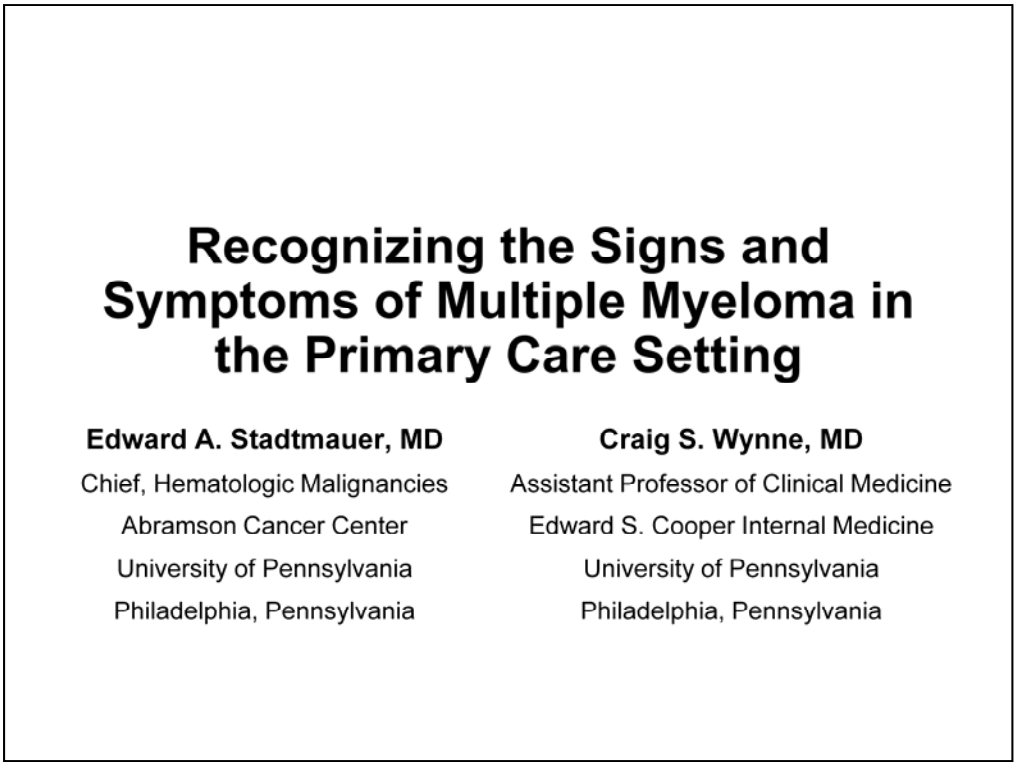
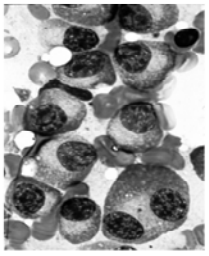
Recognizing the Signs and Symptoms of Multiple Myeloma in the Primary Care Setting

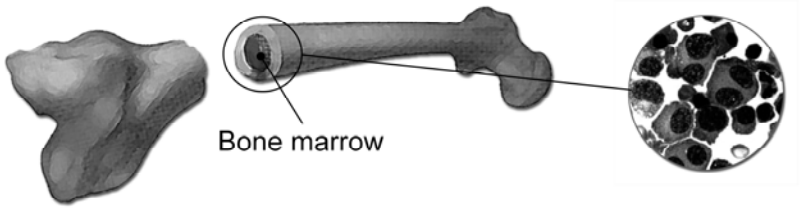


Edward Stadtmauer: Hello and welcome. I am Dr. Edward Stadtmauer, chief of the Hematologic Malignancy Section of the Abramson Cancer Center of the University of Pennsylvania in Philadelphia, Pennsylvania. Today, I am joined by Craig Wynne, assistant professor of clinical medicine at the University of Pennsylvania Health System in Philadelphia. Thank you for joining me today Craig. We would like to take the next 30 minutes to discuss what we believe to be the important role that primary care physicians and providers can play in uncovering multiple myeloma patients in the primary care setting. Early recognition and referral of multiple myeloma patients before they have significant disease burden is important and has been demonstrated to translate into improved patient outcomes. However, as we will discuss, no single test will provide a diagnosis of multiple myeloma, and so primary care physicians must be able to navigate the differential diagnosis of this malignancy.

What Is Multiple Myeloma?

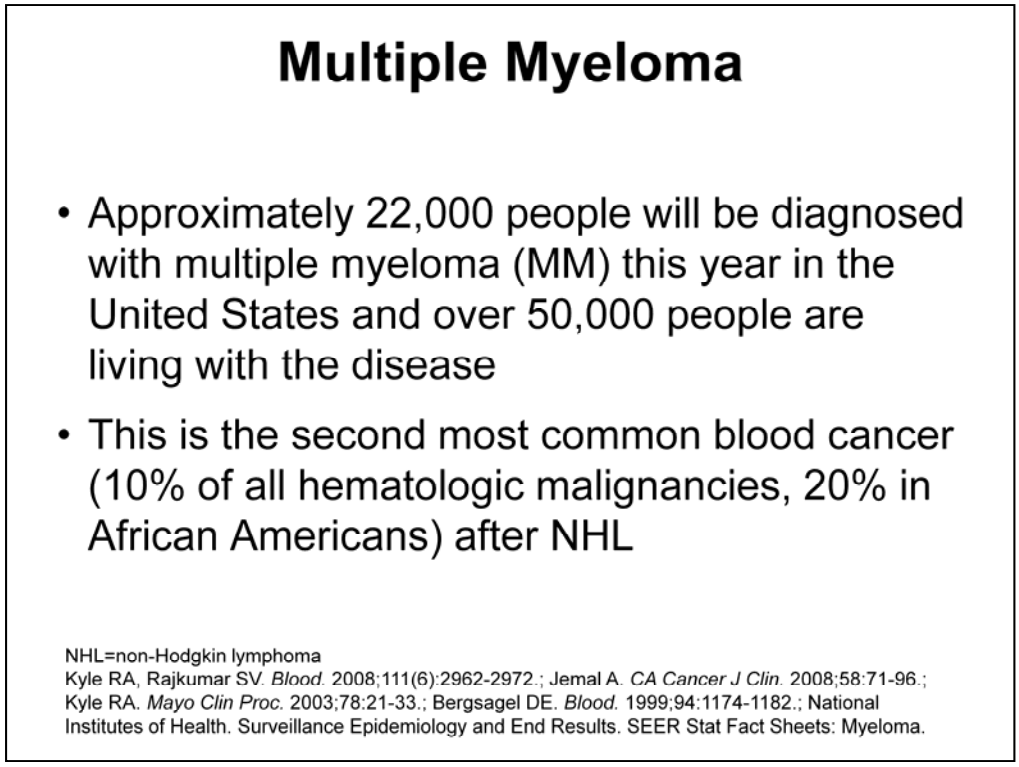


- Cancer of the plasma cells in bone marrow
- Growth of myeloma cells
  - Disrupts normal bone marrow function
  - Reduces normal immune function
  - Results in abnormal production and release of monoclonal protein into blood and/or urine
  - Destroys and invades surrounding bone

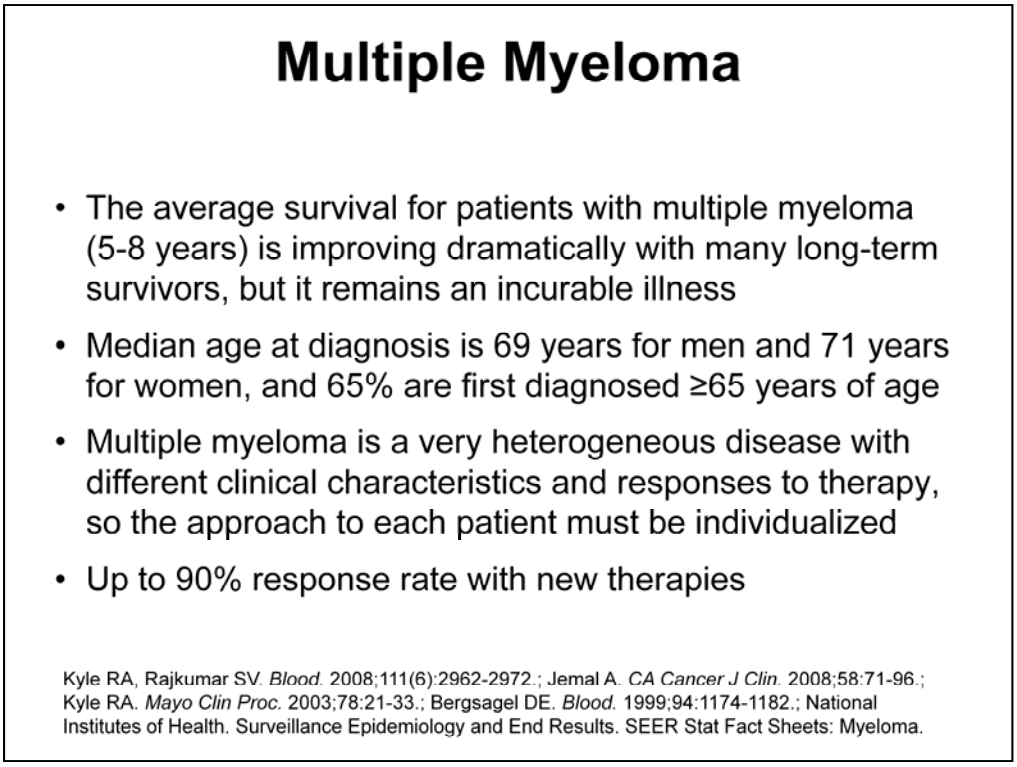


Barlogie B, et al. In: *Williams Hematology.* 7th ed. 2006:1501.;
Durie. International Myeloma Foundation. 2007. *www.myeloma.org.*

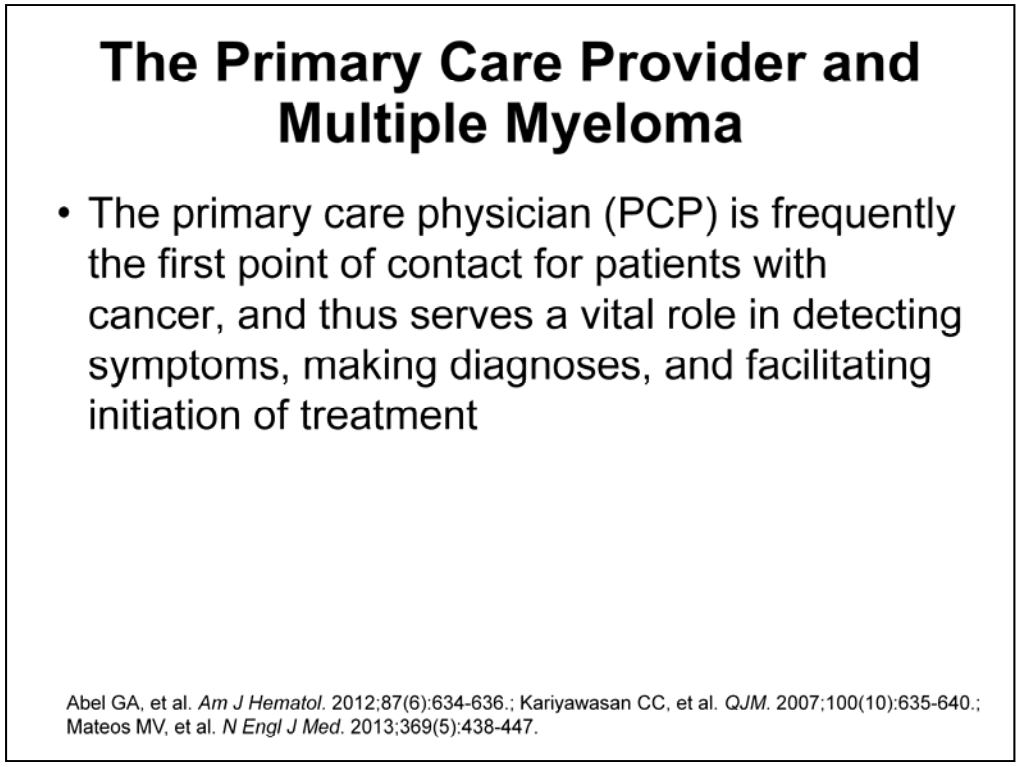
Let me first start by reminding us what is myeloma. Myeloma is a cancer of plasma cells. Plasma cells are the cells in the bone marrow that make the antibodies that fight infection. Once myeloma has been produced in the bone marrow, it leads to the production of many other cytokines and disruptive the factors that lead to low blood count, abnormal immune function, and invasion into bony tissues and lytic lesions.



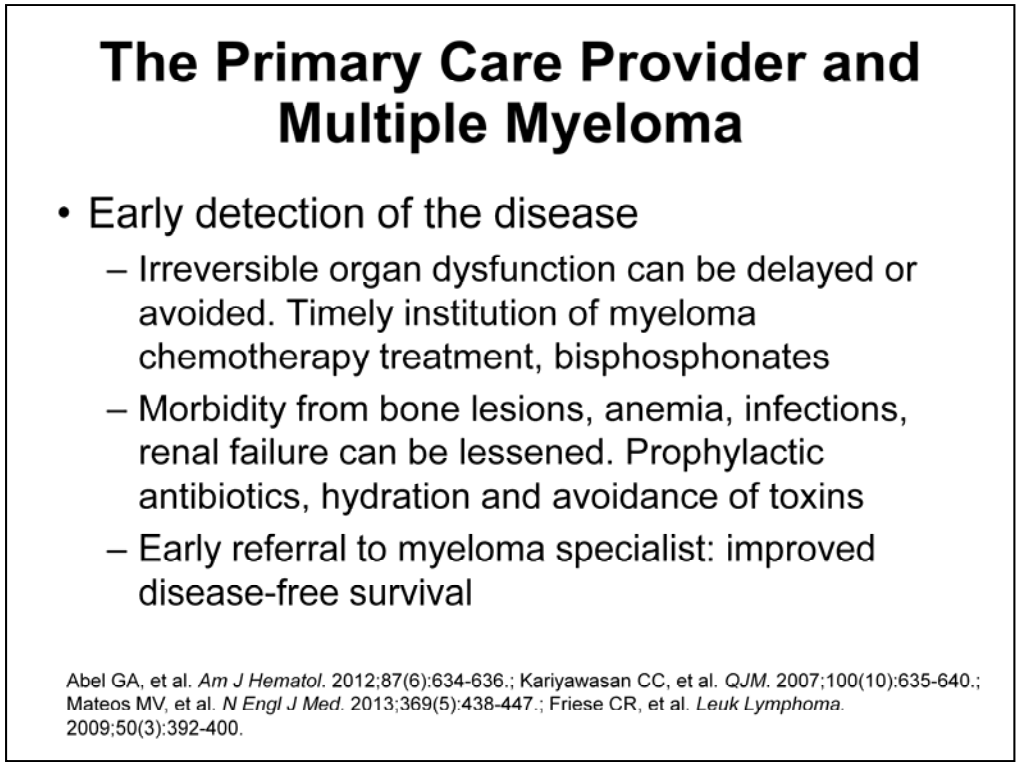
Approximately 22,000 people will be diagnosed with multiple myeloma this year in the United States, and over 50,000 people are living with this disease. This is the second most common blood cancer, about 10% of all hematologic malignancies, and in African Americans, it accounts for 20% of the patients. Only non-Hodgkin's lymphoma has more incidents in the United States than multiple myeloma.



The average survival of patients with multiple myeloma is improving dramatically from when Craig and I started caring for these patients. We were happy a decade, two decades ago, if a patient responded and survived with the disease for perhaps two or three years. Now, the median survival of patients with myeloma is over five to eight years and it continues to improve. Unfortunately, this disease remains an incurable illness. This is a disease of adults. The median age at diagnosis is 69 to 71, and two-thirds of the patients are first diagnosed greater than age 65 years. It is a very heterogeneous disease, different clinical characteristics and responses to therapy, and the approach to each patient must be individualized. But one of the major success stories is that up to 90% of patients will respond to the initial therapy that they receive.



Craig Wynne: Thank you Ed. Thank you for having me with you today for a really important topic. As a primary care physician, we see such a broad variety of topics, and very commonly, we will get a standard CBC and the patient will come back with mild anemia, usually normocytic, and the questions I often have to run through my head is, “What kind of work up do I do, and when do I have to think about diseases like multiple myeloma?”



Edward Stadtmauer: So Craig, I definitely believe that the primary care physician is a critical member of the team that cares for and diagnoses multiple myeloma. Could you provide us with some sense of how you see that role?

Craig Wynne: I do see us playing a primary role in the initial evaluation of a disease like multiple myeloma. When patients come to us, they have no undifferentiated disease. They may come in with no symptoms at all and come in for a general checkup.

Likelihood of Referral for Multiple Myeloma: PCPs First Reported Clinical Action

When Patient Presents with New-Onset Anemia (Hg = 80% of normal)*

PCP Action	% Reporting
Iron studies	93.2
Differential	85.7
B12/folate	85.0
Stool guaiac	69.2
Reticulocyte count	66.2
Two-week follow-up	30.8
Colonoscopy	26.3
SPEP	17.3
Depends on age	12.0
EGD	8.3
Refer to hematologist	3.8
Obtain imaging	1.5

*Respondents could choose more than one action

When Patient Presents with New-Onset Anemia (Hg = 80% of normal) and One Additional Sign or Symptom*

Sign/Symptom**	Imaging (%)	Hematologist Referral (%)	2-Week Follow-Up (%)
Fever	46.6	8.3	58.7
Leukocytosis	33.1	37.6	51.1
Leukopenia	15.8	63.9	28.6
Lymphadenopathy	67.7	42.9	28.6
Night sweats	69.2	25.6	37.6
Pancytopenia	9.8	88.7	12.8
Thrombocytopenia	15.0	63.9	32.3
Thrombocytosis	15.0	42.9	48.1
Weight loss	54.1	23.3	43.6
Insistent family	21.1	39.9	57.9
Patient feels unwell	32.3	6.8	77.4

*Respondents could choose more than one action
**All row differences were significant at $P \leq .01$

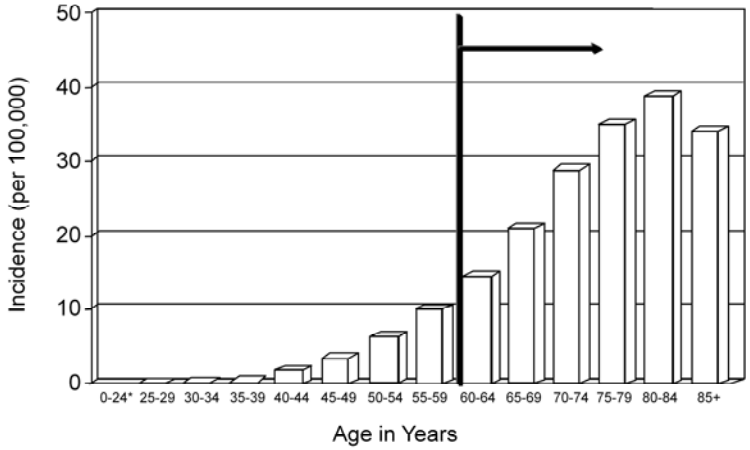
- Among patients most likely to be referred to a hematologist (those with pancytopenia, thrombocytopenia or leukopenia)
- PCPs reported recommending low levels of two-week follow-up in addition to the referral (10.6%, 16.7% and 15.6%)

Hg=hemoglobin; SPEP=serum protein electrophoresis; EGD=esophagogastroduodenoscopy
Abel GA, et al. *Am J Hematol.* 2012;87(6):634-636.

They might come in with fatigue symptoms, and often it is just a simple test like a blood count that gets us on the way to making this diagnosis. And it is a very common practice that I will have a patient come in, I will get the CBC on them, maybe they will have some fatigue symptoms but often not much more than that, and I will get back CBC with a normocytic anemia. The question that always comes to mind is how much workup to do and what to do first.

Incidence Rates

Age-Specific Incidence Rates for Myeloma, 2001–2005



*<6 cases for this age group

SEER Cancer Statistics Review, 1975-2005, National Cancer Institute, 2008.

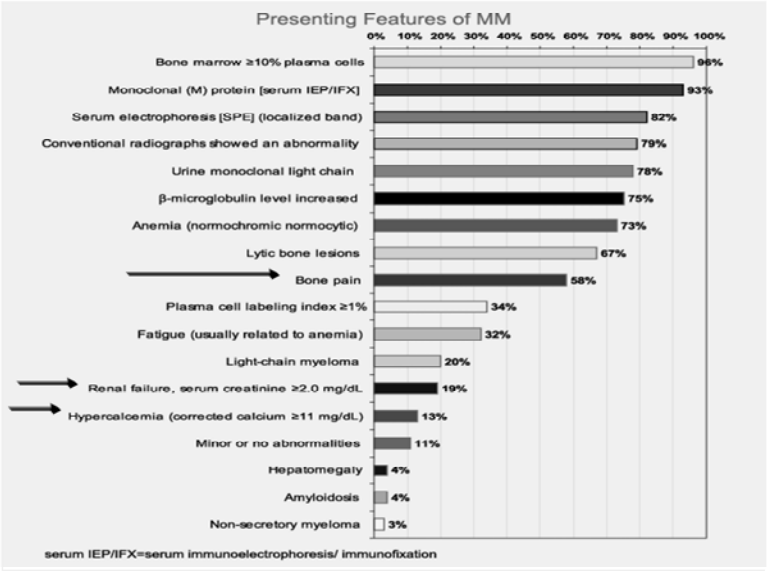
In many cases, I am thinking about diseases like myeloma, particularly in my older patients, people over 60.

I have to admit when I have a 30-year-old, I am not thinking about this and I probably should not be thinking about it.

Edward Stadtmauer: I think that is appropriate.

Clinical Features at Presentation

11% are asymptomatic or have only mild symptoms at diagnosis

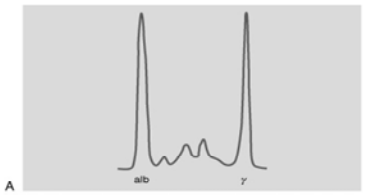


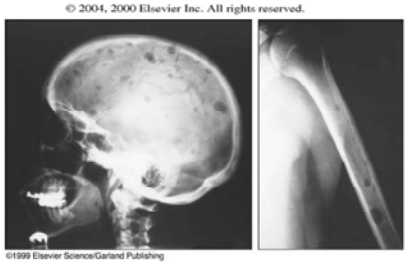
Kyle RA. *Mayo Clin Proc.* 2003;78:21-33.

Craig Wynne: But when I have an older patient I am. Of course, it is easy when they present with some of the unfortunately more severe later symptoms, bone pain, or if on their blood test they have elevated calcium, they have an elevated creatinine, that is a little bit more straightforward.

Multiple Myeloma Features

- Clinical features
  - Presence of monoclonal protein
  - Bone destruction (lytic bone lesions)
  - Anemia
  - Renal failure
  - Increased risk of infection
  - Hypercalcemia
  - Neurologic
    - Spinal cord compression
    - Peripheral neuropathy
    - Hyperviscosity





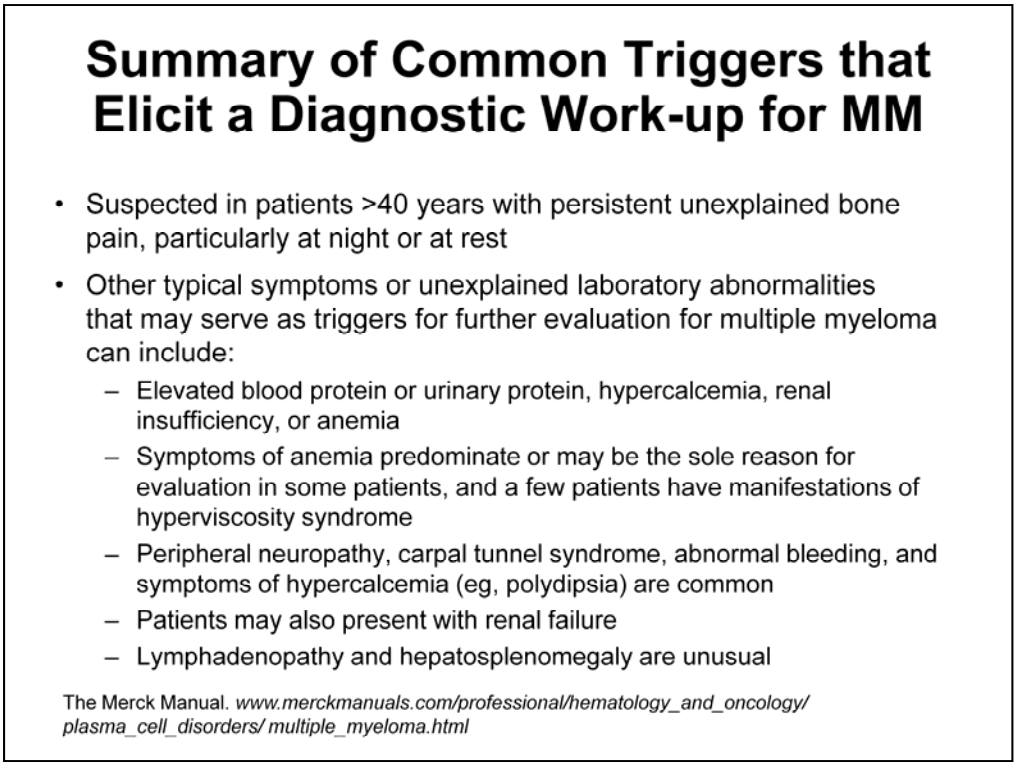
Adapted from: Saba HI, Mufti G, eds. *Advances in Malignant Hematology*. John Wiley & Sons. 2011;320:table 20.1.; Kyle RA, et al. *Blood.* 2008;111(6):2962-2972.

The question for me is when do I do that workup in the patient who has just a little bit of anemia because I am trying to make this diagnosis early, in the care of the patient and try and get them to someone like yourself sooner so that they can get the appropriate care they need. I kind of pride myself in trying to have a close working relationship with the specialists. I think we have that very nicely at Penn, the ability to pick up the phone or communicate through electronic medical record about the patient care; and even after I send the patient to you, I want to know, and the patient calls me up and maybe they have diabetes or some other issues, what do I have to worry about? What do I have to think about? What toxicities of the treatment should I think about? What should I worry about that might tell me, hey, this is progressive disease. Does this patient need to see Ed back already?

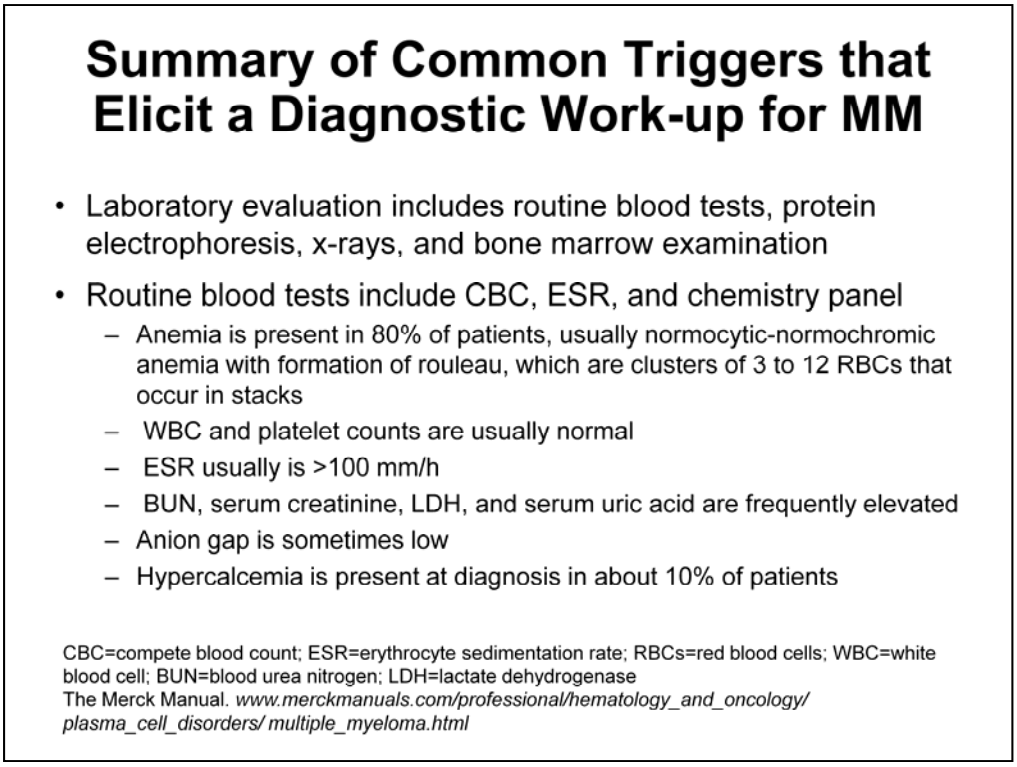
Edward Stadtmauer: So yes, I agree. I mean I am always, and I speak I believe for all myeloma specialists that we are so happy and find it necessary to have the primary care physicians as part of this process. It is remarkable. I always say in myeloma, it always rationalizes the fact that I had an internal medicine training before becoming an oncologist because it can affect so many organs. It can affect so many symptoms, so many blood counts, and then these patients start developing hypertension from their therapy or hyperglycemia or a thrombosis, and having the partner with the primary care provider is just so helpful and so important.

Craig Wynne: Thank you for saying that.

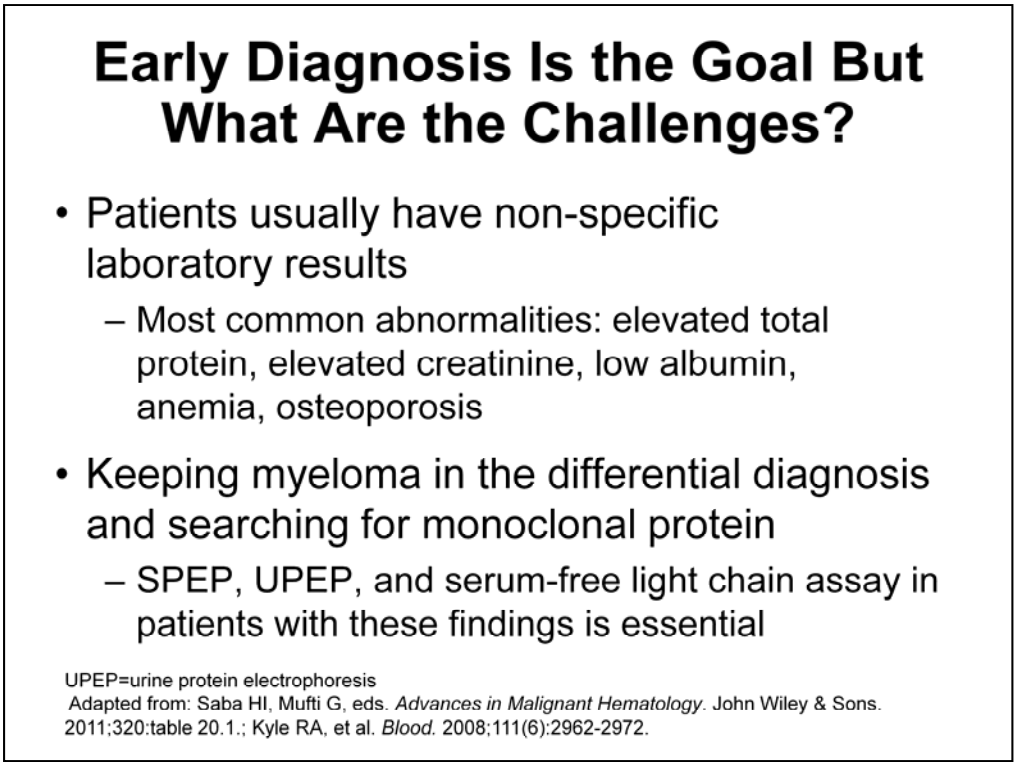
Edward Stadtmauer: So, let us delve a little bit more into that initial diagnosis because I agree, it is so important to have early detection and you are the frontline, and that is why we again appreciate you so much because when almost every time I see a new patient, I am always very impressed that the primary care provider picked up this disease. I have the easy part. I know how to treat myeloma, but picking it up is the hard part. So, what makes a primary care physician pause and ask, “Does this patient have myeloma?”



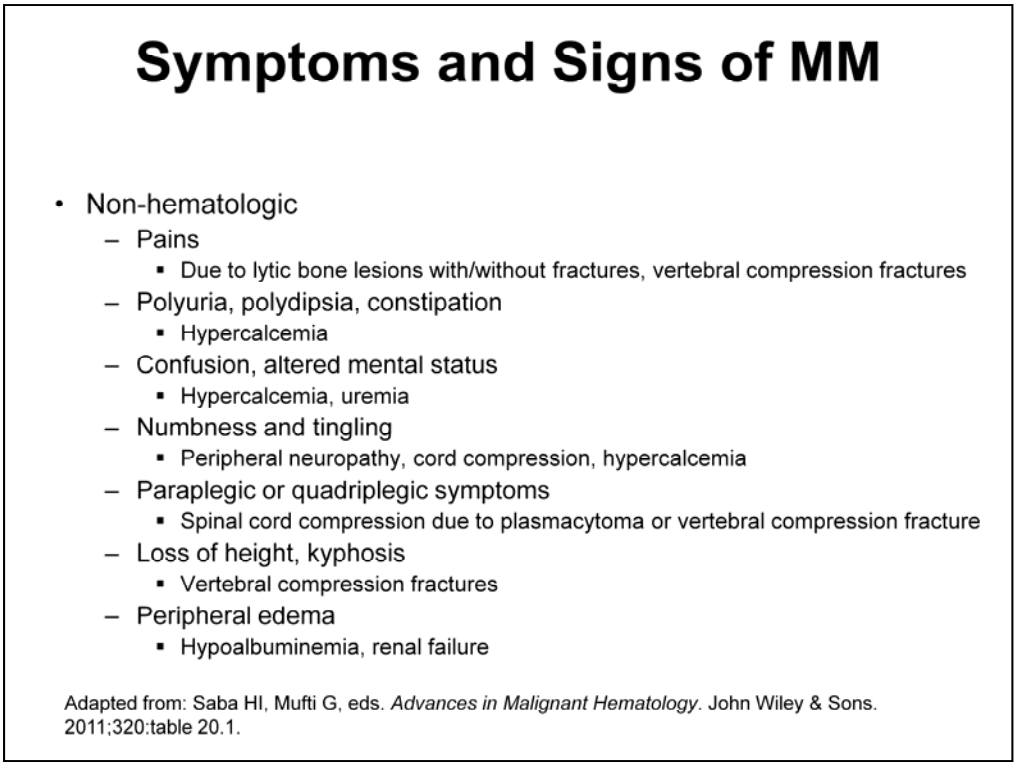
Craig Wynne: Well, I think there are the obvious cases that might come in, and I have to admit that I think in my practice that is the rare patient. The patient who walks in to my door and says, “Dr. Wynne, I have never been so fatigued, never so worn out in my life, and I am aching all over,” that maybe they are describing spine pain for them, and I get a lab test on them and it shows that they have an anemia, usually a normocytic anemia.



I will get a basic chemistry on them, and it shows that their calcium is 11 or 12. The creatinine is now 2, and I had one from a year or so before and it was 1, clearly something is going on. That is pretty straightforward, and I can sort of do my normal workup.



In many cases, the patients do not present with all those symptoms. They might say fatigue or they might just be coming for a general checkup. I happen to get a blood count and I note why is this hemoglobin 9, what is going on here? And that is where the start of that whole workup begins. Now if it is more microcytic, I am going to do iron studies to look for iron deficiency anemia. I might think of is there a reason for anemia of chronic disease in this patient? If they are more macrocytic where there is a mixed picture, I might get B12 levels, but particularly if it is normocytic or if those tests do not really pan out, then I am starting to do the next test; and from being in to me from early on to get an SPEP and I remember in the back of my head, get the SPEP, but remember, the SPEP will not pick up everyone, so get that UPEP, and I still remember setting people down with a jug to get the UPEP and hopefully collect it and call them back several times to do that, and I am happy to see that we have some newer techniques that can help us, sort of, bypass doing that test.



I certainly want to get a chemistry, again to look for calcium to look at creatinine, and I think some of the things that I do not maybe always get upfront and we can talk about a little bit is things like beta-2 microglobulin, and that is not something that always comes to mind when I first see a patient. Certainly, if someone is presenting with bone pain, I will think about doing a skeletal survey. I try to look for that and I try and have a very high instance of suspicion, particularly if there is potentially disease of the spine in those cases. Some of my patients that have presented to me are presented with neurologic symptoms. A foot drop that is unexplained, peripheral neuropathy that is unexplained. I am surprised as I have noticed how often it is neurologic symptoms one of the most common things that I see that make me think about myeloma. When I see that combination of anemia and an unexplained neurologic symptom, and so, that pushes me along the way a bit more as well. Certainly, the older the patient is, the more I am going to think about this. In my patients over 60, I am going to be much more vigilant about this, although I have to admit in my practice I start thinking around 50 a lot more because I have had enough patients who really are in that age group, who are presenting like this or they might present with sort of an MGUS picture, and I begin that kind of monitoring of them earlier on.

Edward Stadtmauer: And certainly, the median age or the average age is 60s, 70s, 80s. My youngest patient was 24 with myeloma. So I do in my heart think of it as a disease of the entire age spectrum of adults. I really do not think of it as a pediatric disease, but you are right, the incidents under age 40 is so low that it is reasonable to be considering that maybe a little later than other differential diagnosis.

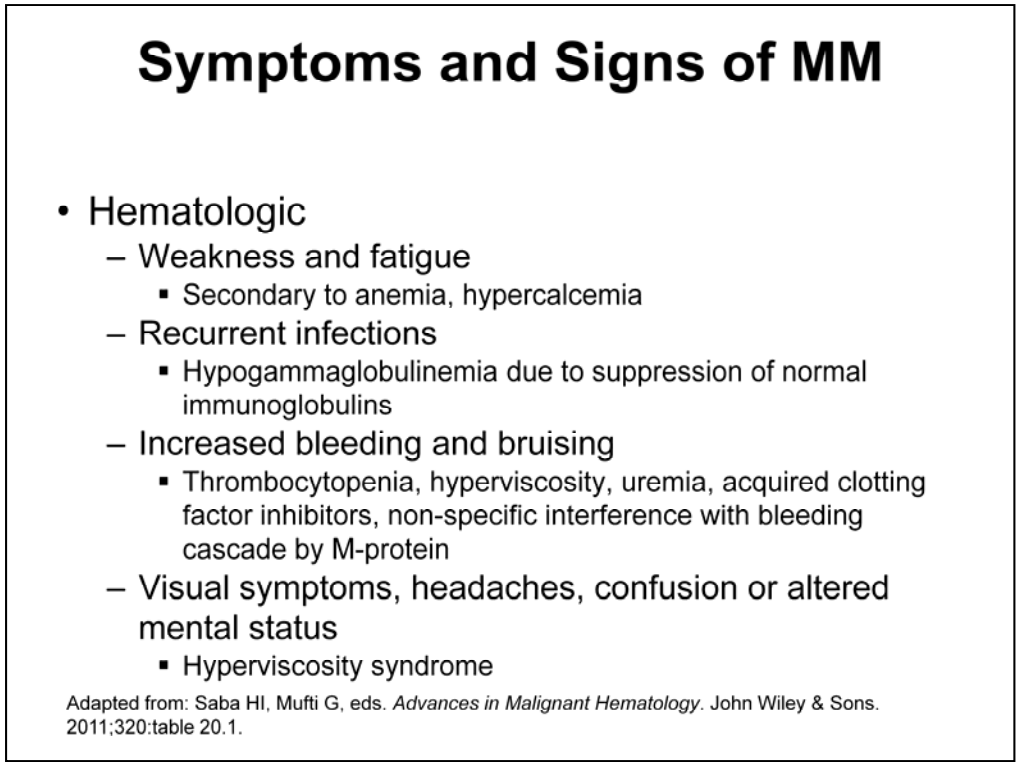
Craig Wynne: Well, that is good. I mean one of the things as a primary care doctor, we are trying to diagnose it up early, make the right diagnosis, but not be accused of over testing.

Edward Stadtmauer: Exactly**.**

Craig Wynne: Sometimes it is a difficult to walk to cross. My sense is that we are trying to make this diagnosis earlier so that when the patient gets to you, you have a lot of options available to you to do that. I certainly worry when I send you the patients that have already got significant kidney disease, how does that limit or affect your ability to care for them.

Edward Stadtmauer: Definitely.

Craig Wynne: And again, you know, when I see someone with some of the early signs, unexplained pain, unexplained urinary symptoms, polyuria, polydipsia, certainly in my older patients' acute confusional state with hypercalcemia is certainly a red flag for multiple malignancies but myeloma is certainly in that group. Sometimes unexplained peripheral edema and that I get a blood count and their albumin is in the 2s and it is not the classic kind of diabetic or nephrotic syndrome. I start to wonder what else may be causing this, and so, hopefully I am not seeing a lot of those patients, and I am picking them up much earlier.



Is there things that when we send patients to you that you see that primary care doctors do well or what we could do better in picking up this disorder at an earlier state?

Edward Stadtmauer: Well, I mean it is sort of interesting. As you have been speaking, I have been thinking about how when we started our training, around that time was probably the end of the TB era. Maybe, it is a little earlier even than that; but back in those days, basically anything could be TB. TB, tuberculosis should be in the differential diagnosis. I think what you are describing really tells me that in the current era, myeloma is in the differential diagnosis of so many different things. I think that is great. I think the awareness of that from the primary care physicians has really helped tremendously, so where maybe a decade or so ago we would see patients and we would just say, oh, if only they came to us earlier that would be great, I think nowadays the awareness is great, and I think programs like this will increase the awareness to make sure that the patients come early in the course of their diagnosis.

Craig Wynne: That is wonderful.

Edward Stadtmauer: So from your point of view, what are the challenges that you have to thinking about the diagnosis and confirming the diagnosis of myeloma?

Craig Wynne: You know, certainly having it in my head first. I always say you do not have to, as a primary care doctor, know everything, but you have to have enough sense to know when we will have to look a little deeper. And, you know, I think with the electronic medical records and other ways, we can quickly pull information to go further.

Edward Stadtmauer: So, let me tell you a little bit about the workup of a patient who either has myeloma or we are considering for myeloma. Usually, one of those triggers -- a low anemia, a high calcium, some renal insufficiency, a lytic bone lesion -- is what stimulates you to obtain one of the tests that will look for monoclonal protein; and usually after the monoclonal protein is detected, that is when you will send the patient to us.

Diagnostic Evaluation

Test	Finding (s) With Myeloma
CBC with differential counts	↓ Hgb, ↓ WBC, ↓ platelets
Chemistries: BUN, creatinine electrolytes, calcium, **albumin**, LDH, uric acid	↑ Creat, ↑ Ca+, ↑ Uric acid, ↓ **Alb**
Serum electrophoresis with quantitative immunoglobulins	↑ M-protein in serum, may have ↓ levels of normal antibodies
Immunofixation	Identifies light/heavy chain types M-protein
β_2-microglobulin	↑ Levels (measure of tumor burden)
C-reactive protein	↑ Levels (marker for myeloma growth factor)
24-hour urine protein electrophoresis with immunofixation	↑ Monoclonal protein (Bence-Jones), proteinuria
Serum-free light chain	↑ Free light chains (lambda or kappa)
Bone marrow biopsy & cytogenetics, FISH, IHC	≥0% plasma cells
Skeletal survey	Osteolytic lesions, osteoporosis
MRI or PET/CT as clinically indicated	Evaluation of involvement of disease

FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; MRI=magnetic resonance imaging; PET/CT=positron emission tomography/computed tomography; Hgb=hemoglobin; Creat=creatinine; CA+=calcium; Alb=albumin

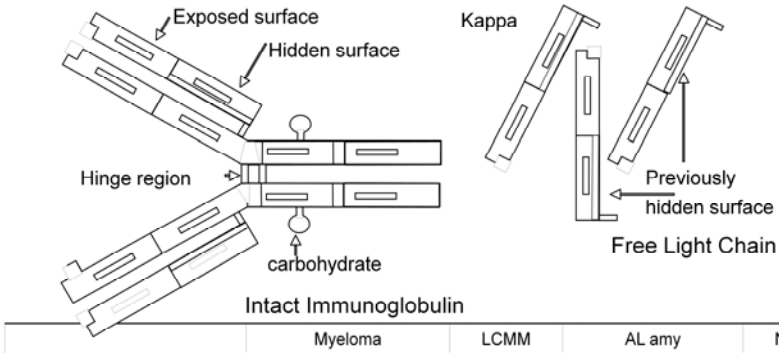
NCCN. Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.1.2014 (release date 9/6/2013).

In addition to that test, every patient, and most patients of course do, should have a CBC, a complete blood count with differential, very standard serum chemistries such as BUN, creatinine, uric acid, albumin, etc, If they found the light chain or the monoclonal protein by serum protein electrophoresis, they should also have quantitative immunoglobulins, the total level of immunoglobulin, as well as an immunofixation of the tests to see what subtype it is, is it IgA or IgG? Is it a kappa or lambda? The patient should have…every patient even with the newer technology, I believe every patient should still have at least one 24-hour urine for urine protein electrophoresis and looking both for the Bence Jones proteinuria for the light chain in the urine and to quantify it. I think it is really helpful to know whether somebody is producing grams of protein in the urine versus small amounts, I think that is helpful. I think the serum-free light chain test has really been a major change in the way that we can both detect and follow the disease. In particular, in the old days, we used to have maybe 5% or more of patients who had active myeloma where we could not find any monoclonal protein; and with that test, two-thirds or three-quarters of those patients have something that we can monitor. To the chagrin of the patients, every patient should have a bone marrow biopsy test, and we of course try to do that as painlessly as possible.

Craig Wynne: As primary care physicians, we let you to talk to them about that.

Edward Stadtmauer: I am sure. Now, the important thing though is in addition to doing the routine bone marrow biopsy and aspirate, all of those samples should also be sent for cytogenetic analysis, immunohistochemistry and the FISH analysis, the fluorescence in situ hybridization. I love the fact that you recognize that it is the skeletal survey, the bone survey that we use in myeloma. Frequently, we see bone scans but bone scans are not as revealing of lytic bone lesions because these lesions are not actively metabolizing because of the suppressive effects of the cytokines that are produced by the myeloma cells, and so, frequently a bone scan will be negative while a bone survey will be full of lytic lesions. Though with the more modern technologies we have, we sometimes think of a skeletal survey as a sort of an old procedure. It really is among the most revealing tests for whether a patient truly has bones that are at risk, that are at risk of fracture whether they really have lytic lesions. On the other hand, more and more we are also looking for what we called extramedullary disease. We are finding that myeloma is not just a disease of the bone marrow with lytic bone lesions, it is tumors. There are multiple myelomas, and so MRIs and PET scans, as appropriate, probably doing some sort of imaging in the early diagnosis of patients just to make sure that it is there. You keep mentioning the light chain test and that is probably the newest test since, so I think it is probably an important test for us to talk about.

Most Recent Test Added to the NCCN Required Workup: Serum-Free Light Chain Assay



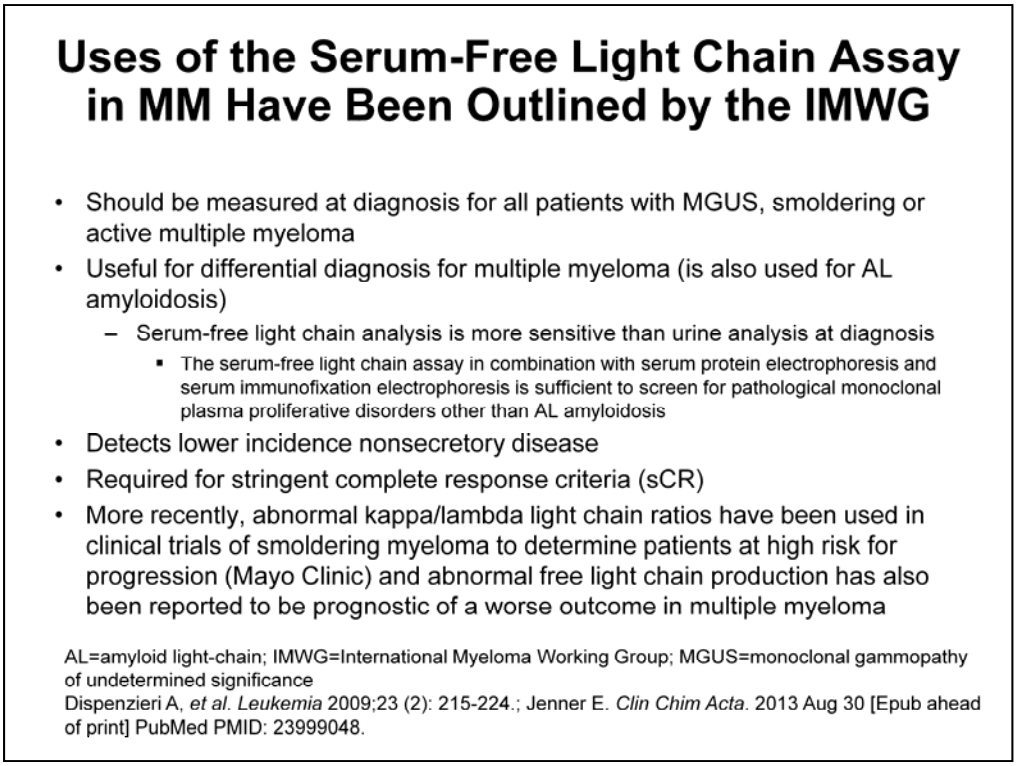
	Myeloma	LCMM	AL amy	NSMM
SPEP alone	~ 90%	45%	50%	0%
Free Light Chain	>90%	>99%	>80%	>80%

NCCN=National Comprehensive Cancer Network; LCMM=light chain only MM; AL amy=systemic light chain amyloidosis; NSMM=nonsecretory MM

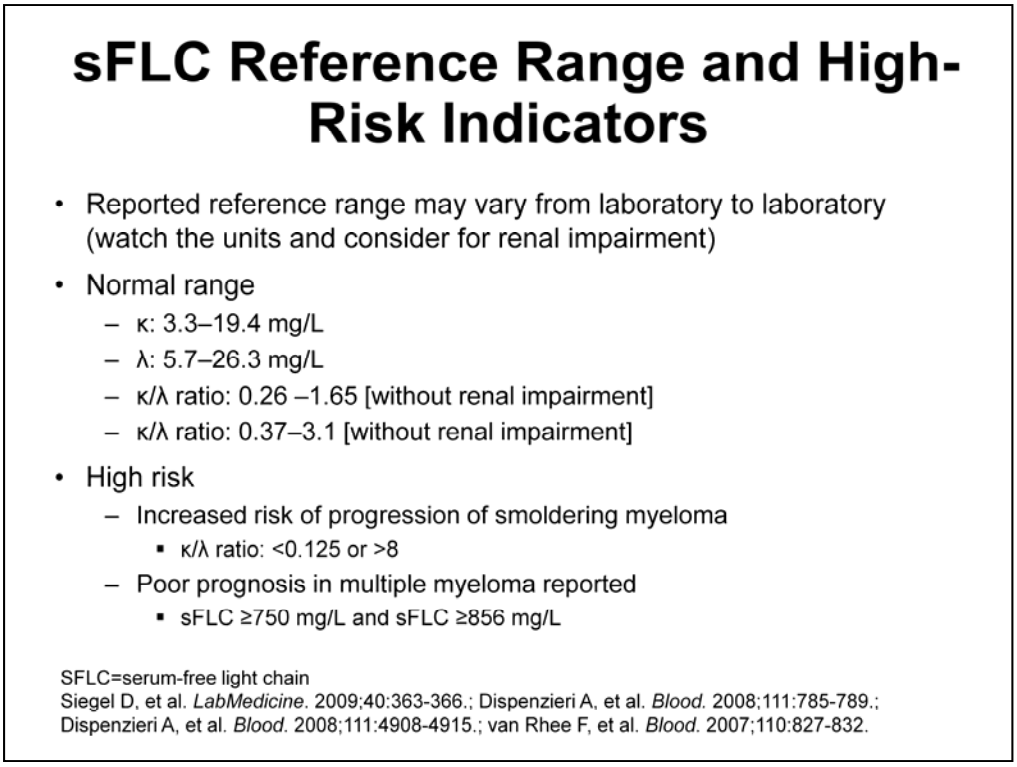
Bradwell AR, et al. *Clin Chem*. 2001;47(4):673-680.; Lachmann HJ, et al. *Br J Haematol*. 2003;122(1):78-84.; Katzmann JA, et al. *Clin Chem*. 2002;48(9):1437-1444.; Dispenzieri A, et al, International Myeloma Working Group. *Leukemia*. 2009;23(2):215-224.

Craig Wynne: And this is really helpful. First of all, I actually like the fact that you mentioned the value of getting the UPEP as a complementary test that tells us some information that even the free light chain does not so that we should not just get rid of that test. There is still an important role in it and it makes sense to understand the degree of proteinuria that a patient has. I found it is wonderful that we have the new test, I can do it, it will help me sort through this.

Edward Stadtmauer: It is interesting that we talked about the bone marrow biopsy being one of the procedures that perhaps the patients are not the most thrilled about. I would say a 24-hour urine collection is probably number two. Even though it is painless, it is a little bit awkward carrying around the jug to whatever you are trying to do. So, we try not to do that test all the time, but it can give us information. In particularly, patients who have significant proteinuria, I do like to continue to use it. But remember, what we are measuring. What we are measuring in myeloma is the monoclonal protein, and each patient has their particular antibody that is being produced by the malignant and abnormal plasma cells and sometimes it is not even a whole antibody, it is just a piece of an antibody in light chains. Remember, antibodies have heavy chains that are IgG or IgA as well as light chains; the kappa and the lambda. So, if you just monitor patients with serum protein electrophoresis, perhaps, in active myeloma, the majority of the patients will have a positive serum protein electrophoresis or urine protein electrophoresis if you do them both together, but there is a subset of patients who just have light chain myeloma, and in that group of patients, only maybe half of the time will an SPEP, serum protein electrophoresis, show a quantifiable monoclonal spike. Of course then, there is a subset of patients who have a very low level of malignant plasma cells but have very malignant light chains, and that is amyloidosis, primary systemic amyloidosis. Of course in that disease being primarily a light chain disease, the serum protein electrophoresis will only really show a quantifiable value in perhaps 50%. And then, there is that group of patients that we used to call non-secretary myeloma, and of course, none of those have a positive SPEP by definition.



Fortunately, with this more sensitive light chain test, we now in myeloma, in light chain myeloma and in amyloidosis, the vast majority of patients will have some skewed ratio of kappa to lambda on their light chain test, and then even those what we used to call non-secretary myelomas, perhaps two-thirds to three-quarters of those patients will have a monoclonal protein on light chain analysis that can be monitored. So, it really makes things much, much easier. Actually, it is now part of the International Myeloma Working Group recommendations that the light chain test should be measured at diagnosis. This is why it is so important again to have the primary care providers be part of this whole process because frequently by the time we see the patients, things may have happened to them. They may have gotten some steroids, they may have gotten some sort of therapy; and the sooner we get these measurements as a baseline as a way of beginning, to then follow is so important. So, MGUS, the monoclonal gammopathy of undetermined significance, smoldering myeloma, and active myeloma all should have some light chains tested, of course amyloidosis, and there are response criteria that we use as part of determining whether our therapies are working in myeloma. We have now added the light chain test as part of the definition of a very stringent complete response.



So, I think incorporating this test into our patients is very helpful. Interpreting it, as you have mentioned, it is not that easy to do sometimes. You have to make sure you are doing the right test. There are different tests that you can order, clicking the way on your electronic medical record that may not be the actual tests. It is very important to look at the units of the test. For instance, a range of kappa tends to be 3 to 19 mg/L and normally a range of lambda is 5.7 to 26 mg/L, and the normal ratio of these two things is somewhere in the neighborhood of 0.2 to 2. Another important thing to remember is that these light chains are excreted by the kidneys and people with renal insufficiency have baseline numbers that are higher the normal range. So, you have to look both at the absolute numbers of the light chain as well as the ratio of the light chain.

Craig Wynne: I think for every patient that we may see with myeloma is going to be large number than who probably have an MGUS and trying to figure out how to interpret those patients who can just be monitored and those who really need to see you more quickly I think is helpful. I have to say I still think for the foreseeable future, I will still ask your advice on these patients how to interpret them, especially those patients who are really, kind of, have the borderline results and how aggressive to be with our monitoring process.

Edward Stadtmauer: No, I think that is wise, and of course, we are constantly revising our interpretation of these tests and our comfort level with these tests.

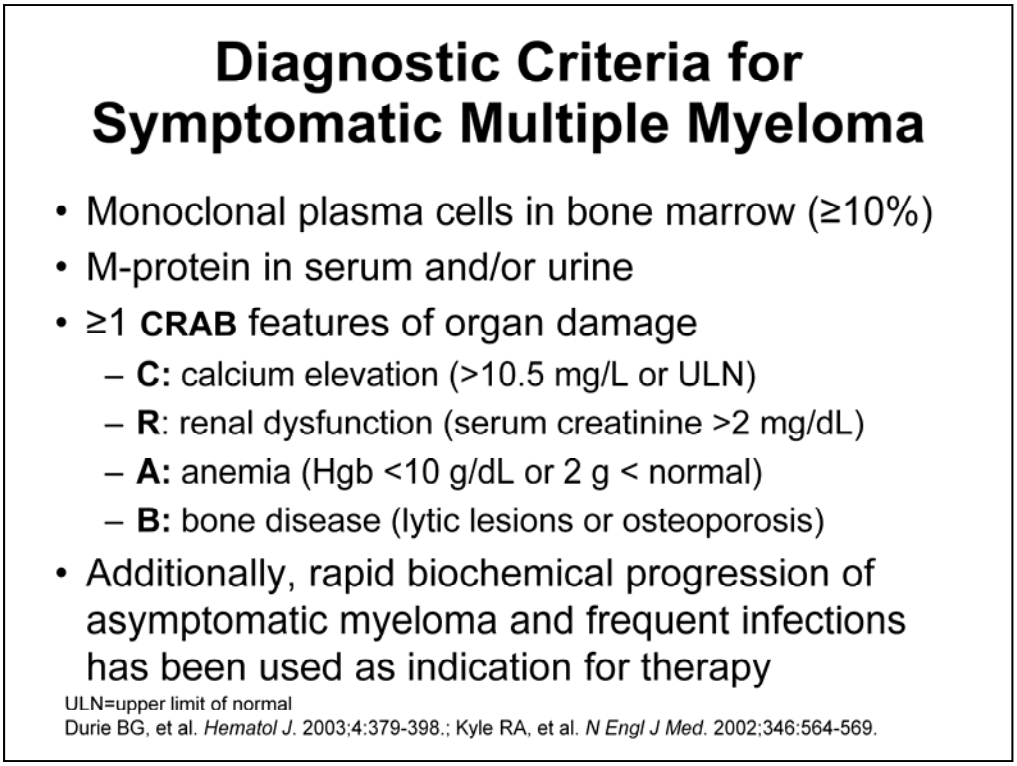
Myeloma Disease Classifications

Name	Definition
MGUS	• Monoclonal protein present • No underlying disease state • *Monitor (30% progression to symptomatic myeloma)*
Asymptomatic myeloma	• Higher level of disease than MGUS but still no symptoms or organ damage • *Monitor*
Symptomatic myeloma	• Monoclonal protein and ≥1 CRAB features of organ damage present • *Begin treatment*

CRAB=calcium elevation, renal dysfunction, anemia, bone disease
Kyle RA, et al. *N Engl J Med.* 2002;346:564-569.; Durie. International Myeloma Foundation. 2006. *www.myeloma.org.*; The International Myeloma Working Group. *Br J Haematol.* 2003;121:749-757.

Craig Wynne: Can you give me a little bit of a better sense of different types of plasma cell dyscrasias that we should be thinking about?

Edward Stadtmauer: Sure. Well, I mean it is basically all myeloma. Certainly when you see an IgM monoclonal protein, that tends to be associated more with lymphoma and the most common lymphoma that we see with that is called Waldenstrom macroglobulinemia; but when you see an IgA and IgG or one of the light chain tests, and incidentally there is an IgD myeloma and IgE myeloma, very uncommon but part of the reason why they are probably uncommon or even more uncommon is because we do not routinely test for those. So, I think it is very likely that some of the light chain myelomas that we see are actually IgD and an IgE. With the light chain test, it actually makes it less important for us to search for those others because we can monitor with that. These are all diseases of abnormal plasma cells, and so remember, if you have a monoclonal protein but you do not have more than 5% to 10% abnormal plasma cells in the bone marrow, we call that a monoclonal gammopathy of undetermined significance or MGUS. If you actually see the malignant plasma cells, I do not really call that a benign disease, but patients can putter around for many years just with monitoring. With asymptomatic or what we more commonly say smoldering myeloma, that is where you definitely have myeloma by virtue of the bone marrow that is full of malignant plasma cells and monoclonal protein but none of those manifestations of myeloma, and then symptomatic myeloma is when the patients, in addition to having monoclonal protein and bone marrow problems, also have these systemic manifestations of the disease.



Craig Wynne: So, how do I know when my patient may have symptomatic myeloma that I have to really be moving more rapidly?

Edward Stadtmauer: Well, since frequently the reason that you have picked up the disease in the first place was because they had pain in their bones, or because they had the anemia, or because you noticed a renal insufficiency, almost always, if you start off with an organ dysfunction and then you look and you find myeloma or monoclonal protein, almost always those will be symptomatic myeloma, and so we define symptomatic myeloma not necessarily only by people who are short of breath and tired and symptomatic but having these organ dysfunctions by lab test make you symptomatic. So those patients definitely need treatment and the criteria that we use, I guess in myeloma we are starting to like certain acronyms and the acronym for myeloma is the CRAB criteria.

Craig Wynne: And so the CRAB stands for?

Edward Stadtmauer: Well, you are the primary care physician. Tell me about what the CRAB criteria...

Craig Wynne: I would assume C would stand for calcium elevation in that way and R for kidney dysfunction or renal dysfunction in some way. A for anemia and B I guess bone disease.

Edward Stadtmauer: Right.

Craig Wynne: Pretty easy to remember and stuff for that. So that is helpful to think about. I will also just say that since this is a disease that we see actually, I think, more commonly than many people would suspect but oftentimes presents somewhat atypically, I would add that in my practice, I have seen patients present with unexplained neuropathy as their first sign with a broad differential there but that's led to me I have got a neuropathy or anemia I might think of it, or I might have a patient even in some case present with thrombosis or some other issue, maybe associated with decreased viscosity that they might have, and so, I am amazed at the kind of myriad of ways they can present and stuff for them. The only thing I can say in all cases is at least I always know that I am looking for anemia. And then I think because these tests are so easy to get, I can just work that up without having to say, is this precisely the kind of case that makes me think of myeloma?

Edward Stadtmauer: I think you are so right and that is the part of the reason why I made a little comment about the acronym. You know, we are looking for those CRAB criteria, but those are not the only reasons to either think of myeloma or to treat myeloma. We know that this is a disease where you have an increased production of a useless antibody, but you tend to have decreased production of the normal antibodies, so a susceptibility to infection. Infections can be a reason to do active treatment. Patients who have rapidly rising monoclonal protein, the writings on the wall, and more and more we are learning that if we treat those patients early before they… you do not want… this is an art form and that is why it is a great field for a generalist and for a specialist because it has so many manifestations and it is so interesting, but the art of this is to not treat people three years before they need treatment but you do not want to treat people three months after they needed treatment. You want to do it about a month or so before they need treatment, and that is why it requires such skill and observation particularly from the primary care providers.

Myeloma Prognostication/ Staging Systems

Stage	Durie-Salmon Staging System[1]	International Staging System[2]
I	All of the following: -Hemoglobin value >10.5 g/dL -Serum calcium value normal or ≤12 mg/dL -Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only -Low M-component production rate — IgG value <5 g/dL; IgA value <3 g/dL -Bence-Jones protein <4 g/24 hours	Beta 2-microglobulin <3.5 mg/dL and Albumin ≥3.5 g/dL
II	Neither stage I nor stage III - A = No renal failure (creatinine ≤2 mg/dL) - B = Renal failure (creatinine >2 mg/dL)	Beta 2-microglobulin <3.5 mg/dL and Albumin < 3.5 g/dL or beta-2-microglobulin ≥3.5 <5.5
III	-High M-component production rate - IgG value >7 g/dL; IgA value >5 g/dL -Bence-Jones protein >12 g/24 h	Beta 2-microglobulin ≥5.5 mg/dL

IG=immunoglobulin
[1]Durie BG, Salmon SE. *Cancer*. 1975;36(3):842-854. [2]Greipp PR, et al. *J Clin Oncol*. 2005;23(15):3412-3420.

Craig Wynne: So after I do those tests and I am really thinking that this is what may be going on, it seems to me that more and more one of the things that I see you guys get and think about is a beta-2 microglobulin. I hopefully have gotten some chemistries and got an albumin with that. I know that you use that test as well. Can you tell me how you use it to kind of stage the patient or understand about their prognosis?

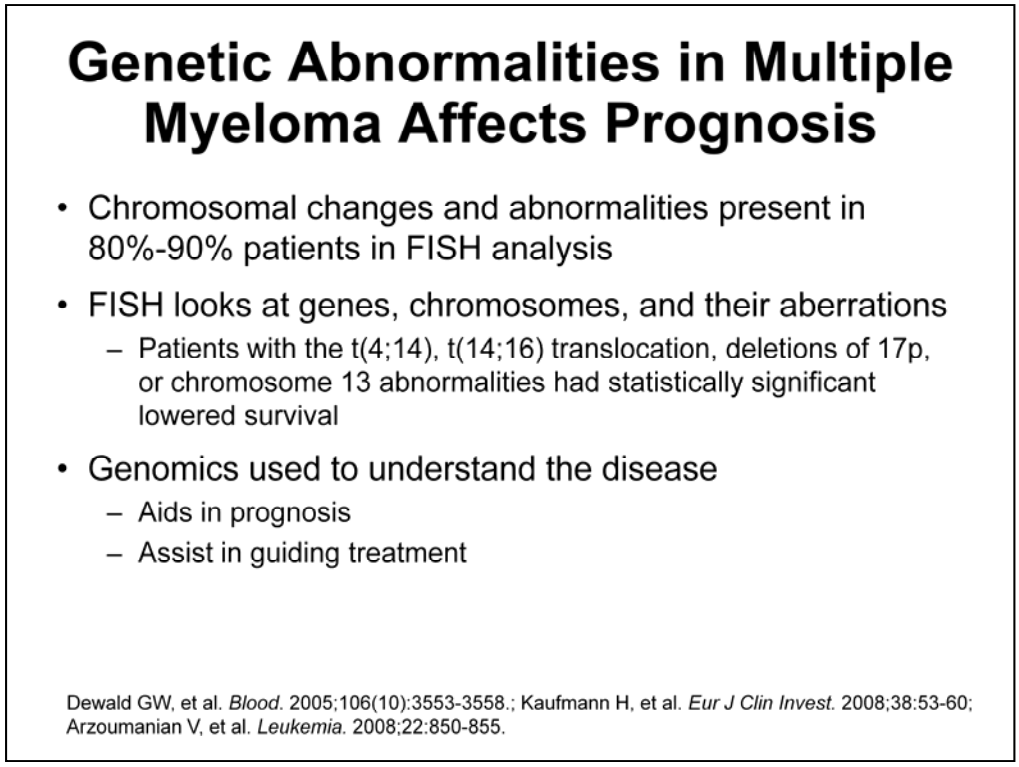
Edward Stadtmauer: Yes, definitely. This is really very helpful for us for you to get because this is another test where it turns out the most important and really the only prognostically important beta-2 microglobulin measurement is the measurement that is done before therapy. So, sometimes by the time we see the patient, the patients have had therapy and there has been no beta-2 microglobulin and then it is difficult to see. But beta-2 microglobulin throughout the last decade or so remains one of the more important prognostic indicators in myeloma. It actually is a piece of the HLA antigen that is circling around in our body, and it is very clear that patients who have an elevated beta-2 microglobulin have more active, more rapidly dividing and active disease, have a poorer prognosis in terms of survival and also in terms of time to progression, and it has been incorporated into the most recent form of our staging system which is really a prognostication system in myeloma called the International Staging System. As you know, we all grew up with the Durie Salmon Staging System, which is a very useful and still frequently referred to staging system looking for bone disease and hemoglobin, etc. Then they did a big meta-analysis where they looked at every single parameter in 10,000 patients in prior studies and they found that there were actually two parameters, or you could break it down to just two parameters that would tell you about a patient's prognosis, and it was the blood test beta-2 microglobulin and the blood test albumin. And so patients who have a normal or low beta-2 microglobulin and a normal or high albumin have the best prognosis and patients who have very high beta-2 microglobulin and lower albumins have a more difficult prognosis, but it is not the test that you follow throughout time though frequently on clinical trials we follow it. It is really only important in that it helps with the decision making and probably more so from the myeloma specialist point of view, it helps us if we are going to place someone on a clinical trial to characterize the patients as higher risk or standard risk.

Craig Wynne: So, did I hear you right that a change in the beta-2 microglobulin in treatment does not necessarily tell you about the prognosis.

Edward Stadtmauer: That is correct.

Craig Wynne: But the initial test prior to therapy is really the key point.

Edward Stadtmauer: And therefore, the primary care provider is the key to the whole thing.



Craig Wynne: So, the other thing even for a practicing physician like me is genetics, right? Get lost in genetics and try to understand all this stuff, and so, what genetic abnormalities are particularly important in multiple myeloma that can you give us some information about prognosis and how do you use some of these tests?

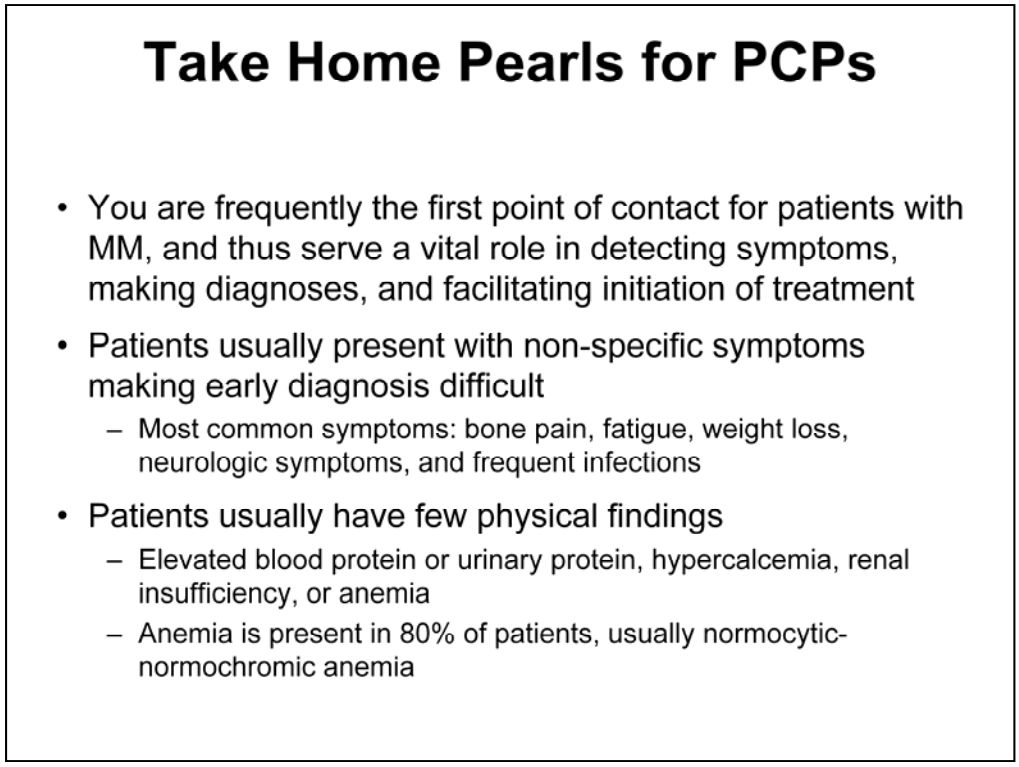
Edward Stadtmauer: I think that is an excellent question, and we have learned as in every cancer, there are chromosomal breaks and genetic translocations that occur leading to the normal plasma cells to become a malignant plasma cell. And if you do sensitive enough tests of the plasma cells, usually from the bone marrow test, up to 90% of the time, you can find some chromosomal abnormality by the sensitive test such as the FISH evaluation, etc. What is important is to differentiate an abnormal chromosomal abnormality and a prognostically important chromosomal abnormality. For instance, on the FISH evaluation, there are about three that are really pretty clearly abnormalities in the chromosomes that suggest that this patient has a higher risk disease both for progressing and survival, and that is called the 4;14 translocation or 4:16 translocation and deletions of the 17p chromosome which are associated with the p53 abnormality. It turns out that most patients with myeloma will have a chromosome-13 abnormality, that is not prognostically significant if it is determined by FISH, but if you do a standard karyotype and you see cytogenetic abnormalities in chromosome 13; and in fact if you see chromosomal abnormalities in general, that is not a good sign, that suggests a more proliferative disease because when you do standard karyotype, generally plasma cells are not my topic, and so, you cannot really… it is a failure of the test usually. So, if the test does not fail, that usually means those cells are growing more rapidly. There is a whole newer area called gene expression profiling, and there is more and more evidence that there are certain profiles of genes that are turned on and turned off that can assist in prognosis and maybe in treatment. I would still say that as of this moment, that is more of a test to be used in clinical trials to make sure that when you are comparing one treatment to another treatment that the groups are balanced, and we are still trying to figure out whether there is a better therapy based on these genetics.

Craig Wynne: So what I am hearing you say is right now these tests do not necessarily tell us, okay, if you have this result you clearly want to do this protocol or that protocol as we have in maybe some other cancers now where the test results, such as in breast cancer, really can tell you what the best or less good treatments are.

Edward Stadtmauer: I definitely agree with that statement. I feel that we are about five years behind both acute myeloid leukemia and breast cancer in being able to utilize this data.

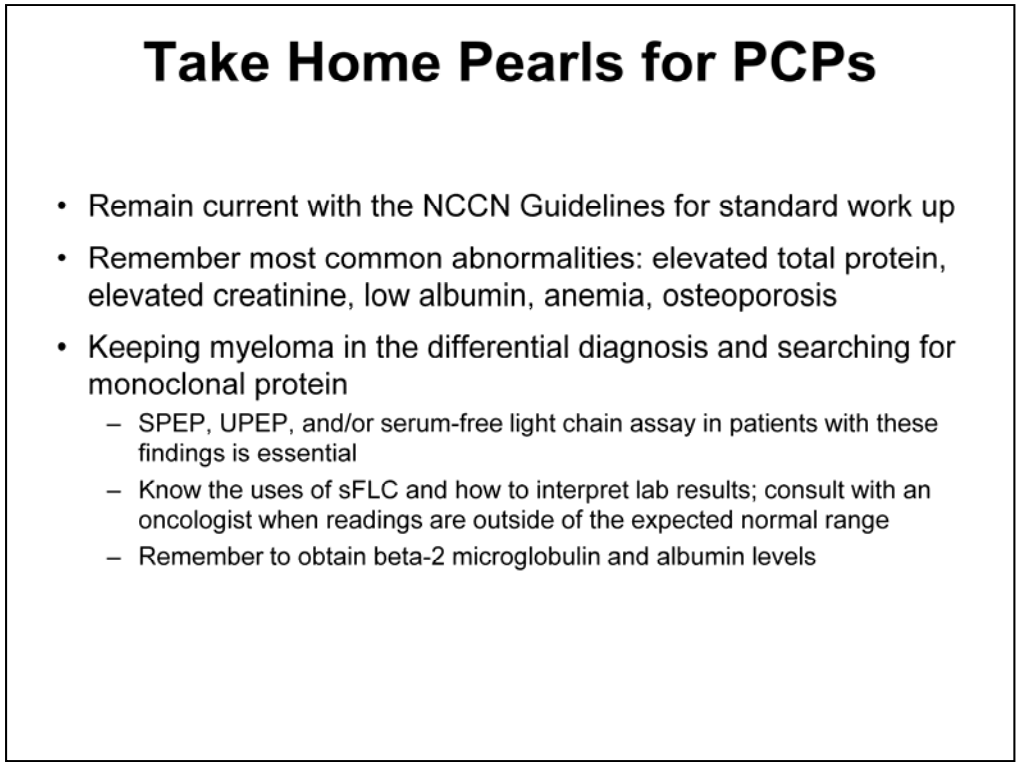
Craig Wynne: And just to clarify for the primary care physicians, these tests are done on your bone marrow sample.

Edward Stadtmauer: Correct. That is right. Obviously, there is a small subset of patients, but you do not really need these tests because these are high-risk patients who have plasma cell leukemia where there are actually circulating plasma cell. A real interesting area of investigation is can we do a blood test and detect small levels of circulating plasma cells and then do studies on them but that again is an area of interesting investigation.



Craig Wynne: Ed, thank you so much for this even today. I feel much more confident in being able to make the early diagnosis of myeloma and to do test appropriately that will prepare the patients to see you and further their care.

Edward Stadtmauer: Well, this is such an important topic of how the primary care physician and the myeloma specialist can work together with all of the other members of their team for the benefit of our patients. So, thank you and it has been a great talk t**oo.**



So, this brings us to the conclusion of our program. I would love to thank my colleague, Dr. Craig Wynne for joining me today. Thank you Craig. We hope that you have found this information beneficial to you and your practice, especially when faced with what you suspect as multiple myeloma in your patients. Please be sure to complete the post-test and evaluation to receive your CE credit and stay logged on to *www.ManagingMyeloma.com* for all the latest oncology education and tools. Thank you very much.