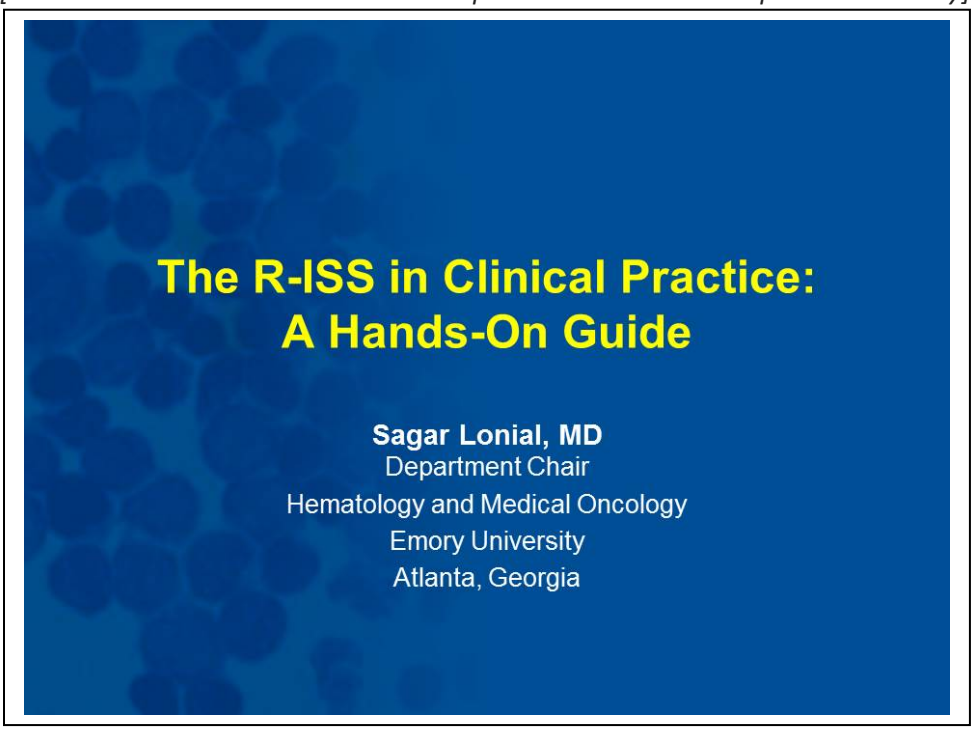
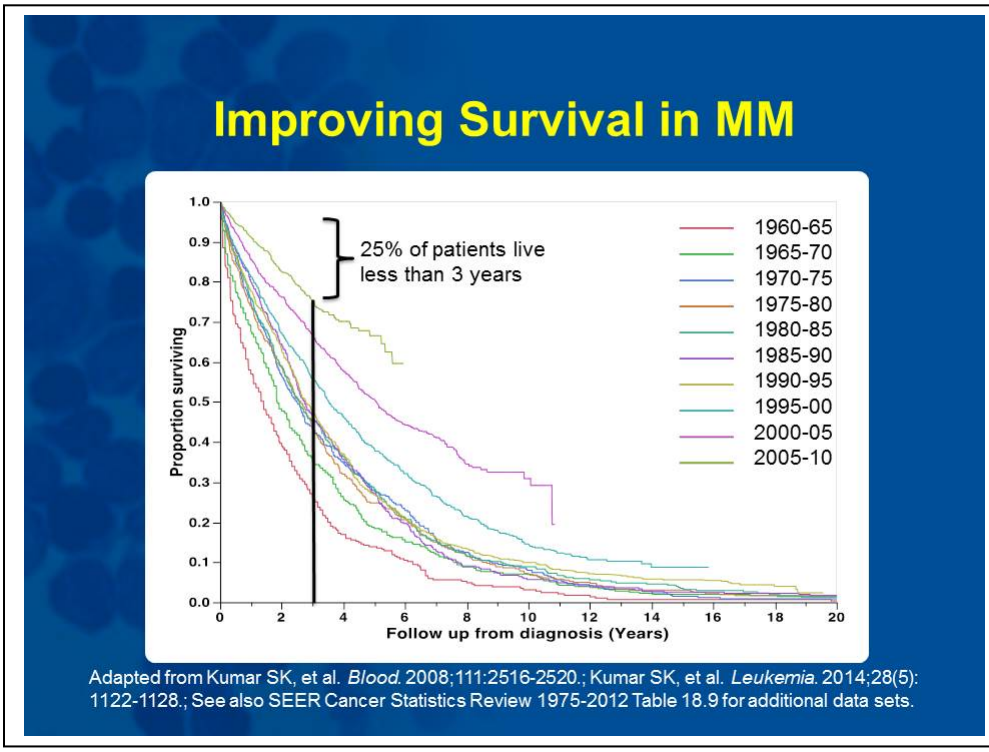
[Editor's note: Dr. Lonial's video transcript has been edited to improve readability]

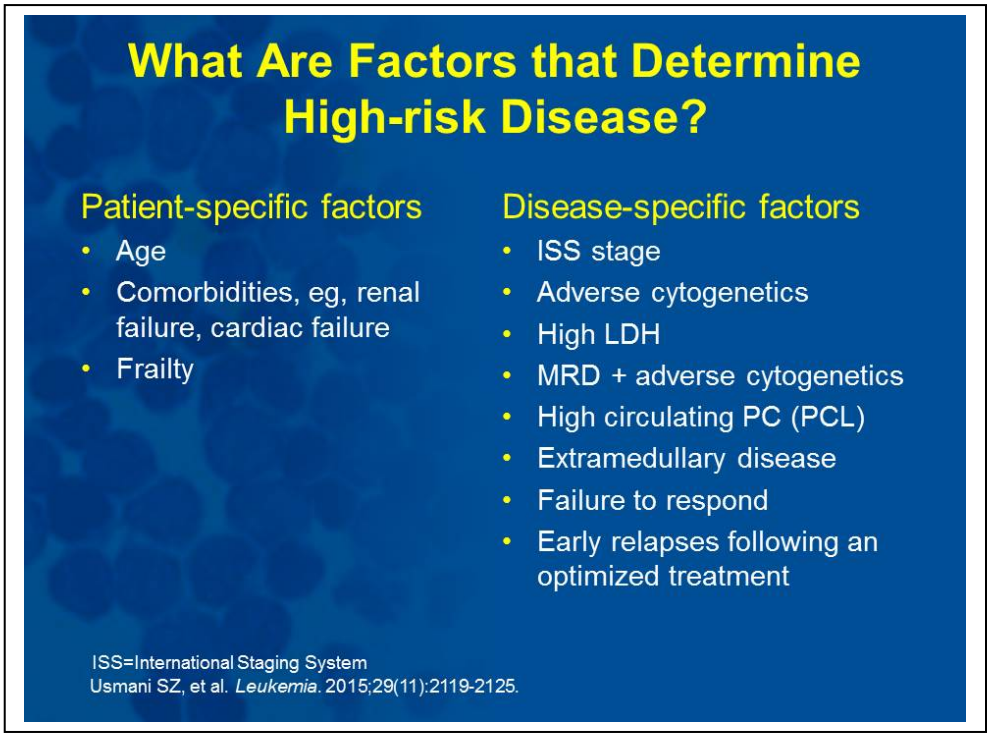


I am Dr. Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta, Georgia, and I would like to talk to you a little bit about personalizing treatment, and the new Revised International Staging System criteria that were recently published by the International Myeloma Working Group.

As we begin to talk about this, let's give you a little bit of background on the history of risk assessment in the context of multiple myeloma. As you can see from this curve, it's pretty clear that, over the last decade or so, treatments have had significant impact on progression-free and overall survival for cohorts of patients, based on the time of their diagnosis. In large part, this does reflect the fact that we have had many new treatments approved in the last 5 to 10 years, and we are more commonly using a high-dose therapy in autologous transplantation for the management of appropriate patients with newly diagnosed symptomatic myeloma, as well. These two things coupled together have allowed us to move the natural history of the myeloma curve from a median survival of only 3 to 3.5 years many decades ago to, now, expected median survivals of between 7 and 10 years; this doesn't necessarily even include the four new drugs that we have had approved in the last 12



months. Now, despite much of this improvement in progression-free and overall survival, there still remains a group of patients, about 25%, who have a median survival of less than 3 years. It's important to try and define the characteristics of those patients so that we can optimally first identify them, and then second, tailor treatments to help those patients get more aggressive maintenance therapy or novel treatments. This is an important part of what we're striving to do, in the context of improving outcomes for patients with multiple myeloma.

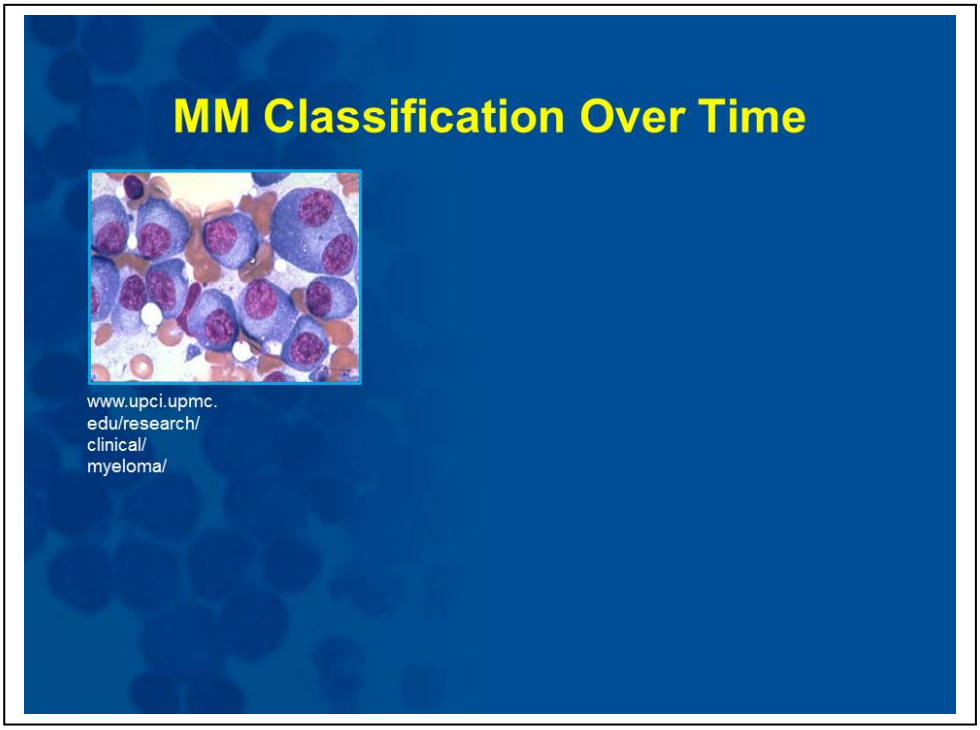


What are the factors that determine high-risk disease? There are a number of patient-specific factors and disease-specific factors that play into this. First among the patient-specific factors is age, and then second, comorbidities such as concomitant renal failure, cardiac function failure, or poor cardiac reserve. The third patient-specific factor is obviously frailty, and this is an important factor to consider, because frailty does have significant impact on our ability to deliver effective combination therapy, especially to older patients; but this may apply to younger patients, as well.

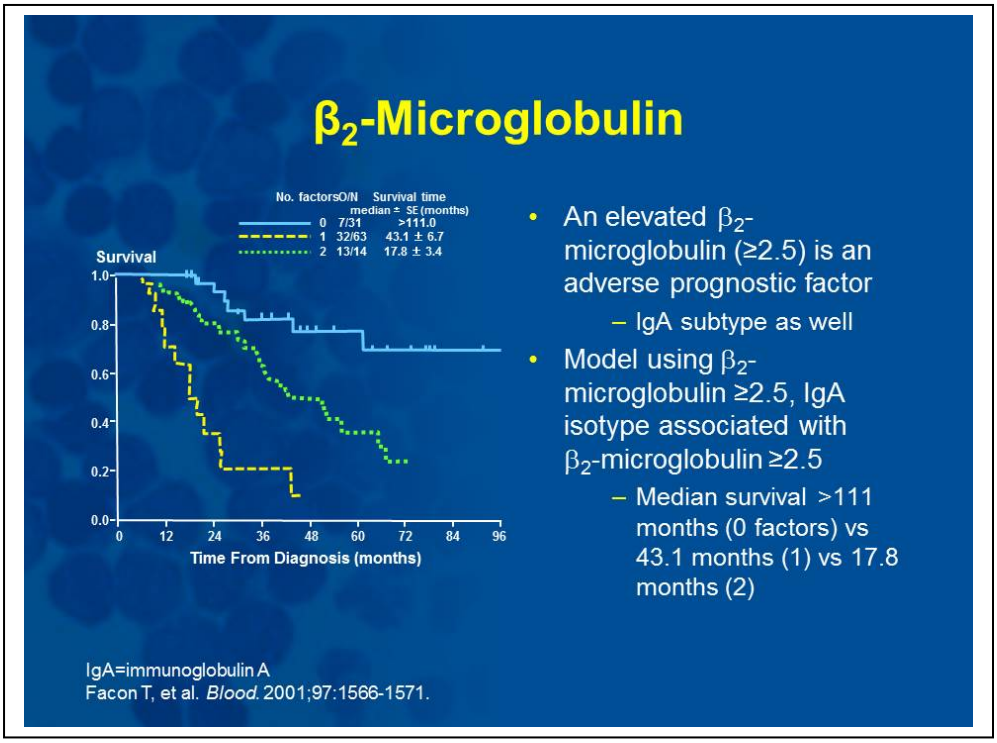
There are a number of disease-specific factors that are important, as well. These include:

- ***ISS stage***
- ***Adverse cytogenetics***
- ***High LDH***
- ***MRD and adverse cytogenetics***, which are certainly important in trying to determine the intensity and duration of maintenance therapy.
- High numbers of ***circulating plasma cells*** is a critical factor in determining high-risk disease, as well. This is not even necessarily plasma cell leukemia, although that certainly does confer a high-risk patient. But even having 1% or 2% circulating plasma cells is prognostically worse than having less than 1% circulating plasma cells.
- ***Extramedullary disease*** is a very important endpoint. This does not necessarily include patients who have bone-based extramedullary disease, but really relates to patients that have non-bone-based extramedullary disease.
- ***Failure to respond***: there is some controversy about failure to response as a potential disease-specific factor. I think failure to respond depends on what treatment is being employed. For a long time, there has been a debate in the myeloma community about two drugs versus

three drugs. Failure to respond to a two-drug induction regimen is probably different than failure to respond to a three-drug induction regimen, but this may be less of an issue in 2016, as most patients are receiving triplet-based induction.

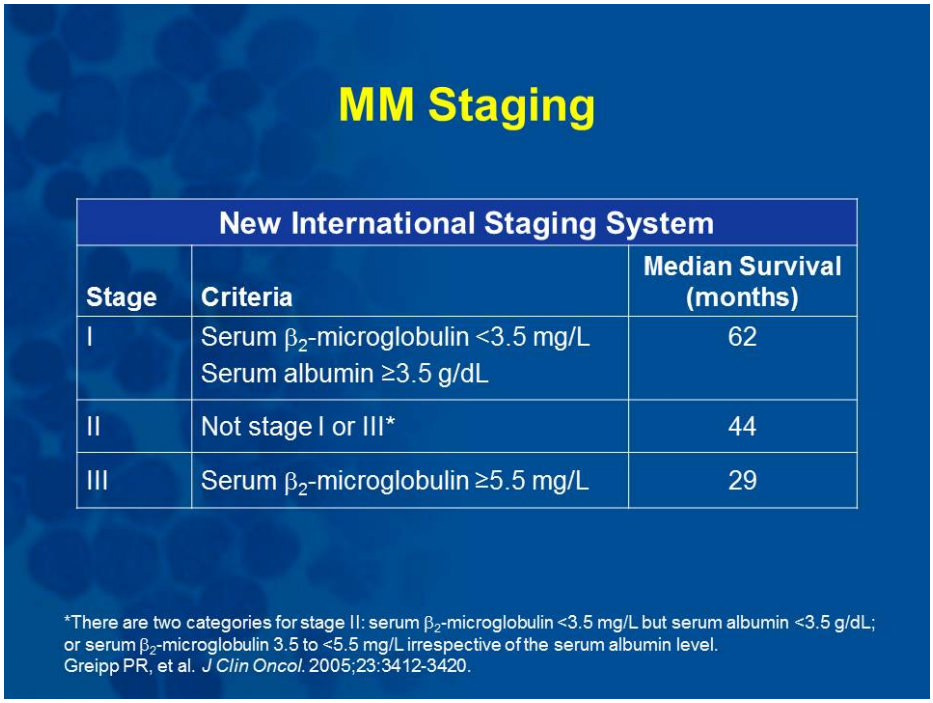


What about MM classification over time? If we begin to look at the way that we've classified myeloma over time, you can see quite clearly that, until the last five years or so, what we've been relegated to has been microscopic evaluation of the bone marrow by a pathologist. While this was useful to tell us that, yes, the patient has clonal, and what looks like, malignant plasma cells, it did not really give us significant insights into differences and heterogeneity amongst patients. It didn't even give us information about heterogeneity within a patient, what we call intraclonal heterogeneity. We couldn't appreciate any of these important differences when all we really had to go by was routine light microscopy.

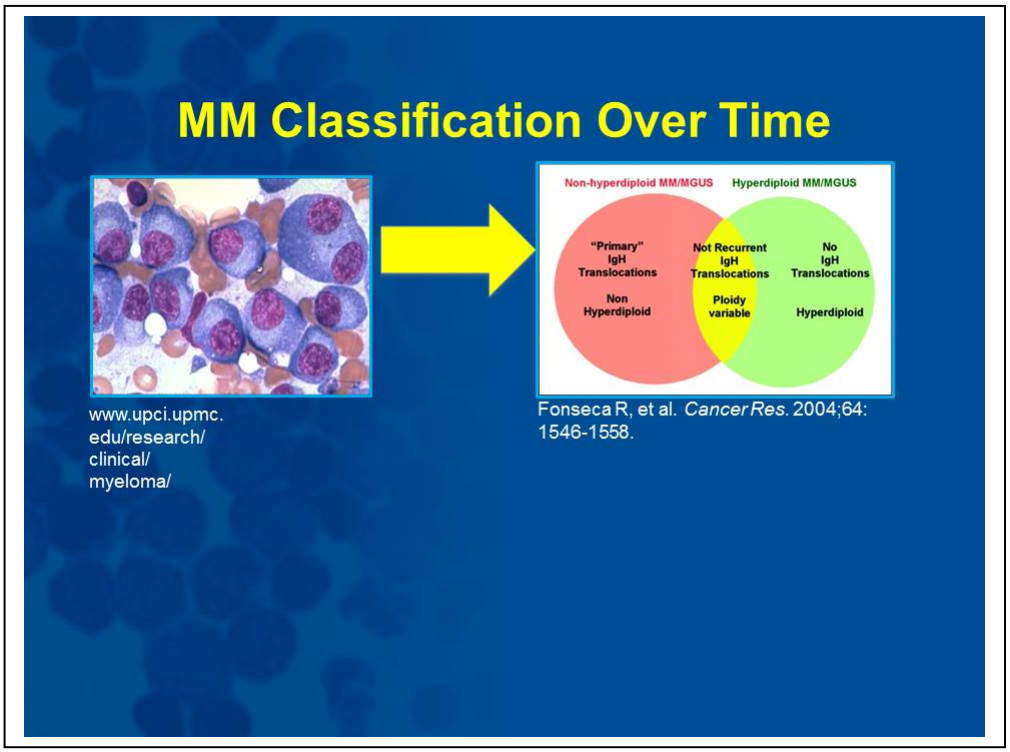


We started to use biomarkers to try and predict progression-free survival for patients, beginning initially with the use of the beta-2 microglobulin. Almost a decade ago, we identified that beta-2 microglobulin was, in fact, able to differentiate three different groups of

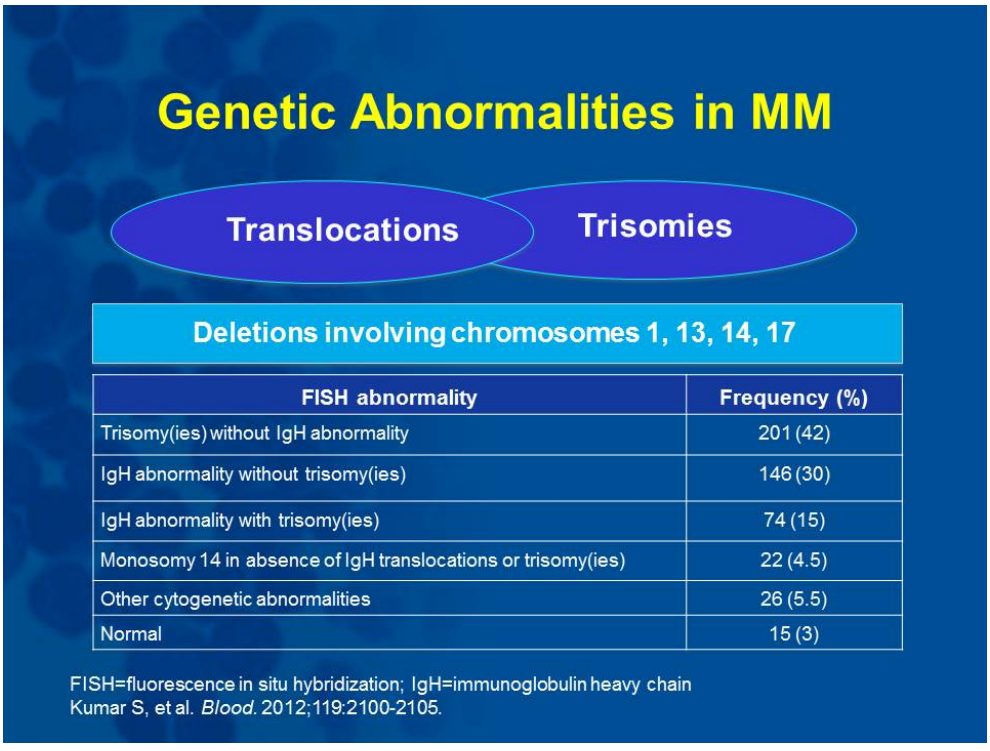
patients. You can identify patients with very poor-risk disease who had a high beta-2 microglobulin, or patients with very good-risk disease who had a low beta-2 microglobulin. When we began to try and put these things together into risk-adapted stratification, this is one of the tools that was used to initiate how we risk-stratify patients. Again, patients with a high beta-2 had a very short overall survival, with a median overall survival of less than 2 years, versus patients with a low beta-2 who had a median survival that was not even reached with a follow-up of almost 8 to 10 years, as you can see from the specific criteria here.



Based on that, the International Staging System criteria was created in 2005, and it basically linked both beta-2 microglobulin and albumin, and created ISS stage 1, stage 2, and stage 3 patients. I think it's important to realize that this ISS staging replaced Durie-Salmon staging. Durie-Salmon has the grading of 1, 2, and 3 with A and B, based on renal function, and is no longer used to risk assess patients in 2016. It's not a useful metric; it's an old metric, and really, its function was to identify tumor burden, not necessarily prognostic risk. The ISS staging which replaced the Durie-Salmon staging is much more effective at giving us predicted median overall survivals. As you can see, patients with ISS-3 have a median survival of 30 months versus double that in patients with ISS-1. So, this does have both clinical benefits and ease of utility benefits for an average practicing clinician.



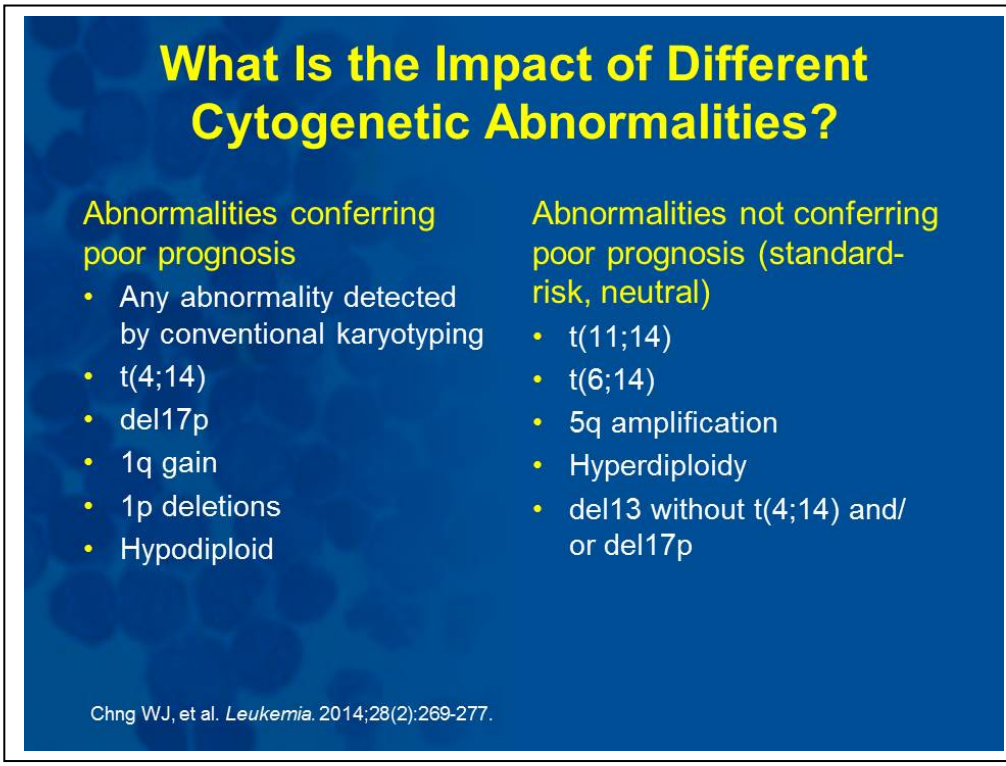
As we began to go from just light microscopy to using certain biomarkers to try and predict outcomes using the ISS, it was subsequently identified that there were genetic differences between patients with multiple myeloma. There were patients who had primary IgH translocations, who basically had non-hyperdiploid abnormalities. There were patients that had no IgH translocations but had what we now call a hyperdiploid-type myeloma. And then, there were some overlaps, where ploidy was somewhat variable. Each of these different sets of patients had different prognostic risks and outcomes compared to other patients, that again, using light microscopy, all appeared to be the same. This was an important step forward, and was led by investigators such as Rafael Fonseca or Avet-Loiseau from the IFM, Nikhil Munshi from the Dana Farber Group, and others who really began to question whether just blood biomarkers and light microscopy were sufficient to help us differentiate patient risk.



As you can see from the next slide, we have now identified that there are, in fact, common abnormalities that occur. These can include translocations or trisomies, and, in fact, trisomies without IgH abnormalities are basically the hyperdiploid subset of patients. These

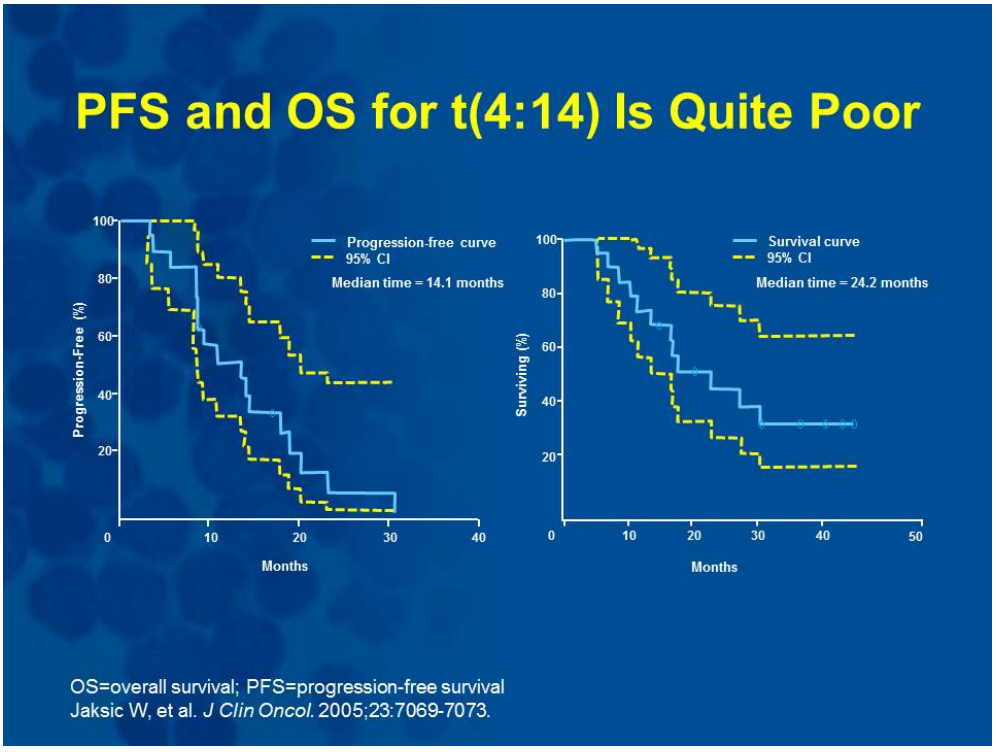
represent roughly 40% of newly diagnosed myeloma patients, and that's good news, because these are patients who have very good outcomes. In fact, if you fall into this category of hyperdiploidy, you have a median expected survival of greater than 10 years with moderate myeloma therapy, based on very nice, large randomized data sets.

There are, however, other genetic abnormalities that perhaps do not fair quite as well, and these include patients with IgH abnormalities without trisomies, who form roughly a third of myeloma patients. Additionally, patients who have IgH abnormalities with trisomies comprise another 15%. Approximately 5.5% of patients have cytogenetic abnormalities in and of themselves, and about 4.5% of patients have monosomy 14 in the absence of IgH translocations. Again, these are the groups of patients who all have very different expected progression-free and overall survivals. This is critically important, because, as we are beginning to think about how to treat these patients, we should potentially be thinking about them in a different fashion.

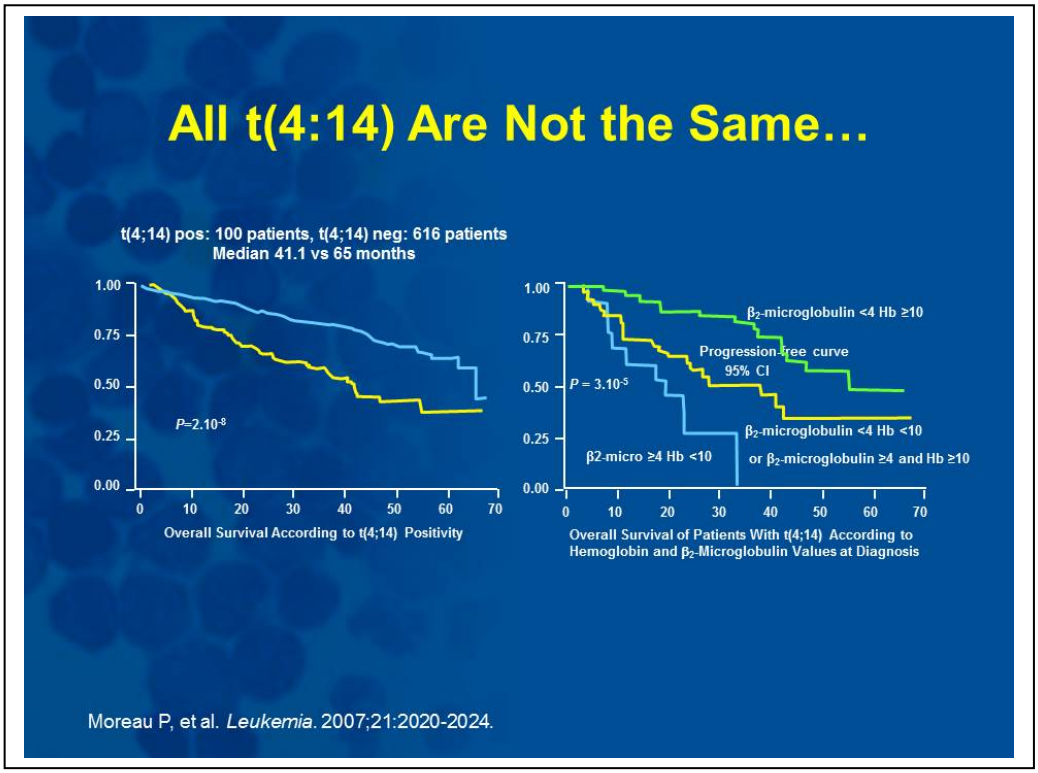


Now, what are some of these abnormalities? Let's go through this more specifically. There are, in fact, abnormalities that confer a poor prognosis, and I would argue any patient with conventional cytogenetic abnormalities represents a poor risk subset of patients. This represents 15% of all patients that have regular karyotyping done, and the fact that they have a karyotypic abnormality tells us that their myeloma cells are proliferating at a higher rate compared to other patients. For patients with the 4;14 translocation, patients with 17p deletion, patients with 1q gain, and patients with 1p deletions, it is not quite as clear that they have a poor risk prognosis in isolation; additional analyses are currently being performed to confirm the risk of prognosis conferred by these abnormalities. Patients who have a hypodiploid karyotype clearly have poor-risk genetics.

What about abnormalities that do not confer poor risk? These are considered standard risk or somewhat neutral. These include patients with 11;14 translocation, 6;14 translocation, hyperdiploidy as I mentioned before, and the one that is often quite confusing is deletion 13. Deletion 13 without 4;14 and without 17p deletion is, in fact, considered neutral: it has no negative prognostic factor that was actually proven to us by the IFM over time.

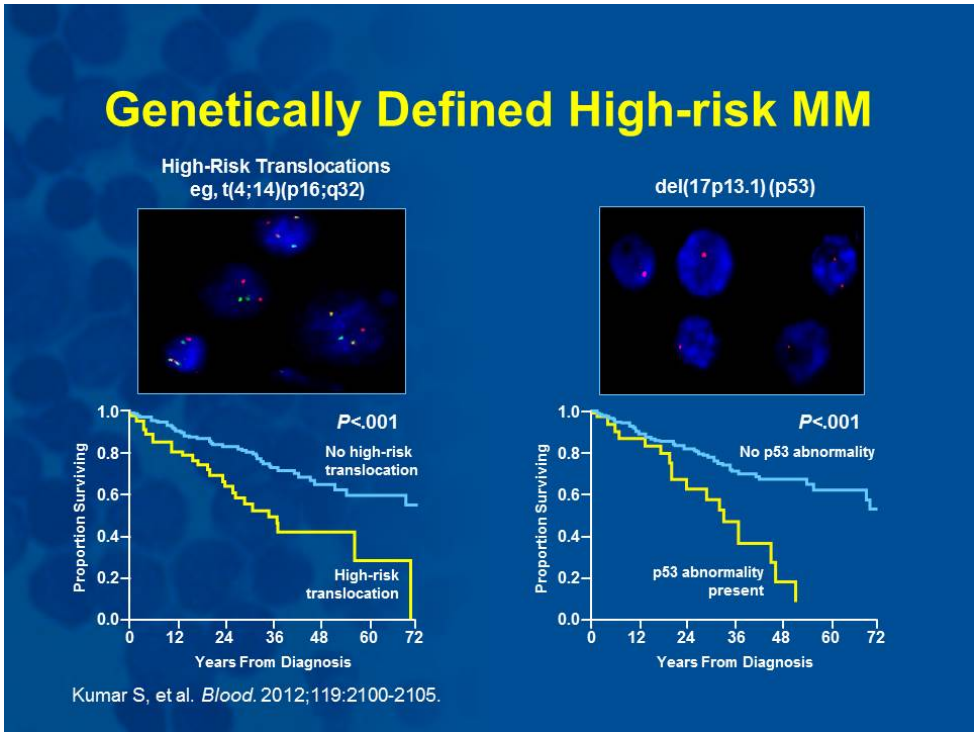


Let's look specifically at the 4;14 subset of patients. From a large, older trial done in Canada, you can see that 4;14 patients had an expected progression-free and overall survival of less than 2 years for PFS, with a median expected survival also of less than 2 years. This suggests that patients with 4;14 translocation do, in fact, have a very poor progression-free and overall survival.



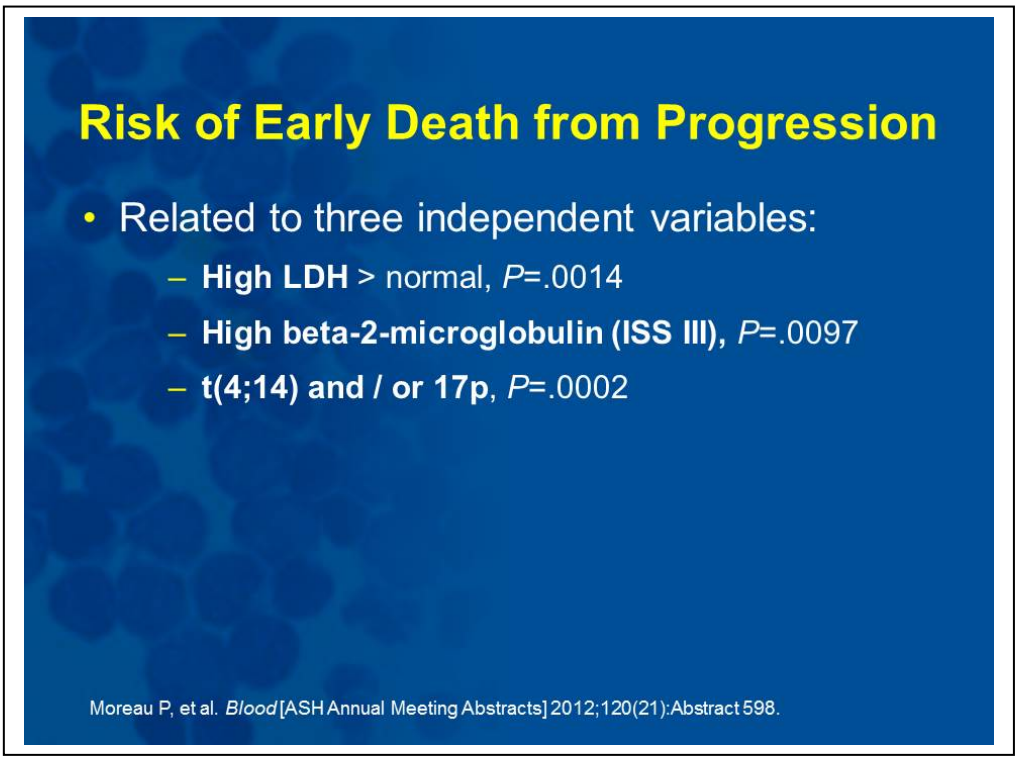
It's important to realize, however, that not all patients with 4;14 are the same; the genetics in isolation does not give you all the answers. In this graph, all 4;14 patients in this study are represented by the yellow line, with non 4;14 patients represented by the blue line, and what you can see is a clear difference in progression-free and overall survival between the two groups. However, if you begin to separate out the

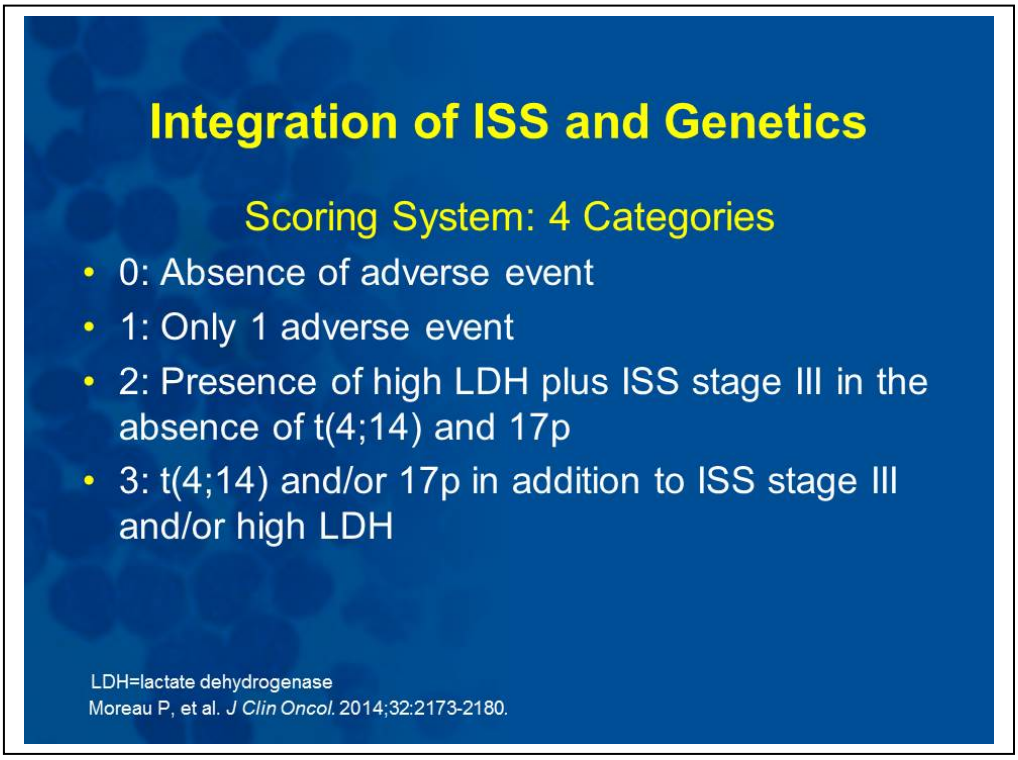
4;14s based on beta-2 and hemoglobin at presentation, in the right side of the slide, you can see quite nicely that there are patients with a low beta-2 and a normal hemoglobin in the green curve who have 4;14 and whose expected progression-free and overall survival is no different from patients who do not have 4;14 translocation. On the other hand, the light blue curve on the right side suggests that if you have a high beta-2 and a low hemoglobin and 4;14, expected overall survival is less than 2 years. This again speaks to the fact that biomarkers in combination with genetics may help us to tailor which patients have the best prognosis, and which patients ultimately have the worst prognosis over time.



Shaji Kumar performed an analysis of retrospective data on 4;14 and 17p deletion that was published in *Blood* a few years ago. What Dr. Kumar found is that, if you have 4;14, represented by the yellow line in the left-hand graph, you can see a very different survival curve versus if you do not have 4;14, represented by the blue line. On other hand, if you look at 17p deletion (right), you see a very different survival there, as well, based on whether you have 17p abnormalities or not. So, we can see that these important genetic and FISH-based assessments can give you important prognostic and predictive markers for both progression-free and overall survival.

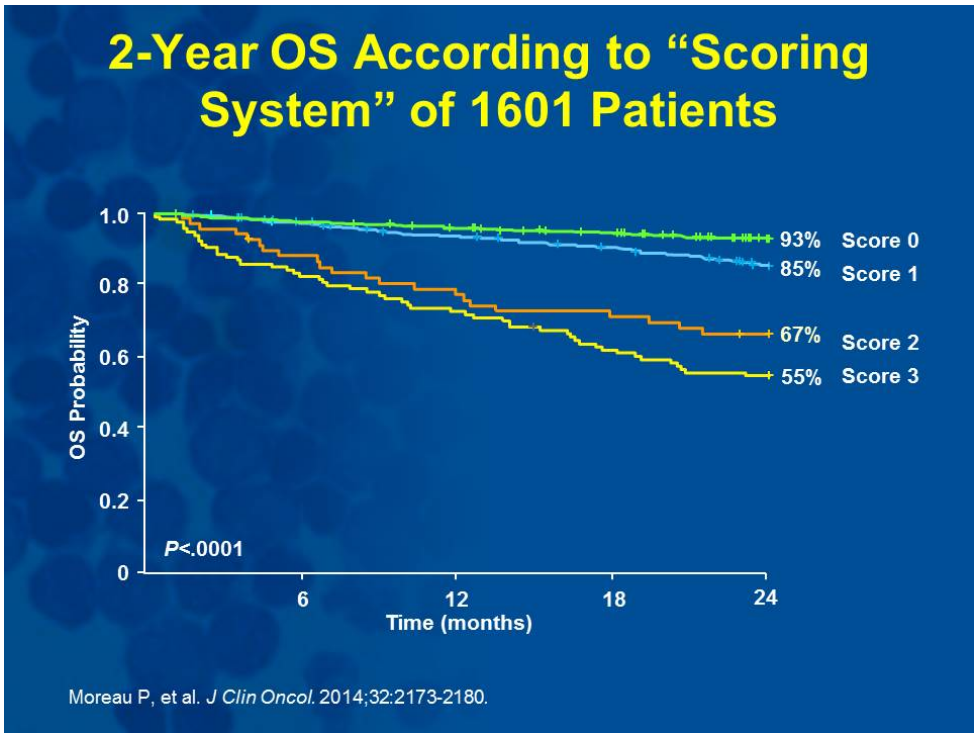
When the group in France began to look at multiple covariates and risk of progression, they identified three different independent variables, looking at multivariate analysis, that predicted poor survivals. The first was a high LDH, which was not a surprise, as patients with a high LDH clearly have a worse overall survival compared to patients with a normal LDH. The second variable was beta-2 microglobulin. If you had a high beta-2 as an independent predictor of survival, those patients did much worse than patients who did not. The third variable was the 4;14 translocation and/or the 17p deletion. So, out of all of the variables that were looked at in terms of patient-, disease-, and age-specific criteria, these three fell out in multivariate analysis as being the most important predictors of progression-free survival and early death in patients with newly diagnosed myeloma.





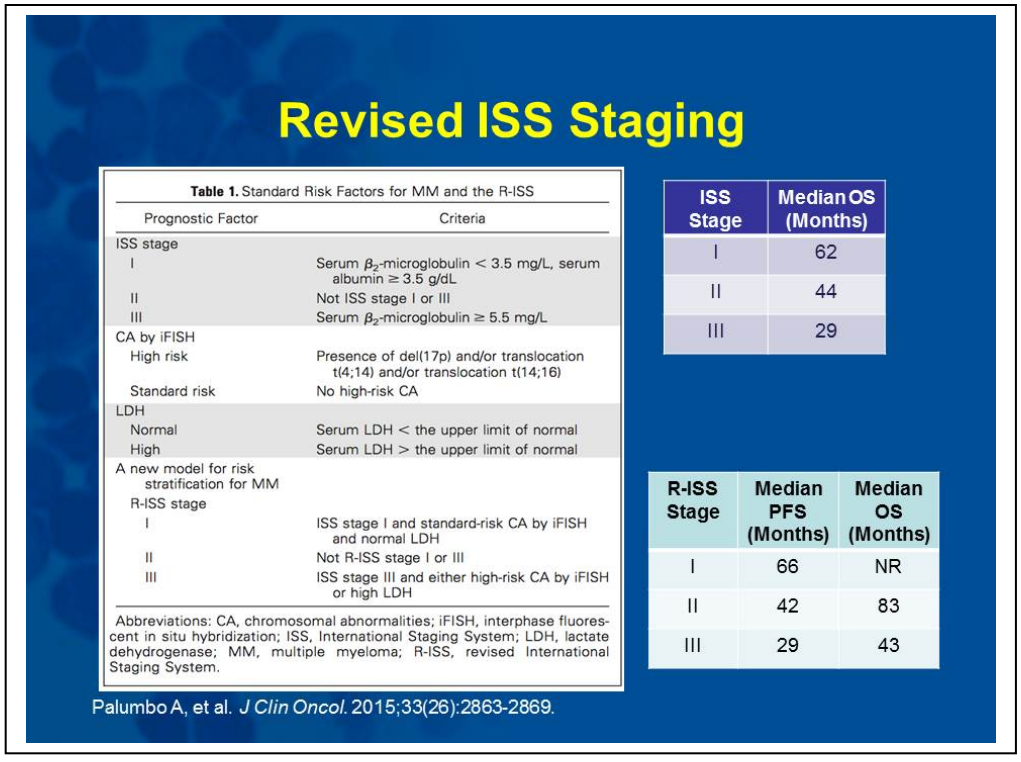
Based on this study, Philippe Moreau proposed in the IFM analysis to create a scoring system that broke patients up into four categories: patients with no adverse events scored as "0"; patients with one of those three variables scored as "1"; patients with an LDH plus ISS stage 3 without 4;14 and

17p scored as "2"; and patients with 4;14 and/or 17p in addition to ISS stage 3 and/or high LDH scored as "3".



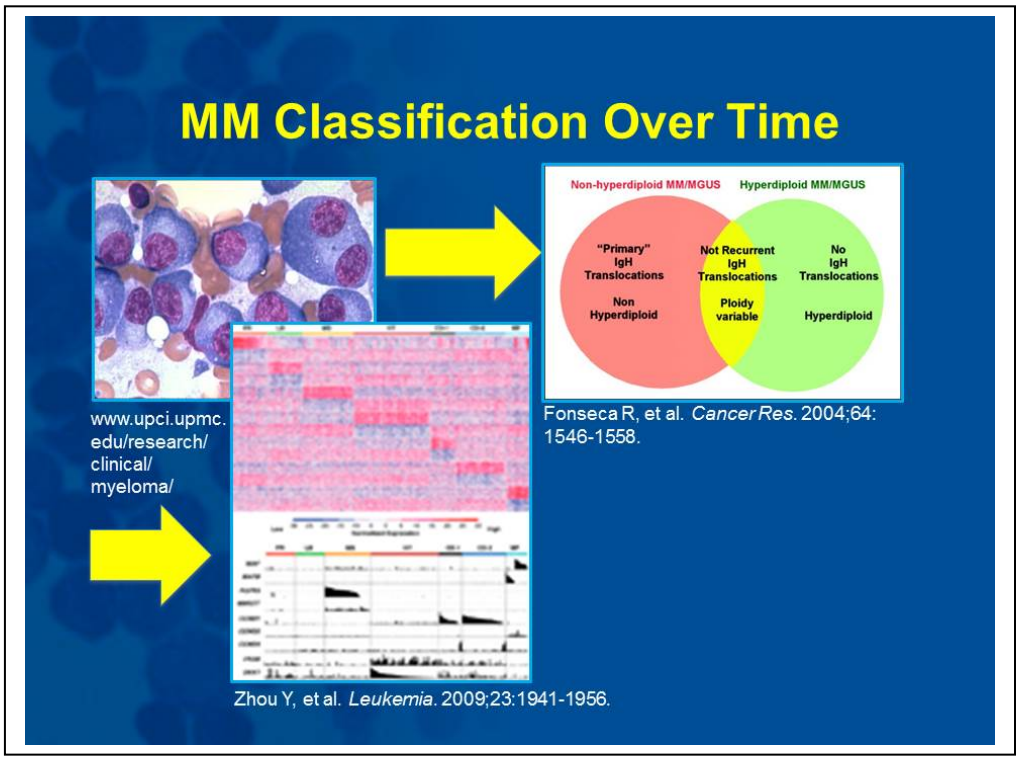
This gave rise to what was initially published by Philippe Moreau as a new revised scoring system that can nicely differentiate survival at 2 years, based on whether or not you have the score of 0, 1, 2, or 3.

This 1600-patient analysis was then broadened to a much larger group of patients, and gave rise to what we now use as the revised ISS system. As you can see from Dr. Palumbo's paper published in the *Journal of Clinical Oncology* last year, the R-ISS used the ISS staging 1, 2, and 3, and added the additional criteria of either absence of 4;14 or 17p, or 14;16, or presence of 4;14, 14;16, or 17p and the LDH. So, this is the new revised ISS that incorporated genetics and LDH into the regular ISS system that we had previously. Based on this, we can now put patients into very nice discrete categories, and, in fact, on the *ManagingMyeloma.com* website, there is a tool that can help you to do this,

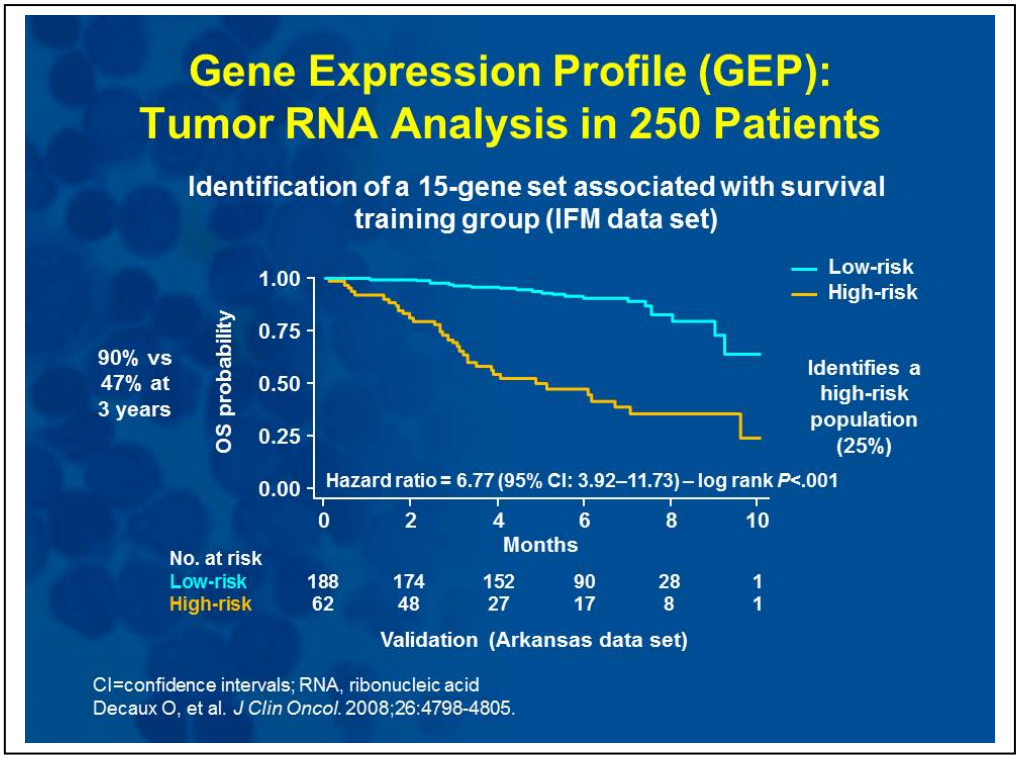


so that you can risk-stratify patients at the time of initial presentation.

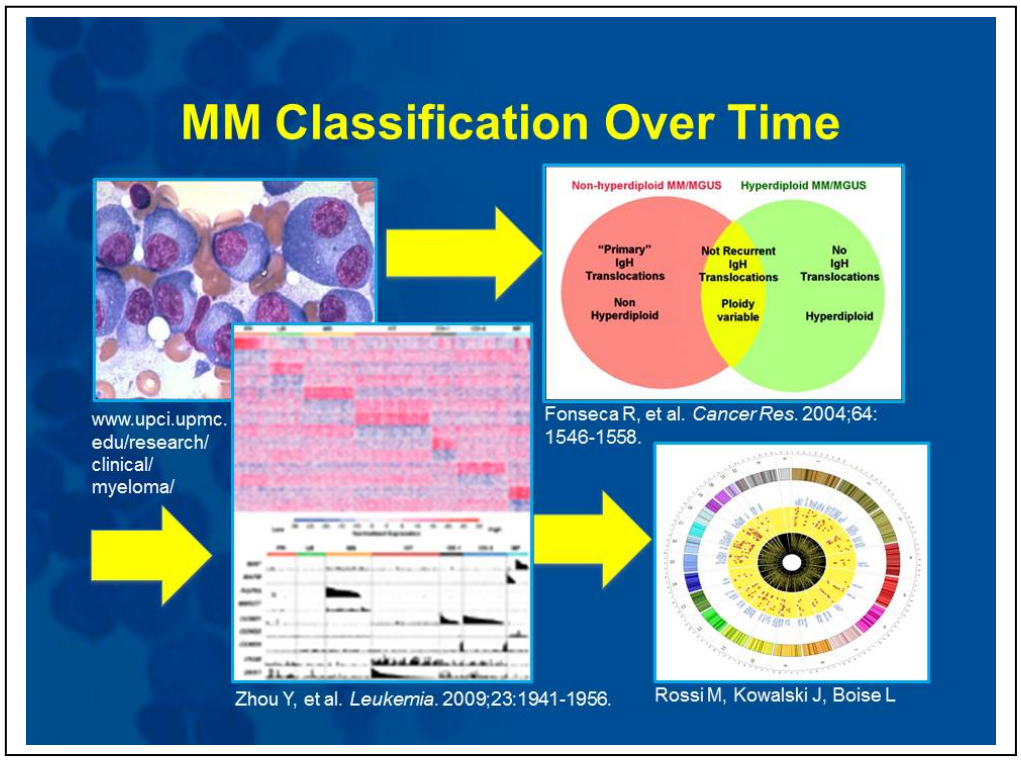
As you know, we are now continuing to evolve and develop as we think about improving predictive value of patients at the time of diagnosis. As such, we have gone from just looking at routine cytogenetics and FISH to now looking at gene expression profiling, and gene expression profiling can, in fact, begin to identify high-risk subsets of patients.



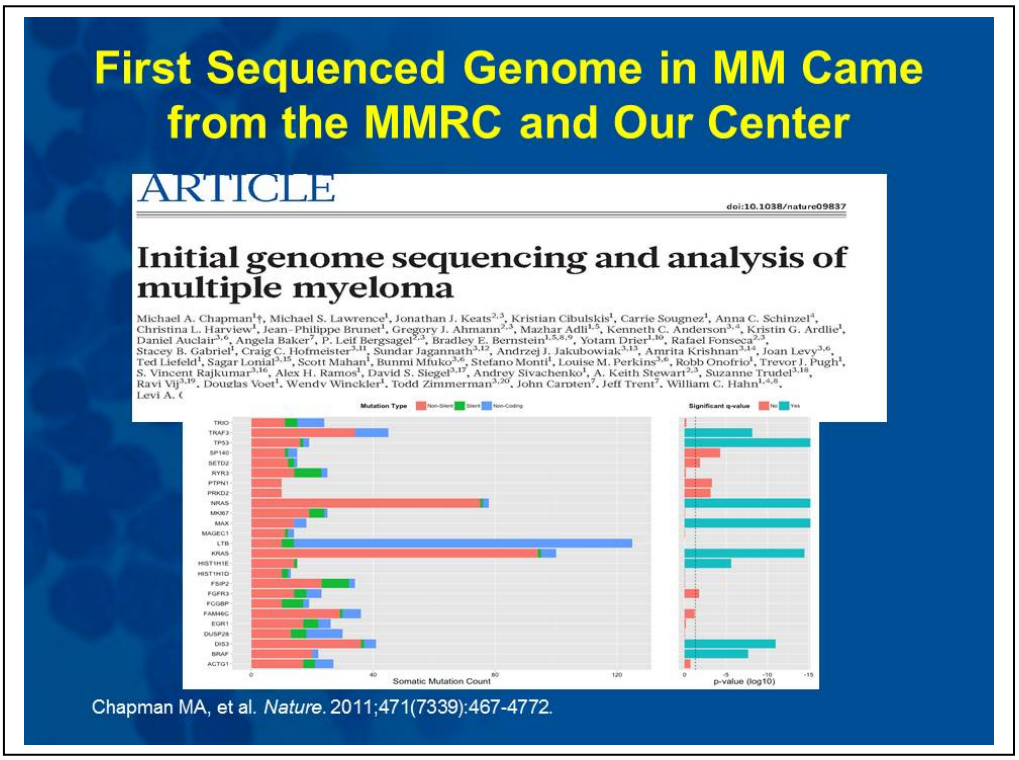
This is the Dutch group's analysis of a 15-gene set predicting survival in the IFM group. As you can see, looking at these 15 genes through gene expression profiling, we are, in fact, able to identify a very high-risk subset of patients who have a median overall survival of less than 1 year, compared to patients who are low risk using the same gene expression profiling pattern. This analysis has been done by the group in France, and by the Dutch group, as well as by the group in Arkansas, and each of



these criteria are able to identify high-risk versus standard-risk patients using gene expression profiling data that has been collected over the last decade or so.

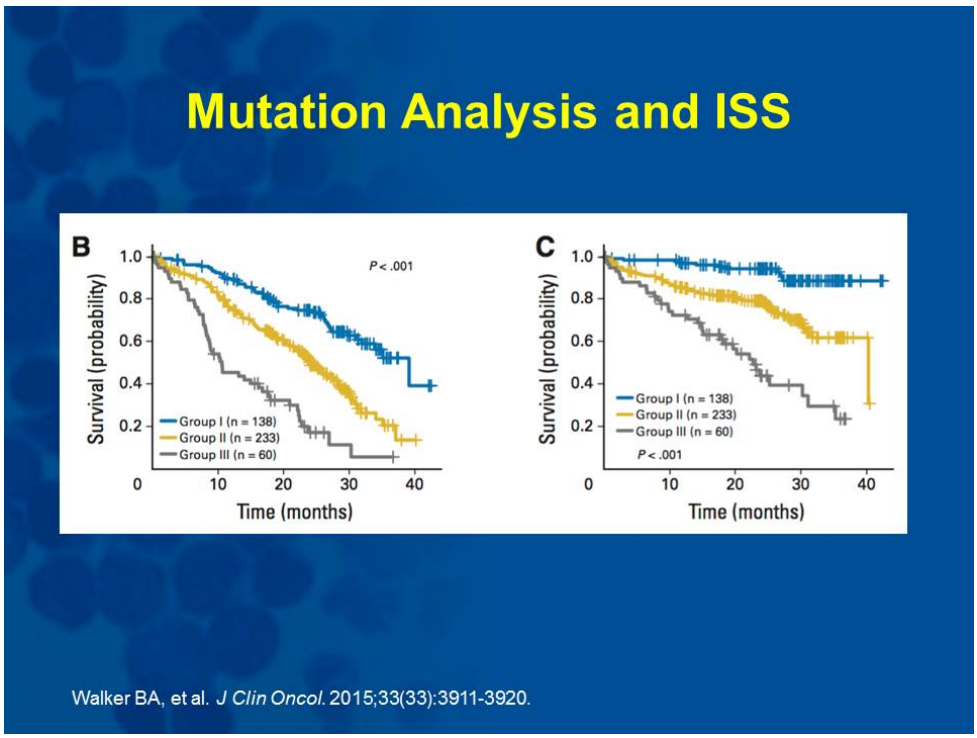


But, as many of you know, we are now not just looking at gene expression profiling, which looks at the genes themselves, but we are beginning to look at mutation analysis, sequencing, and RNA sequencing-based approaches. What RNA sequencing allows us to do, that we cannot do with expression profiling, is not just to get gene expressions, but also to get mutational profiles, as well. And with mutational profiles, we may be able to eliminate FISH and cytogenic testing, because we may be able to get translocations, mutations, and gene expressions, all from RNA sequencing performed in a very focused manner.

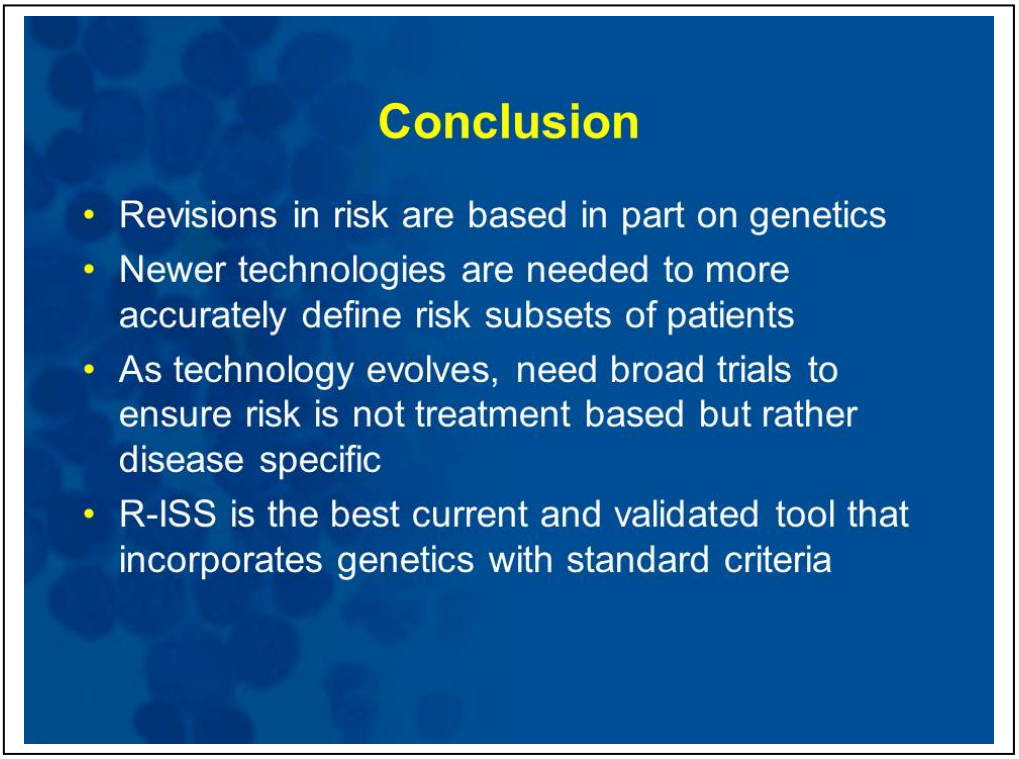


And as you know, the first paper sequencing myeloma patients came out in 2011 and identified several important genes that were mutated, including NRAS, KRAS, as well as BRAF and an unexpected gene that came up with BRAF, as well as many

other genes that were mutated in a variable fashion.



In fact, most recently, the British group has now looked at sequencing over 1000 patients at the time of diagnosis. They analyzed the patients' ISS staging and mutation analyses and identified three very different prognostic subsets of patients, in terms of progression-free survival and overall survival based on incorporating ISS staging with the presence or absence of certain important mutations. We don't know some things about those mutations, however. In this paper from the British group, most of the mutations that were important were mutations associated with DNA repair. That actually may be specific to the treatment that was used, because, as you know, cyclophosphamide is a very important part of induction and consolidation in the MRC clinical trial database, and so, you may be predicting for genes that are important for metabolism of chemotherapy, as opposed to genes that are important for cancer and myeloma outcomes biologically, in a larger global perspective.



In conclusion, it's important to understand that

there are revisions in risks and predicted outcomes, based in part on genetics. As I showed you before, genetics is not the sole important factor that can predict outcomes, but incorporating genetics with traditional biomarkers, such as the ISS staging, is now the current standard of care, and the revised ISS does depend on physicians and patients having that information at the time of initial diagnosis. Newer technology such as gene expression profiling, and now RNA sequencing and gene sequencing, are needed to more accurately define risk subsets in multiple different clinical trials. We do not want the results to be dependent on the specific trial that a patient was enrolled on; we want the results to be more generalized. As the technology evolves, these trials will help us to identify patient- and myeloma-specific risks that are important down the road, as opposed to just treatment-specific risks that are important. In 2016, the revised ISS is the best current and validated tool that incorporates genetics with standard biomarker-based criteria. Use of the R-ISS should become routine practice, eliminating the standard ISS, as well as the Durie-Salmon, from our nomenclature and from our clinical trials, as well as from the way that we talk about patients when we are either referring them or speaking at meetings and conferences and discussing cases. The revised ISS really is the best way to do that, and again, I would encourage you to go to *ManagingMyeloma.com* to look at the tools that can help you to calculate the revised ISS scoring for patients, as well as tools that can give you prognostic information on where your patient may fit at the time of diagnosis based on their genetic, biomarker, and laboratory profile at the time of initial presentation.

Thank you for your attention, and I hope you found this new piece of information from *ManagingMyeloma.com* to be useful in your practice.