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What is the new revised International Staging System or the R-ISS for multiple myeloma and should I be using it?

Welcome to *Managing Myeloma*. My name is Philip McCarthy. I am a professor of oncology at Roswell Park Cancer Institute in Buffalo, New York and also professor of internal medicine at State University of New York at Buffalo. I am frequently asked, "What is the new revised International Staging System or the R-ISS for multiple myeloma and should I be using it?" The R-ISS builds on our knowledge of cytogenetic as well as clinical laboratory features in helping us risk stratify our myeloma patients who are in need of therapy. The old ISS as you may recall was based on beta2-microglobulin and albumin levels and allowed us to stratify from low (ISS-I) to high (ISS-III) and ISS-II is in between. But, there are other features that were not being accounted for and thus last year in *JCO*, Philippe Moreau had a study that looked at several studies and reanalyzed them based on ISS and found that LDH, ISS-III, and karyotypic abnormalities were useful in helping risk stratify patients. By karyotypic abnormalities I mean deletion 17 or 4;14 translocation by interface FISH. It is important to say that interface FISH is critical in helping us risk assess patients. What this entails is doing initially in the laboratory a CD138 selection, and so what the laboratory needs to do is take the marrow, they incubate the marrow with antibodies to pull out this CD138 population, these are the malignant plasma cells, and then do the interface FISH. Whereas just doing interface FISH on unselected marrow alone decreases markedly the yield of karyotypic abnormalities, and this is critically important, I can't emphasize this enough that this needs to be done. There are several laboratories that are starting to do this on a national level, but I think it is really important that you check with your own laboratory to make sure that they are doing CD138 selected interface FISH. The other test that is very important too, easy to order but often forgotten is the LDH, it is not part of a standard chemistry panel. As we know in non-Hodgkin lymphoma it is important to get an LDH, it helps with prognosis and risk stratification, and now the same thing has been seen in multiple myeloma. Those patients who have high LDH are thought to be at high risk for recurrence and thus this is factored into the new scoring system. So the new scoring system essentially looks at the old ISS-I for those who don't have cytogenetic abnormalities and have low burden disease, the III's are those who have high burden disease and have karyotypic abnormalities or a high LDH, and the ISS-II is neither I nor III. I think this is very important because a) it helps us determine what the patient's risk is for progression and early death, it also tells us that this may be a patient, especially if it is a very young patient, somebody we may consider for an allogeneic transplant, or a novel clinical trial, or very close monitoring for a patient who is not going

to go on a study. So the ISS or the revised ISS just was published in *JCO*, *Journal of Clinical Oncology*, September 2015, Antonio Palumbo is the first author and this is very exciting news for us. Now, stay tuned because chromosome 1 abnormalities, 1p and 1q which are also picked up on interface FISH were not being looked for systematically in all these studies that they used for analysis. So I am willing to guess that we will be looking at a new tweak or a wrinkle on the revised ISS in the near future where the chromosome 1 abnormalities are incorporated into the scoring system. We are not also including gene expression profiling, this is GEP70, which is another risk assessment that is RNA expression, that defines a very high risk patient population, and the Europeans have one called EMC or the Dutch do it stands for Erasmus Medical Centre EMC92 which is a 92 gene signature profile that also defines high risk. So these are very exciting times, albeit a little confusing for the clinician, but these are exciting times which allow us to be able to better define our patient outcomes, define risk. Again I can't emphasize more the importance of getting a beta2-microglobulin, albumin, LDH, and CD138 selected interface FISH on the patient's diagnostic bone marrow to help us define best what to do for our patients. Thank you for viewing this activity, for additional resources, please view the other educational activities on *ManagingMyeloma.com*.