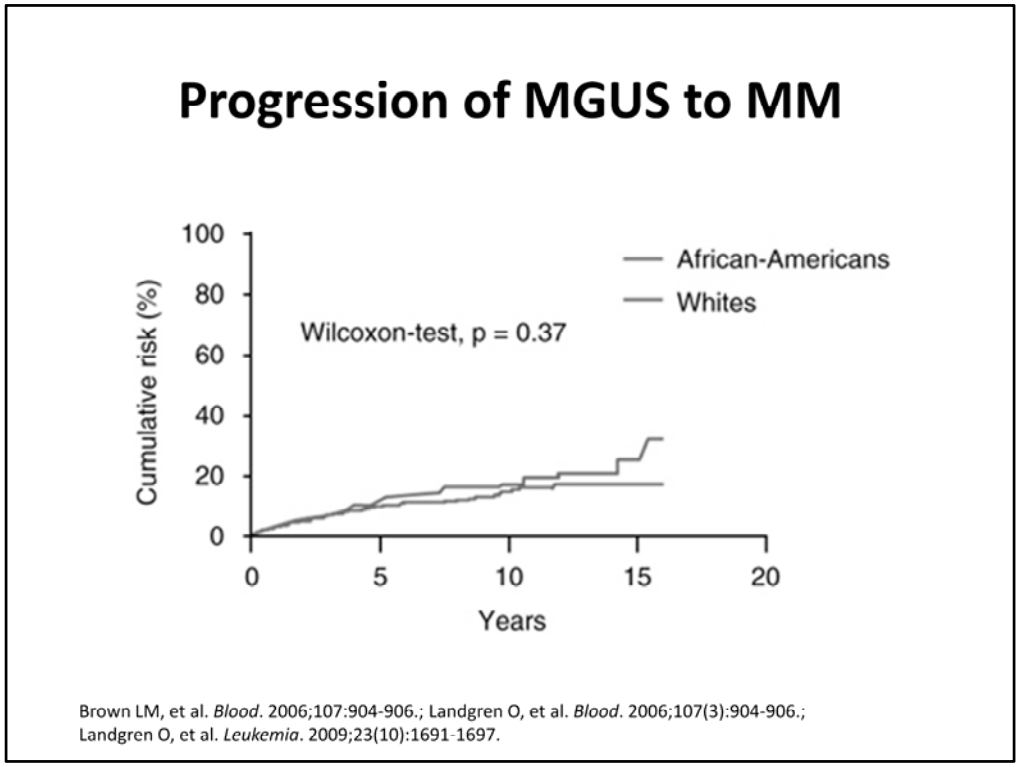

Brown LM, et al. *Blood*. 2006;107:904-906.; Landgren O, et al. *Blood*. 2006;107(3):904-906.; Landgren O, et al. *Leukemia*. 2009;23(10):1691-1697.

The risk of progression is similar for African Americans and for Caucasians.

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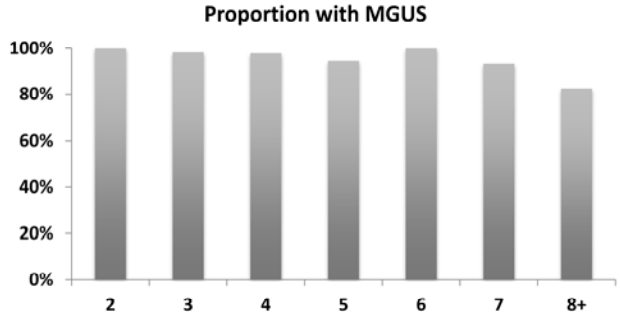
MGUS Is a True "Pre-cancerous" State

- MM is always preceded by MGUS stage
- Among 77,469 healthy adults from prospective PLCO* Cancer Screening Trial: 71 subjects developed MM



*Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Landgren O, et al. *Blood*. 2009;113(22):5412-5417.

As stated before as work by Dr. Landgren, this is truly a precancerous condition, but it is important to also note that most patients with MGUS will not develop myeloma. Actually, most patients with myeloma, we will not be able to identify an episode of MGUS previously, although many of them will state that they had laboratories done 2 to 3 years before the diagnosis was made with mildly elevated total protein.

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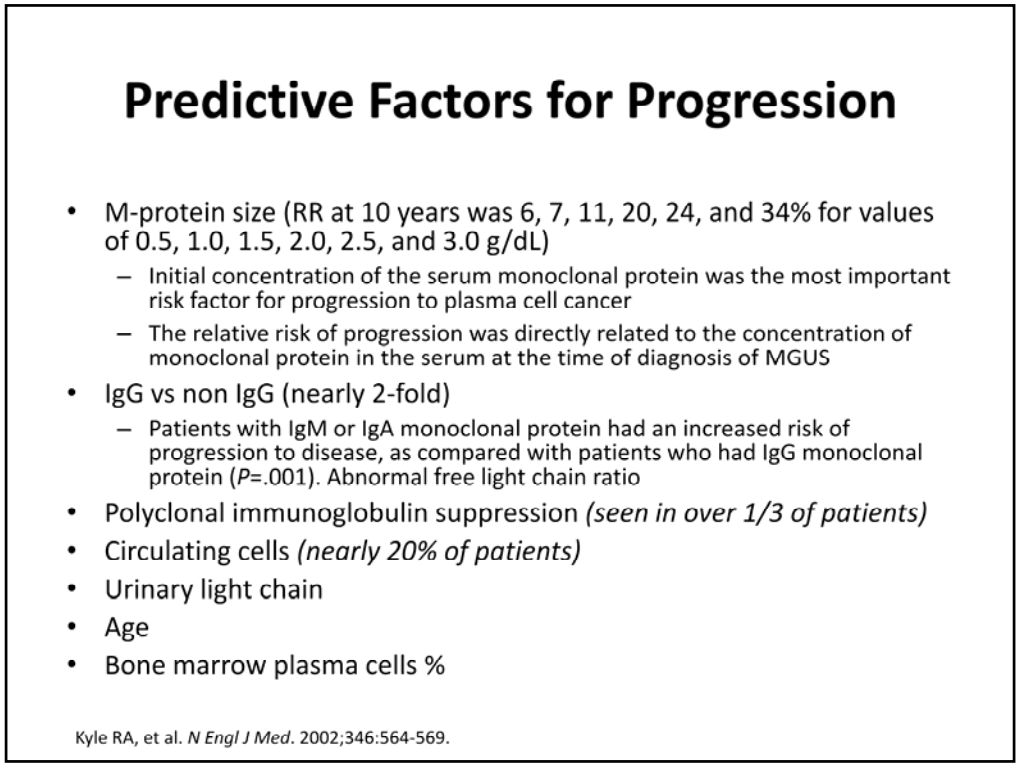

In a patient with MGUS, what are the predictive factors for progression? Obviously, the size of the peak is probably one of the most important predictors. The higher the peak the relative risk of progression to myeloma is higher. The suppression of noninvolved immunoglobulin, which can be seen in up to 30% of patients with MGUS, is also a predictor of progressing to myeloma, and the higher the percentage of bone marrow plasma cells, the closer it is the 10, the more likely it is that this patient with MGUS will be progressing to myeloma, and therefore should be followed more carefully either by the primary care physician, or referred to a hematologist for close followup.

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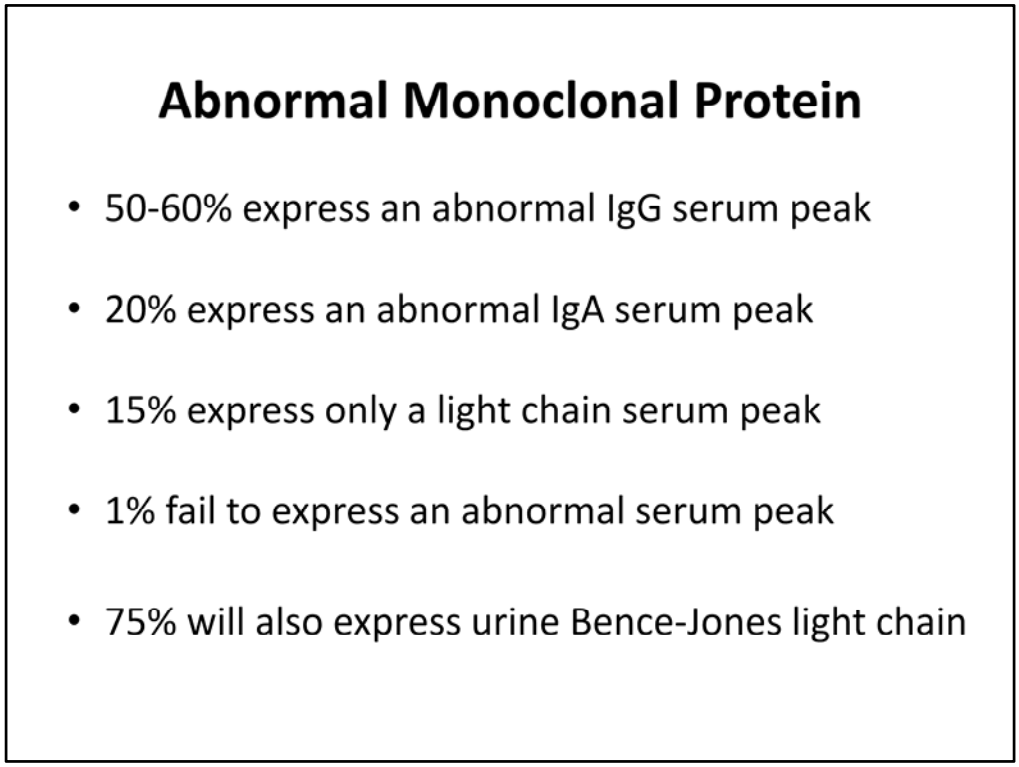

As stated previously, the most common abnormal paraprotein peak is an IgG, the second most common is an IgA, and only 1% of patients with free light chain assays actually are now true nonsecretory disease in which a paraprotein peak or a free light chain will not be detectable on either serum or urine analysis.

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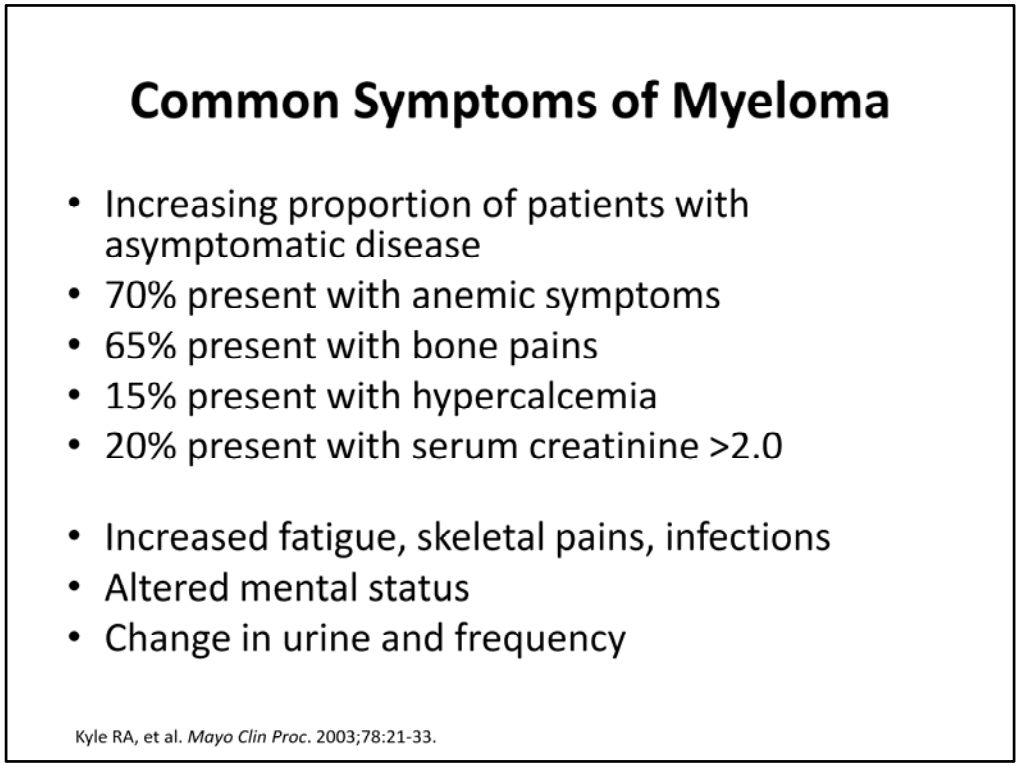

It is important to recognize that currently in North America, 30% of patients with myeloma will present without any symptoms whatsoever. This does not mean that they have asymptomatic disease; 70% of patients will be anemic, 65% will have bone pain, 15% will present with hypercalcemia, and 20% will present with serum creatinine of greater than 2. Note, these are the CRAB criteria. In general, what leads a patient to the doctor is increasing fatigue, pain, occurrence of infection, or an altered mental status because of hypercalcemia. It is important to educate primary care physicians that patients with progressive fatigue and anemia in which a source of bleeding is not found should be referred to a hematologist. Likewise, patients with recurrent infection should have immunoglobulins checked, and a decrease in immunoglobulins or an elevated IgG or IgA level should be considered for further workup of suspicious myeloma.

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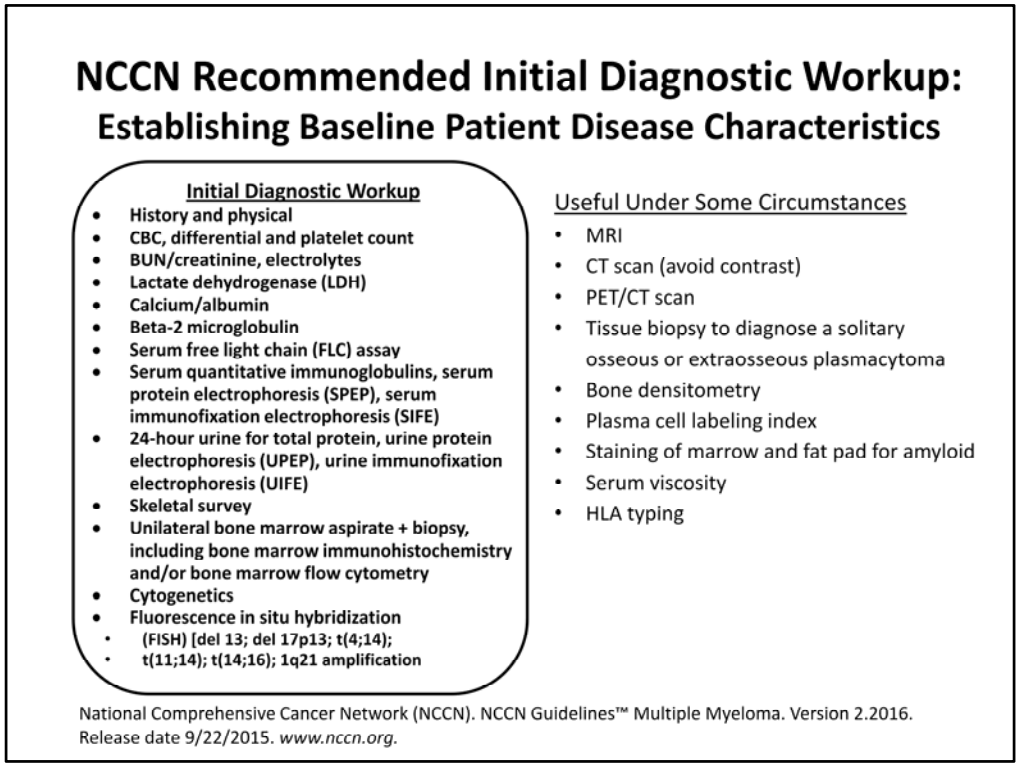

The NCCN now recommends a basic diagnostic workup that will allow to establish extent of disease, extent of organ damage, and then will allow us to establish prognosis and help us decide what is the specific therapy needed for induction, consolidation, and maintenance for the individual myeloma patient.

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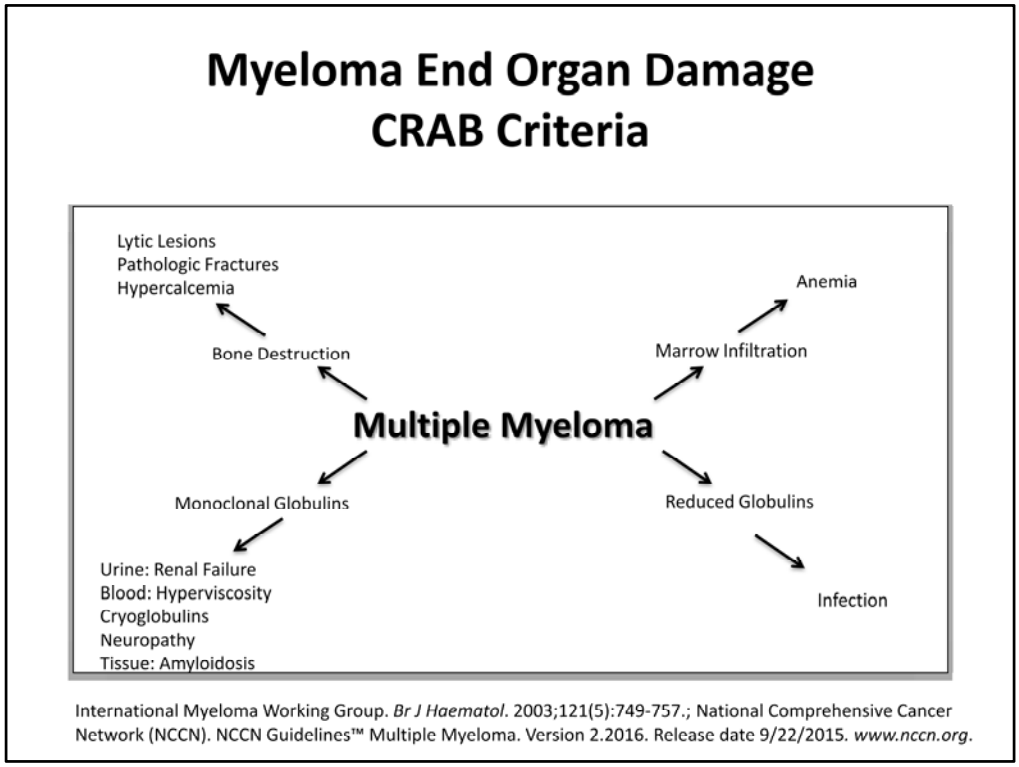

International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.; National Comprehensive Cancer Network (NCCN). NCCN Guidelines™ Multiple Myeloma. Version 2.2016. Release date 9/22/2015. *www.nccn.org*.

As we discussed previously, multiple myeloma is a clonal proliferation of plasma cells. One can imagine that as these plasma cells proliferate in the bone marrow, they will infiltrate the bone marrow and affect the way the bone marrow works and will cause anemia. One can also imagine that they will destroy the bone where they are located causing lytic lesions, pathologic fractures, and hypercalcemia. What is interesting is that myeloma not only causes problems in the place where these tumors are growing, but the paraprotein peak can actually affect renal function, cause hyperviscosity, and on occasion, have immune properties by itself. The myeloma plasma cell grows at the expense of normal plasma cells, and although the abnormal globulin is at very high levels, the uninvolved immunoglobulins are reduced and therefore, there is a risk of infection occurring.

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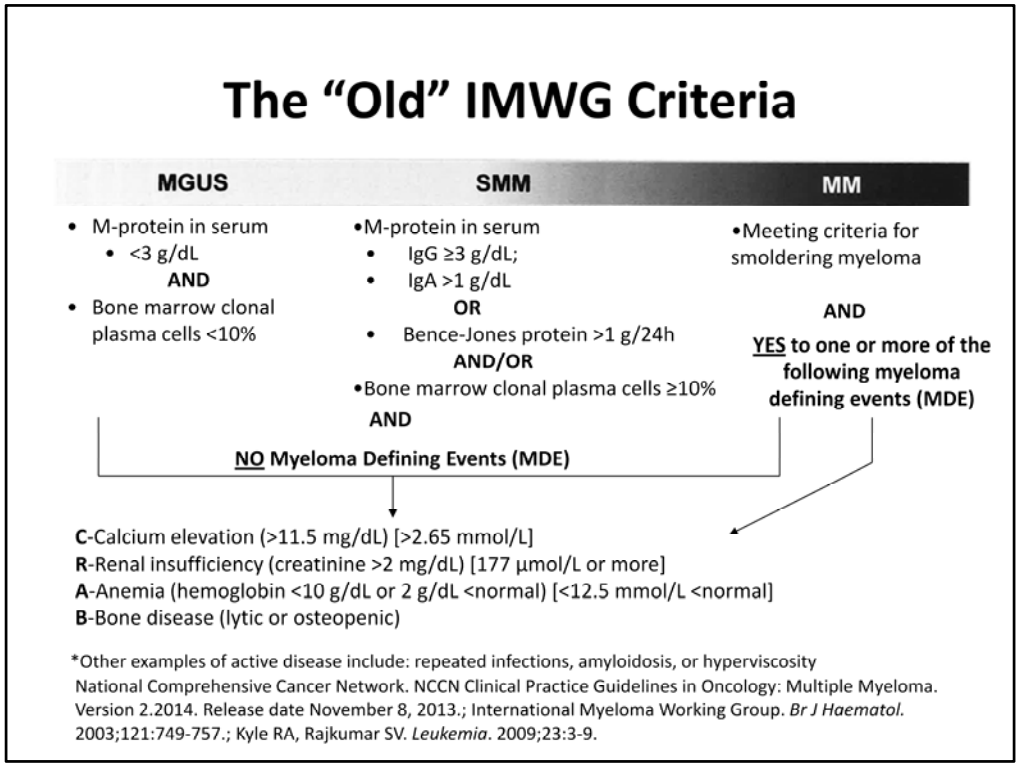

Until recently, the International Myeloma Working Group has separated the plasma cell disorders, with a spectrum of these plasma cell disorders, in three. Patients would have monoclonal gammopathy of uncertain significance if they have less than 10% plasma cells. Patients with 10% plasma cells and a paraprotein peak but without any of the CRAB criteria, meaning a calcium of greater than 11.5 mg/dL, renal insufficiency, a creatinine of greater than 2, a hemoglobin less than 10, or bone disease would be classified as having symptomatic myeloma and would require treatment.

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Summary of the Old Differential Diagnosis

	Premalignant condition	Plasma cell malignancy	
	MGUS[1-4] (Monoclonal Gammopathy of Undetermined Significance)	Smoldering Multiple Myeloma[1-5]	Multiple Myeloma[6-7]
Symptoms	Asymptomatic	Asymptomatic	Symptomatic (~89%)
Active treatment	No	No or clinical trial	Yes
M-protein (per dL)	<3 g	≥3 g	M-spike or plasmacytoma
Clonal plasma cells in bone marrow	<10%	≥10%	>10%
End-organ damage	None	None	1 or more CRAB criteria
Likelihood of progression	1% per year	10% per year for first 5 years; 73% by 15 years	Not Applicable

[1]Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590. [2]International Myeloma Working Group. *Br J Haematol.* 2003;121:749-757. [3]Jagannath S, et al. *Clin Lymphoma Myeloma Leuk*. 2010;10(1):28-43. [4]Kyle RA, et al. *Curr Hematol Malig Rep*. 2010;5(2):62-69. [5]Mateos M-V, et al. *Blood.* 2009;114:Abstract 614. [6]Durie BG, Salmon SE. *Cancer*. 1975;36:842-854. [7]Durie BG, et al. *Leukemia*. 2006;20(9):1467-1473.

This is a summary of, again, the three different states of a clonal plasma cell disorder, from MGUS to symptomatic myeloma.

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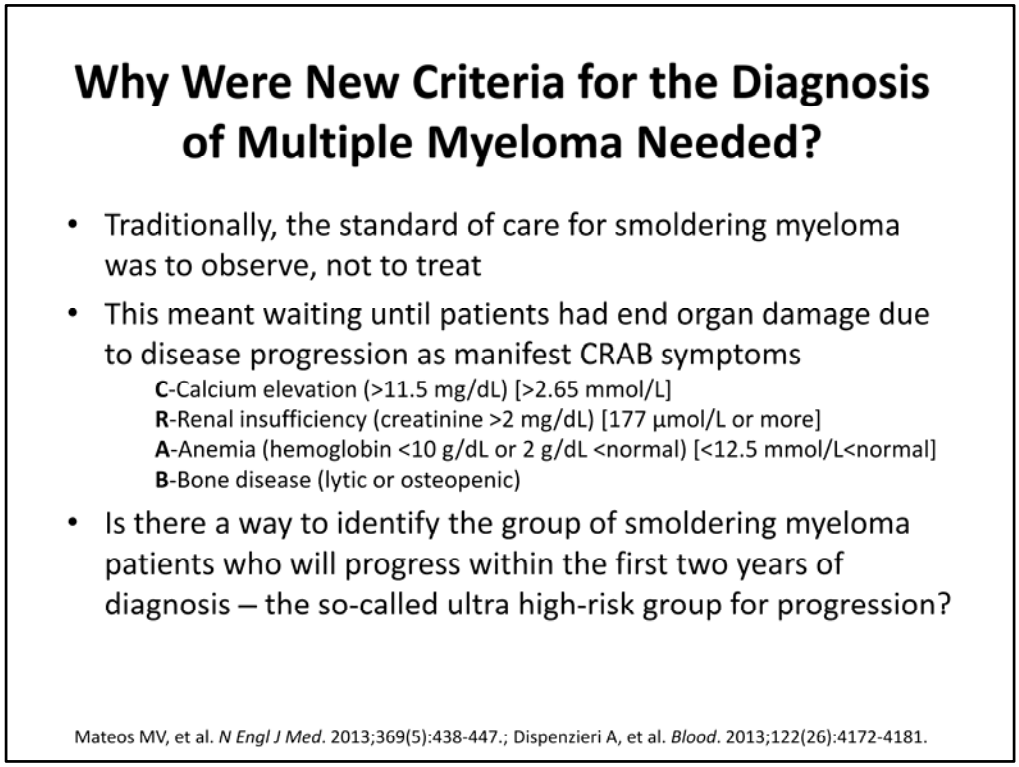

One of the things that has happened is that for patients with smoldering myeloma, since it was the tradition not to treat, many of these patients, their first manifestation of symptomatic disease was either renal failure, severe anemia, a severe infection, or a fracture. It has been well-recognized ,that there are some patients with smoldering myeloma that had an extremely high risk of progression to symptomatic disease. The new criteria recognizes these patients, and now, these patients are considered for early treatment despite the fact that they have not developed “CRAB criteria.” Let’s discuss the rationale for these. First, let’s remember that the risk of progression for universal patients with smoldering myeloma is somewhere 70% at 20 years, but there is a group of patients, almost 50% of them, that will have progression to symptomatic disease within the first two years of diagnosis. Can we identify these patients? Well, there is a risk stratification that we can do.

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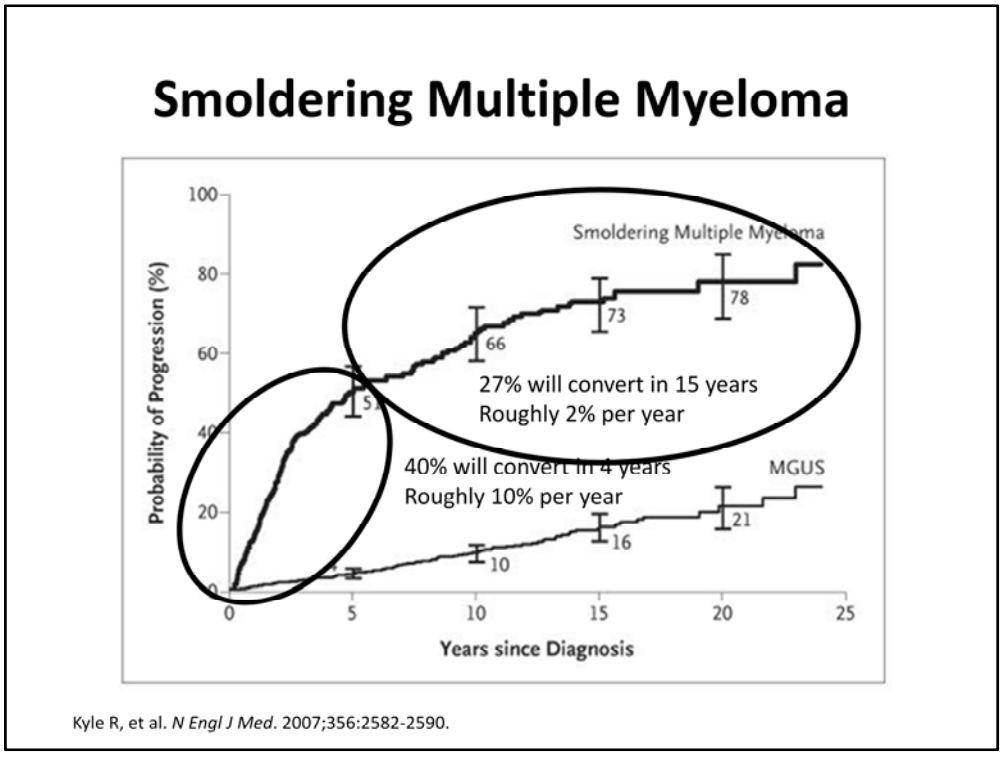

Kyle R, et al. *N Engl J Med*. 2007;356:2582-2590.

So this has been work that has been done by the Mayo Clinic. We recognized that there are certain groups of patients in which progression at 2 years is almost 40% while other patients actually do not progress in 20 years.

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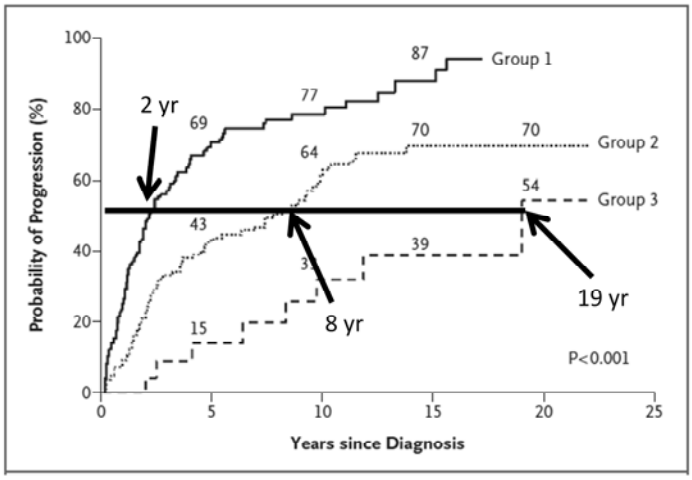
Initial Risk Stratification



Patients with >10% plasma cells and >3 gm/dL M-protein are at higher risk

Kyle R, et al. *N Engl J Med*. 2007;356:2582-2590.

The group at Mayo Clinic has looked at risk stratification of patients with smoldering myeloma and they have showed that there is a group of patients who have a very high risk of progressing to myeloma at the 2-year mark, while there is another group of patients whose risk of progression to myeloma is extremely low, with less than 50% of them progressing within 20 years. They also showed that patients with very high paraprotein peaks of greater than 3, or patients with very elevated plasma cell infiltration of greater than 10, were the ones that actually fell into this high-risk smoldering myeloma.

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Free Light Is Useful for Risk Assessment in SMM

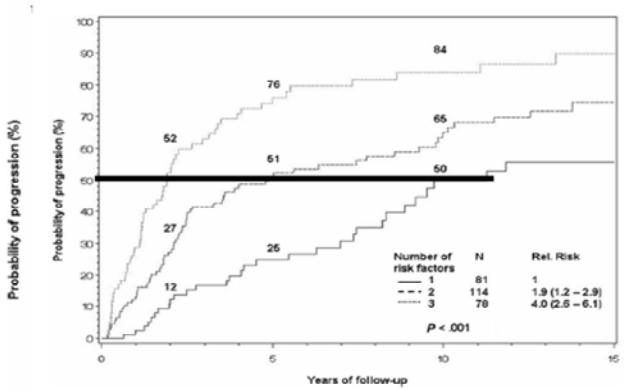

Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

Prognostic factor	Hazard ratio (95% CI)	*P*
Bone marrow plasma cells more than 10%	3.1 (1.6-6.3)	< .01
Abnormal FLC ratio less than 0.125 or more than 8	1.9 (1.3-2.7)	< .01
Serum M protein size, more than 30 g/L	1.9 (1.4-2.6)	< .01

Dispenzieri A, et al. *Blood*. 2008;111(10):4908-4915.

They also showed that free light chain assay was useful in risk assessment in smoldering myeloma. Patients with very high or very low free light chain ratios were at a higher risk of developing progression to symptomatic disease than those with lower levels of free light chain ratio abnormalities.

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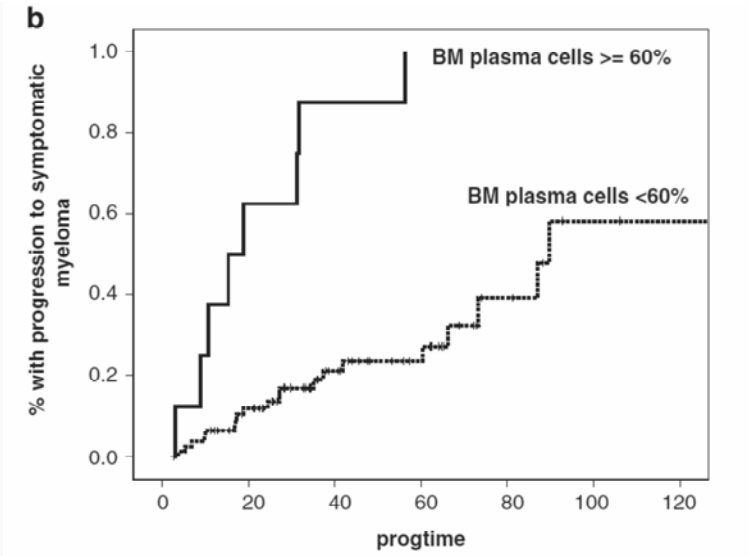
Plasma Cells Can Predict for Progression



Kastritis E, et al. *Leukemia*. 2013;27(4):947-953.

Finally, patients with bone marrow infiltration of greater than 60% had an extremely high risk of progressing to multiple myeloma within the first 2 years.

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Imaging Studies and Sensitivity

Index test	Reference Test	Sensitivity index test	Specificity index test	Detection rate	References
CT	WBXR	0.947-1.00	0.467-0.500	1.10-1.33	(15), (12)
MRI	WBXR	0.916 [0.883-0.940]	0.412 [0.261-0.582]	1.12-1.80	(15, 40-48)
PET-CT	WBXR	0.667-1.00	0.286-0.500	1.27-1.45	(40)
PET	WBXR	0.953 [0.369-0.999]	0.217[0.178-0.679]	1.16-1.50	(49)
PET	CT	0.824	1.00	1.00	(50)
MRI	CT	0.800-1.00	0.782-0.789	1.15-1.25	(9)

If you decide to observe a patient, it needs more sensitive imaging than bone survey

Pianko MJ, et al. *Clin Cancer Res*. 2014;20(23):5888-5897.

As most of us are aware, skeletal survey continues to be the standard of care for imaging patients with multiple myeloma. Notwithstanding, as part of the workup, many of us have done whole body CTs or whole body MRIs or PET-CTs, recognizing that this is a much more sensitive test than bone surveys. So what do we do with the patient who actually has a normal bone survey but an abnormal enhanced radiologic imaging technique, an abnormal CT, or abnormal MRI? We actually have shown, and this slide shows, that the patients with abnormal CTs, or abnormal MRIs are also at significantly higher risk of progressing to multiple myeloma, because these tests are more sensitive and specific than the traditional bone survey.

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Potential Advantages of New Imaging

Imaging techniques	Suggestions for use
CT/WBLDCT	• Consider for patients with bony pain and negative skeletal survey: higher detection rate of smaller lesions not seen on conventional radiography, especially in spine and pelvis • Pathologic fracture risk assessment • 3D imaging for CT-guided biopsy planning and radiation therapy • No contrast or preparation time necessary • Fast acquisition time ideal for patients with bony pain intolerant of longer imaging studies or procedures
PET/PET-CT	• Assess intraosseous and extraosseous lesions for disease activity • Staging of non-secretory myeloma • Assess patients with purported solitary plasmacytoma for more lesions • Monitor metabolic response to therapy
MRI	• Superior sensitivity for imaging the bone marrow compartment • Indicated for patients with neurologic symptoms suggestive of spinal cord or nerve root compression • Staging of non-secretory myeloma • Best for detection of diffuse bone marrow involvement • MRI of spine useful for diagnosis, follow-up after stem cell transplant, evaluation of disease activity • Complementary CT may be indicated to detect presence of osteolytic lesions

Pianko MJ, et al. *Clin Cancer Res*. 2014;20(23):5888-5897.

There is significant advantage for the new imaging. The most important one is that you can actually detect the disease before a lytic lesion is formed.

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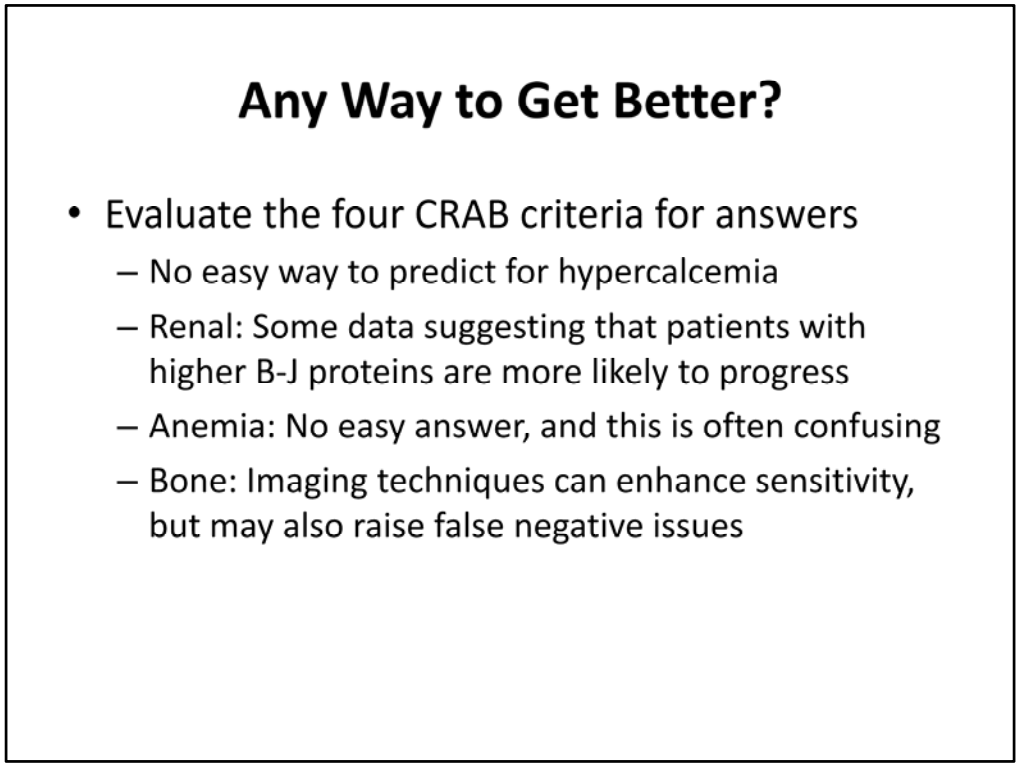

The International Myeloma Working Group (IMWG) spent a significant amount of time discussing should the criteria for treatment of myeloma be changed? Currently, the criteria require that the patients have at least one of the CRAB criteria. The problem with the CRAB criteria is that there is no easy way to predict hypercalcemia. Some data suggests that some patients can progress to renal failure fairly quickly. An early intervention may not reduce or recover renal function. Anemia is sometimes confusing because it is multifactorial, and as we showed, by the moment patients have developed lytic lesions, there has been extensive damage already done and extensive tumor burden. Therefore, we are losing the opportunity of preventing these things from happening by not treating patients earlier in the course of the disease.

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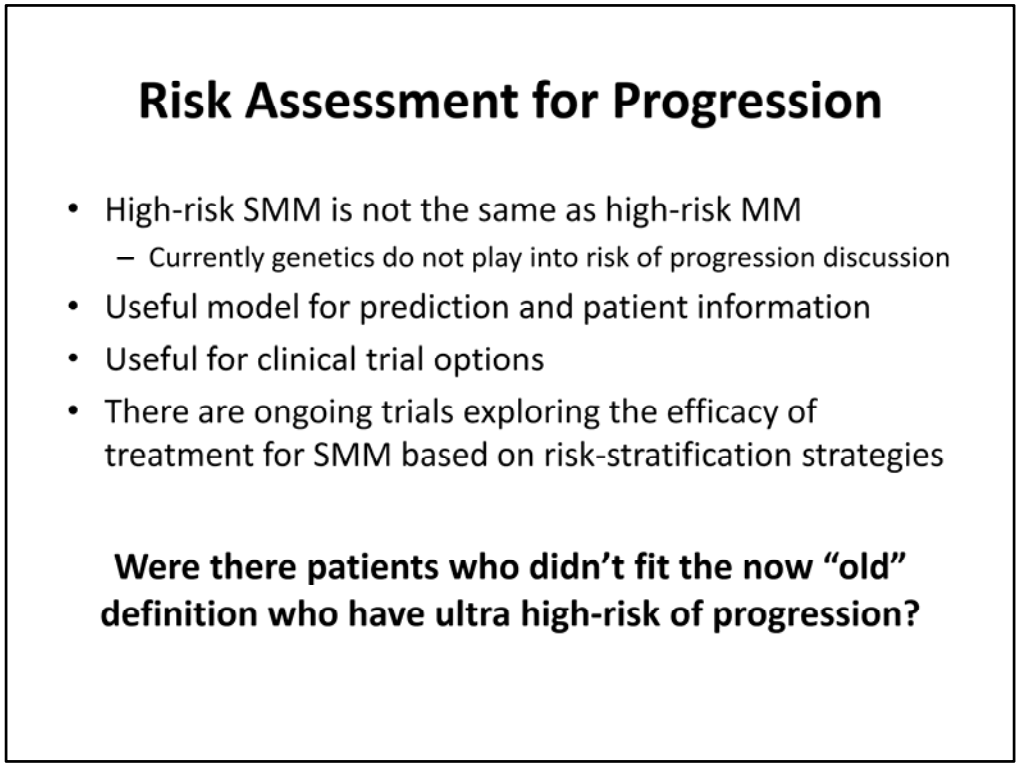

The International Myeloma Working Group (IMWG) sat down and decided, were there patients who did not fit the old definition, and because the risk of progression were considered so high, that they actually should be considered for treatment before developing CRAB criteria.

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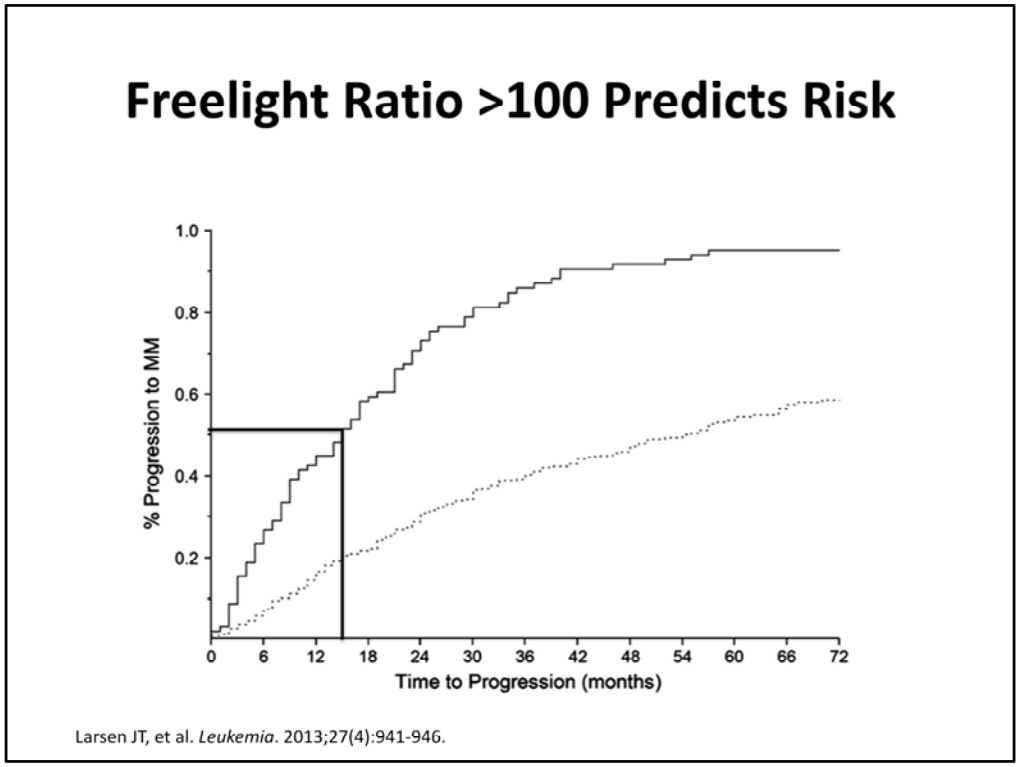
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice



As discussed previously, the free light chain ratio of greater than 100, or less than 0.01, showed extremely high risk of progression.

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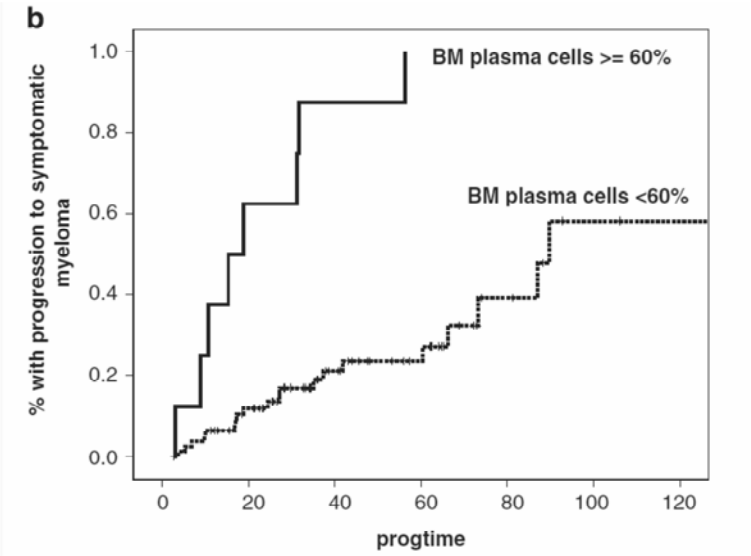
Plasma Cells Can Predict for Progression



Kastritis E, et al. *Leukemia*. 2013;27(4):947-953.

Plasma cells of greater than 60%, again, extremely high risk of progression,

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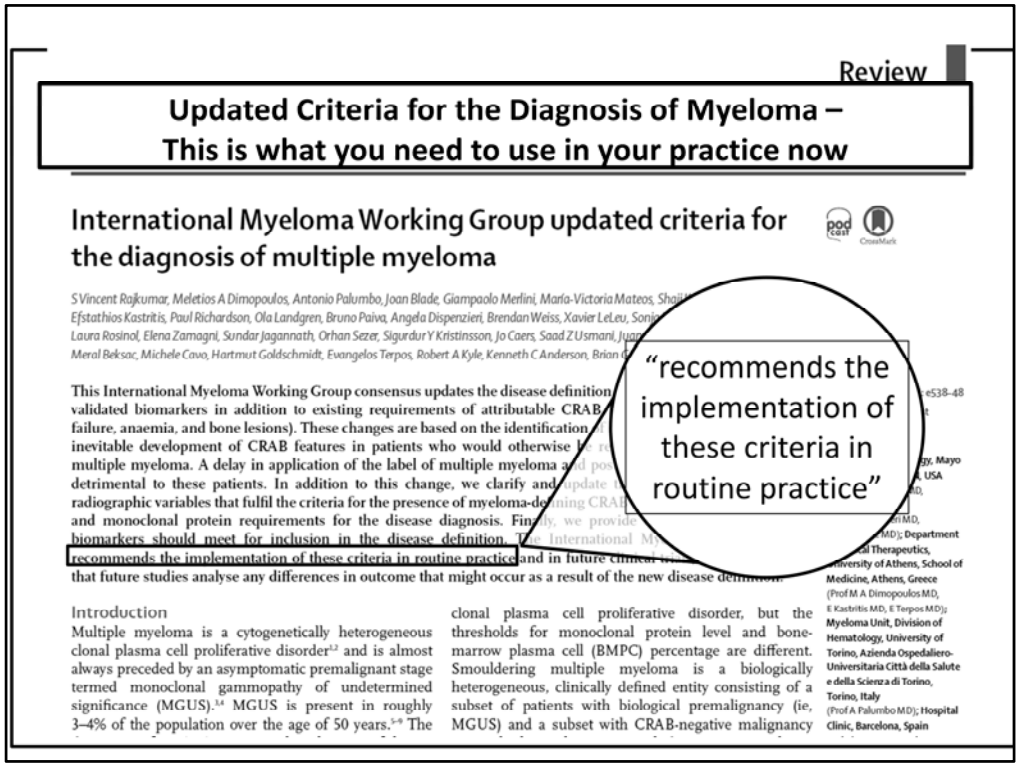

Review

Updated Criteria for the Diagnosis of Myeloma – This is what you need to use in your practice now

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji
Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Soni
Laura Rosiñol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan
Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian

"recommends the implementation of these criteria in routine practice"

This International Myeloma Working Group consensus updates the disease definition
validated biomarkers in addition to existing requirements of attributable CRAB
failure, anaemia, and bone lesions). These changes are based on the identification
inevitable development of CRAB features in patients who would otherwise
multiple myeloma. A delay in application of the label of multiple myeloma
detrimental to these patients. In addition to this change, we clarify and
radiographic variables that fulfil the criteria for the presence of myeloma-de
and monoclonal protein requirements for the disease diagnosis. Fin
biomarkers should meet for inclusion in the disease definition. The International M
recommends the implementation of these criteria in routine practice and in future clinical
that future studies analyse any differences in outcome that might occur as a result of the new disease definition.

Introduction

Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell proliferative disorder[1,2] and is almost always preceded by an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS).[3,4] MGUS is present in roughly 3–4% of the population over the age of 50 years.[5–9] The clonal plasma cell proliferative disorder, but the thresholds for monoclonal protein level and bone-marrow plasma cell (BMPC) percentage are different. Smouldering multiple myeloma is a biologically heterogeneous, clinically defined entity consisting of a subset of patients with biological premalignancy (ie, MGUS) and a subset with CRAB-negative malignancy

e538–48

zy, Mayo
USA

MD,
MD); Department
al Therapeutics,
niversity of Athens, School of
Medicine, Athens, Greece
(Prof M A Dimopoulos MD,
E Kastritis MD, E Terpos MD);
Myeloma Unit, Division of
Hematology, University of
Torino, Azienda Ospedaliero-
Universitaria Città della Salute
e della Scienza di Torino,
Torino, Italy
(Prof A Palumbo MD); Hospital
Clinic, Barcelona, Spain

and because of this, it was decided that it was time to update the criteria for treatment, and definition of smoldering myeloma.

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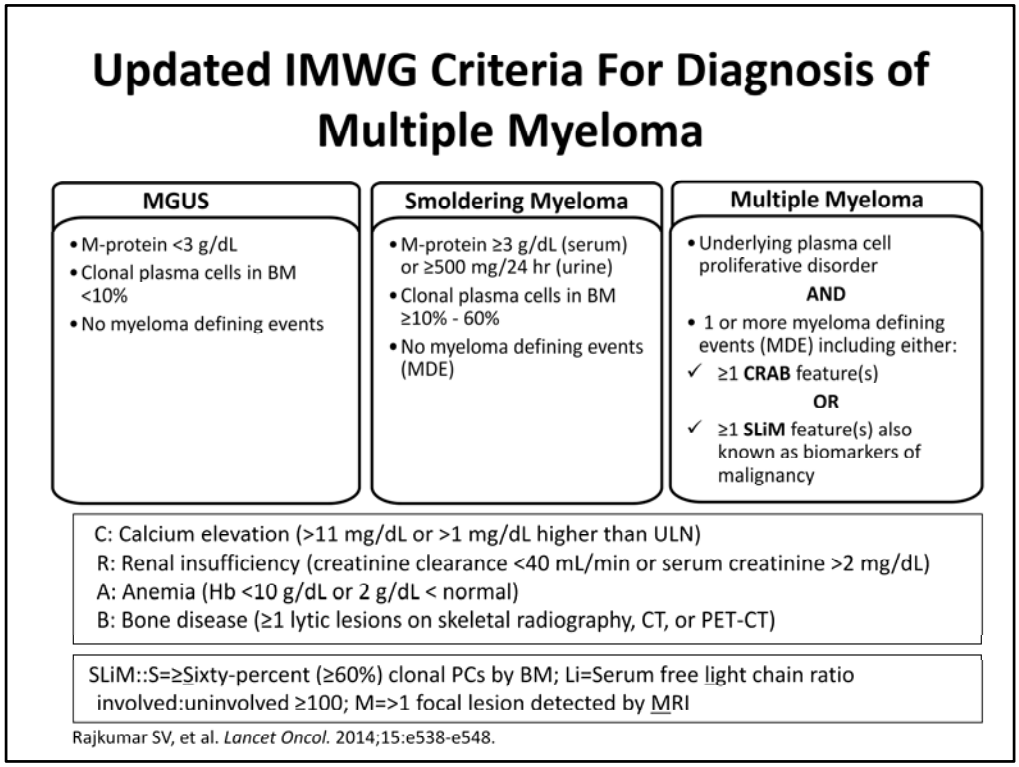
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice



The International Myeloma Working Group (IMWG) met and decided that they would identify these three criteria they call as SLiM, and this is an acronym for 60% plasma cells, serum-free light chain involvement with an involved over uninvolved ratio of greater than 100, and greater than one focal lesion detected by MRI. So the criteria have now changed, and it is actually recommended that for patients who have a plasma cell proliferative disorder, as identified by greater than 10% plasma cells with one or more myeloma defining events as either one CRAB criteria, or one SLiM feature, should be considered for therapy, and these patients should be treated as traditional symptomatic myeloma with induction therapy, consolidation and maintenance, if appropriate.

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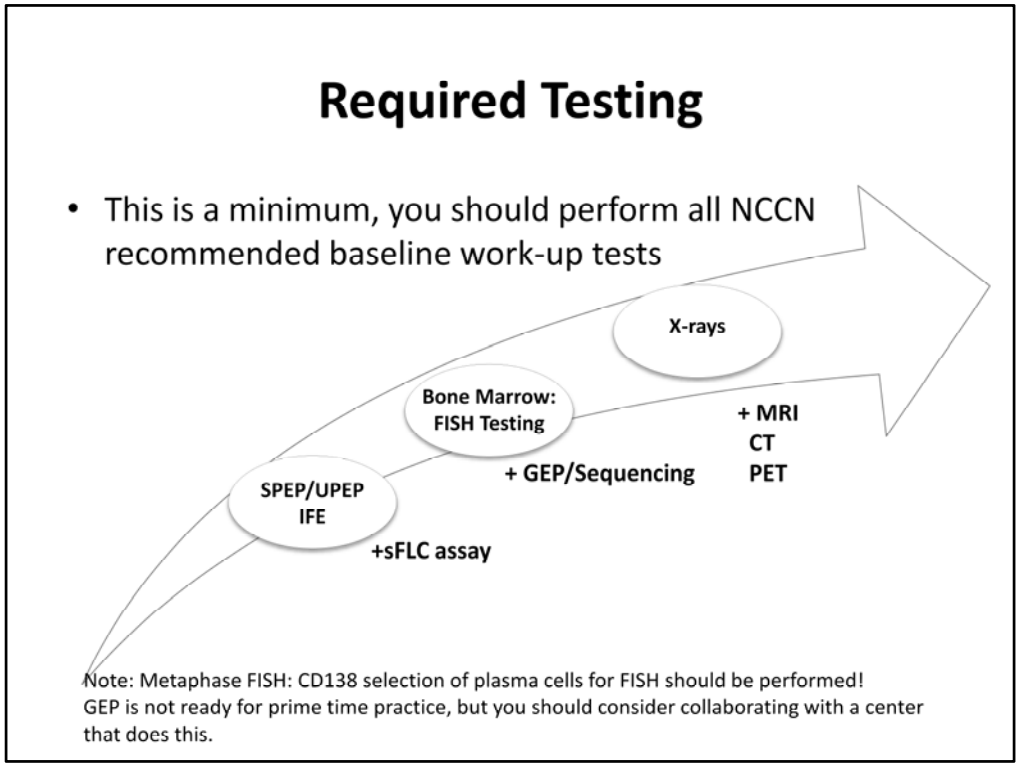

So what's happening? First, we need to have the appropriate amount of testing to be able to stage a patient. So we should be performing all the recommended baseline workups, which include a history and physical, comprehensive metabolic profile, a complete blood count, SPEP, UPEP, and free light chain assays, bone marrow with cytogenetic and FISH testing, and x-ray analysis beyond the bone survey. This would include either a bone marrow, or whole body CT, depending on what is available in the community, or where the place the physician is practicing.

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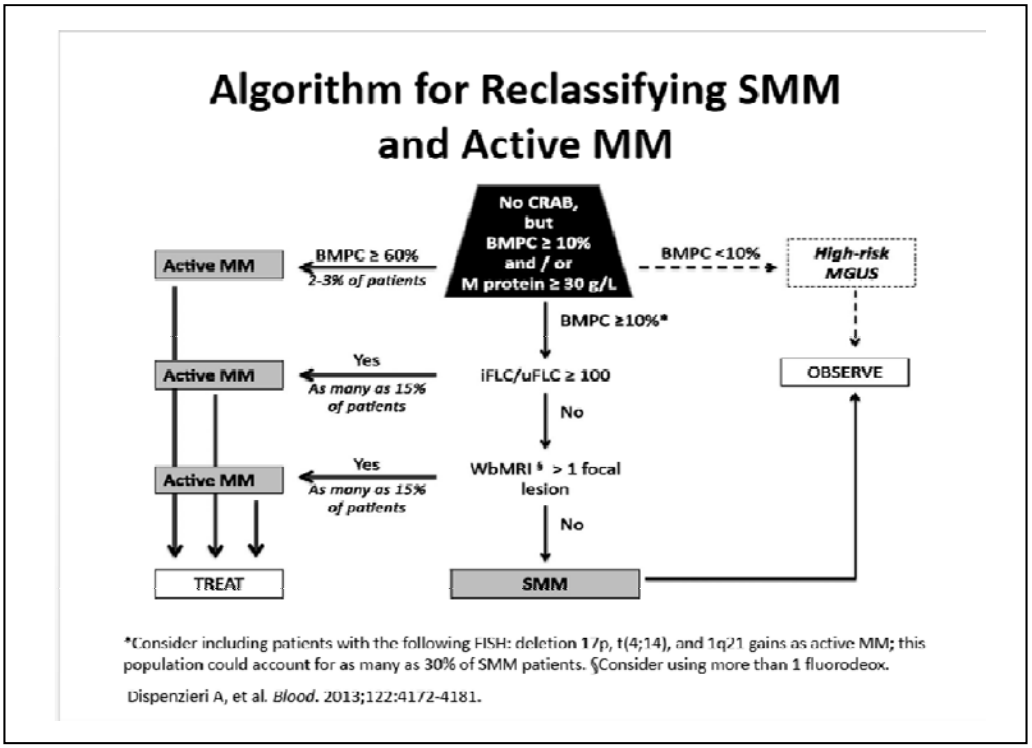
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice



Cytogenetic analysis and FISH analysis should be done in CD138 fraction whenever possible. Dr. Dispenzieri put this all together in a very good review that came out in *Blood* in 2013, and essentially what is summarized in this slide is, patients who have no CRAB criteria but have greater than 10% plasma cells and a paraprotein peak of greater than 3 should be considered for treatment if, (A) they have 60% plasma cells or more, (B) if they have abnormal free light chain ratios of greater than 100, or (C) if they have more than one focal lesion on MRI. Again, these patients should be considered as active myeloma and they should be treated as if they had symptomatic myeloma based on CRAB criteria. Once again, I underscore these patients should not be treated differently. They should be treated the same as if they had CRAB criteria.

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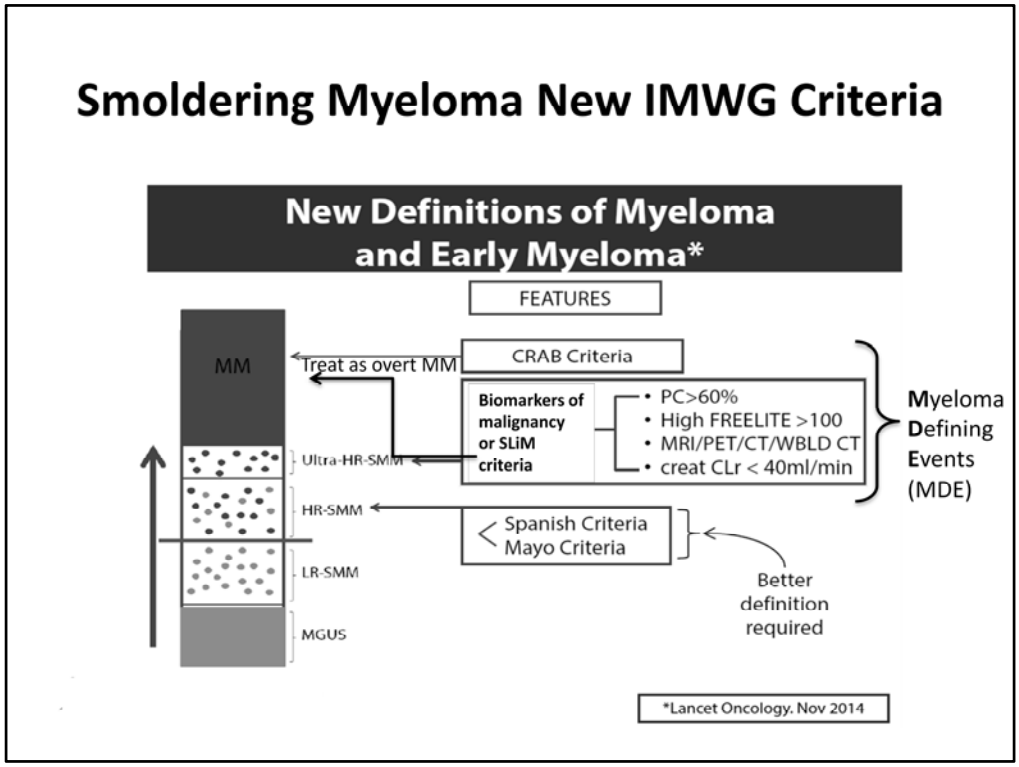

This is put in a schematic view, what is happening now? Let's remind ourselves: plasma cell disorders go from a continuum from monoclonal gammopathy of undetermined significance to smoldering myeloma to symptomatic myeloma. Within the smoldering myeloma, we recognize three groups—an ultra high-risk smoldering myeloma, a high-risk smoldering myeloma, and a low-risk smoldering myeloma. What we used to call ultra high-risk smoldering are patients who are expected to progress the symptomatic disease within the first 2 years. These patients have a plasma cell percentage of over 60%, and abnormal free light chain, or an abnormal MRI. No longer should these patients be considered smoldering, they should be considered as an active myeloma, and therefore should be treated. We do recognize that there is a group of patients who do not have ultra high-risk but high-risk myeloma based on a variety of criteria. These need to be better defined, and these patients should be strongly considered and encouraged to participate in clinical trials as there is a suggestion that early treatment may make a difference in the natural course of their disease.

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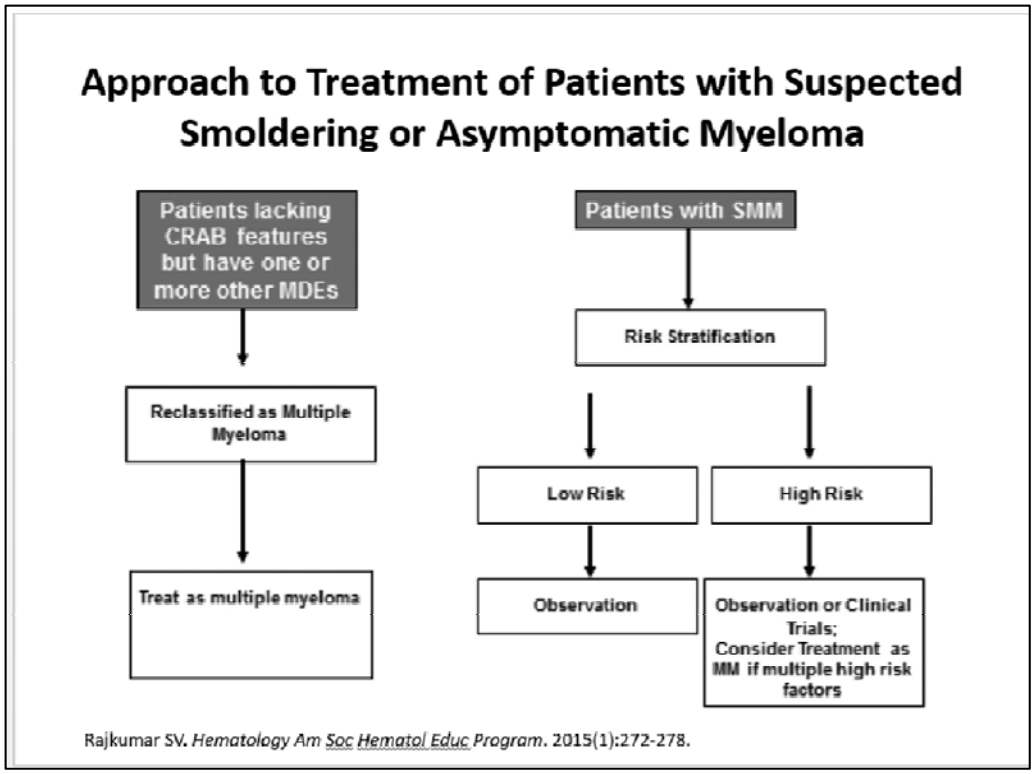
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice



How are we approaching patients at this time? Remind yourself that patients lacking CRAB criteria, but have any of the SLiM characteristics, should be treated as active myeloma. Patients with smoldering myeloma can be risk-stratified. Patients with high-risk smoldering should be considered for clinical trials.

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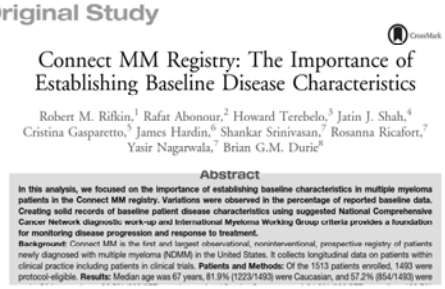
Updated Diagnostic Criteria in Multiple Myeloma: The Impact on Your Clinical Practice

Important Practice Reminder Regarding the Baseline Evaluation of MM Patients

- Many community practitioners will rely heavily on the bone marrow biopsy/ aspirate pathology report
  - This does not provide all the baseline information you will need in your diagnosis of MM and for evaluating response to management later in the life cycle of the disease when baseline information will prove critical
- How do we know that academic and community practitioners are skipping important steps in their initial workup for the diagnosis of multiple myeloma?
  - The Connect MM Registry is telling us as much

Original Study



Connect MM Registry: The Importance of Establishing Baseline Disease Characteristics

Robert M. Rifkin,[1] Rafat Abonour,[2] Howard Terebelo,[3] Jatin J. Shah,[4] Cristina Gasparetto,[5] James Hardin,[6] Shankar Srinivasan,[7] Rosanna Ricafort,[7] Yasir Nagarwala,[7] Brian G.M. Durie[8]

Abstract

In this analysis, we focused on the importance of establishing baseline characteristics in multiple myeloma patients in the Connect MM registry. Variations were observed in the percentage of reported baseline data. Creating solid records of baseline patient disease characteristics using suggested National Comprehensive Cancer Network diagnostic work-up and International Myeloma Working Group criteria provides a foundation for monitoring disease progression and response to treatment.

Background: Connect MM is the first and largest observational, noninterventional, prospective registry of patients newly diagnosed with multiple myeloma (NDMM) in the United States. It collects longitudinal data on patients within clinical practice including patients in clinical trials. **Patients and Methods:** Of the 1513 patients enrolled, 1493 were protocol-eligible. **Results:** Median age was 67 years, 81.9% (1223/1493) were Caucasian, and 57.2% (854/1493) were

Rifkin RM, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):368-376.

Connect MM is the first and largest observational, noninterventional, prospective registry of patients newly diagnosed with multiple myeloma (NDMM) in the United States. It collects longitudinal data on patients within clinical practice, including patients in clinical trials. Of the 1,513 patients enrolled by first publication, 1,493 were protocol-eligible.

I remind patients and physicians in the community that there is a registry that we should all think of participating in, if patients are willing to do so. This registry provides us a real-world picture of what is happening in the myeloma patients, in the community.

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The MM Connect Registry Shows that Both Community and Academic Practitioners Are Not Performing All of the NCCN/IMWG Recommended Baseline Work-up Tests for MM

National Comprehensive Cancer Network Recommended Initial Work-up Fields Completed (N=1493)

Variable	Value
Median Number Completed (P25, P75)[a]	12.0 (10.0, 13.0)
Median Percentage Completed (P25, P75)[a]	80.0 (66.7, 86.7)
National Comprehensive Cancer Network Workup Field Completed, n (%)[b]	
Medical history	1493 (100)
Complete blood cell count	1410 (94.4)
Bone marrow biopsy	1376 (92.2)
Calcium, blood urea nitrogen, and creatinine levels	1344 (90.0)
Bone marrow aspirate	1318 (88.3)
Skeletal survey	1266 (84.8)
Albumin	1258 (84.3)
Protein electrophoresis: serum or urine	1164 (78.0)
β2-microglobulin	1107 (74.1)
Quantitative immunoglobulins	1080 (72.3)
Immunofixation studies: serum or urine	985 (66.0)
Conventional cytogenetic analysis	944 (63.2)
Serum free light chain ratio	927 (62.1)
Fluorescence in situ hybridization analysis	893 (59.8)
Lactate dehydrogenase	574 (38.4)

Abbreviation: P = percentile.
[a]Of a maximum of 15.
[b]Values might not add up to 100% because of missing data.

Rifkin RM, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):368-376.

For example, this registry allowed us to show something which we need to change. As I have stated, the National Comprehensive Cancer Network (NCCN) has said that there is a minimal workup that all patients with newly diagnosed myeloma should have -- they should have a medical history and physical, a bone marrow biopsy, they should have a complete blood count, complete metabolic profile, a bone marrow aspiration biopsy, an albumin level, a beta-2 microglobulin level, a skeletal survey, preferably also with enhanced radiologic assessment, either whole body CT and PET-CT, they should have protein serum electrophoresis, a urine electrophoresis, immunofixation studies, quantitative immunoglobulins, cytogenetics, free light chain, and LDH. And in the bone marrow, CD138 fraction should be sent for FISH analysis.

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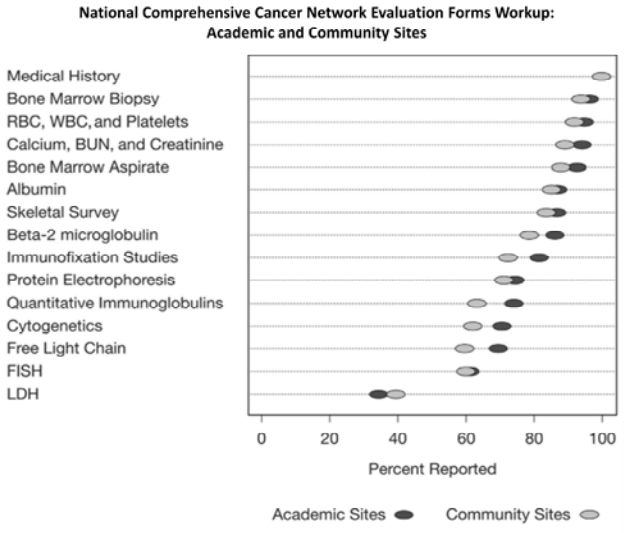
The MM Connect Registry Shows that Both Community and Academic Practitioners Are Not Performing All of the NCCN/IMWG Recommended Baseline Work-up Tests for MM



Rifkin RM, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):368-376.

Unfortunately, when we look throughout the community, even in academic centers, most of the academic centers in the community practices are only doing all the recommended workup in 60-70% of the patients, which means that 30-40% of the patients are not getting the minimal workup that we think is necessary for an appropriate risk stratification, and treatment planning for patients with myeloma today. We are hoping that this registry will be useful for us to show that we are increasing the bar and the quality of care that is provided to myeloma patients, not only in the academic centers, in the myeloma centers of excellence, but also more importantly in the community close to where the patients live.

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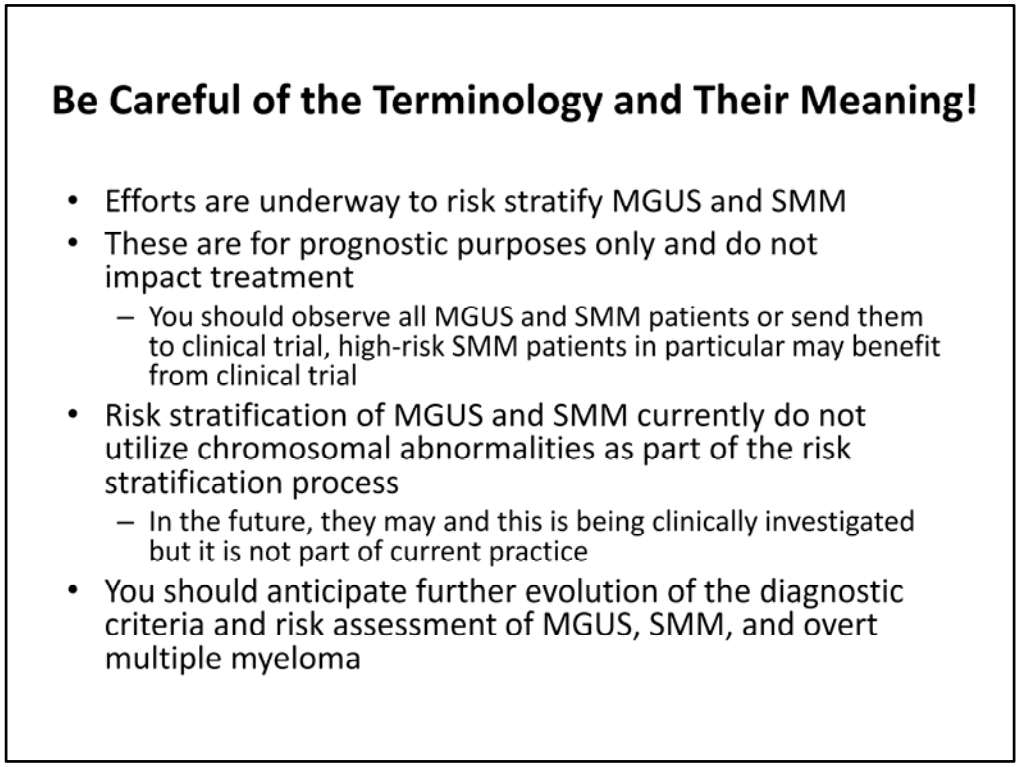

Once again, we recognize that the changing criteria are always difficult to adopt. The reason why the International Myeloma Working Group decided to do this is because we think it is beneficial for the patients to be able to be treated before they develop signs and symptoms of end-organ damage. We will continue to work to risk-stratify patients with both monoclonal gammopathy of undetermined significance, and smoldering multiple myeloma. Our eventual goal is to allow patients to have the longest life, with the best quality of life, with a minimum burden of therapy, and we recognize that some these terminologies are confusing. We recommend all patients and physicians who are dealing with multiple myeloma to stay attuned, and to keep using these educational forums such as *Managing Myeloma,* as well as the patient advocacy websites. They are essential for education, and for keeping us all up-to-date in what is happening with the myeloma field.

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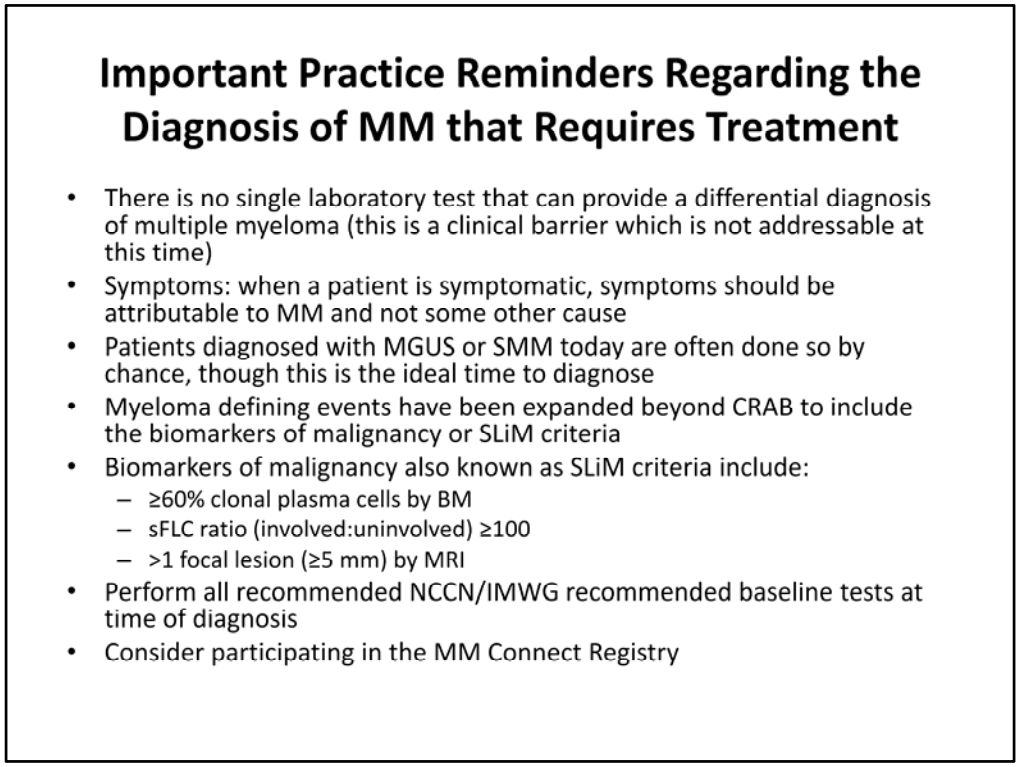

Let me once again remind you that there is no single laboratory test that can allow us to differentiate multiple myeloma from smoldering myeloma from MGUS, that when the patient is symptomatic, symptoms should be attributable to multiple myeloma and not other causes. Patients diagnosed with MGUS and smoldering myeloma are usually done by chance, and that they require further workup. Myeloma defining events have been expanded beyond CRAB to include biomarkers of malignancy or SLiM criteria. These SLiM criteria are now 60% clonal plasma cells or more, a free light chain ratio of involved versus involved over uninvolved to greater than 100, greater than one focal lesion by MRI. We also recommend that all of us that are treating myeloma patients should follow recommended NCCN/IMWG baseline tests at the time of diagnosis. I encourage patients and physicians to participate in the *Myeloma Connect Registry*.

Thank you for viewing this activity. For additional resources, please view the other educational activities on *ManagingMyeloma.com*.

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