



International Staging System (ISS) and Revised ISS (R-ISS)

International Staging System for Multiple Myeloma

Developed in 2005 by the International Myeloma Working Group (IMWG), the ISS was built on clinical and laboratory data from 10,750 previously untreated myeloma patients across 17 institutions in North America, Europe, and Asia. It uses two readily available blood tests to classify patients into three stages. The following are those two blood tests:

Serum β 2 microglobulin (S β 2M): A small protein found on most cells that circulates in blood and urine. Elevated levels may indicate disease activity, though it is a nonspecific marker also associated with lymphoma and kidney issues.



Serum albumin: A protein made by the liver that helps maintain fluid in the bloodstream. Low levels can signal liver disease, chronic inflammation, or kidney problems. Importantly, low albumin also affects total calcium measurements, since albumin binds calcium.

ISS Stages and Criteria

The following table indicates the stages and correlating measurements according to ISS:

Stage	VALUES (β 2M = Serum β 2 microglobulin; ALB = serum albumin)
I	S β 2M < 3.5 mg/L; serum albumin $\geq$ 3.5 g/dL
II	S β 2M < 3.5 mg/L; serum albumin < 3.5 g/dL; or β 2M $\geq$ 5.5 mg/L, irrespective of serum albumin

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WITHDRAW CONSENT

Published by the IMWG in August 2015 ([/international-myeloma-working-group-imwg-criteria-diagnosis-multiple-myeloma](#)), the R-ISS expanded upon the ISS by incorporating two additional prognostic markers assessed from bone marrow samples taken at the time of diagnosis:

Lactate dehydrogenase (LDH): An enzyme whose elevated levels can reflect more aggressive disease activity.

Chromosomal abnormalities (cytogenetic abnormalities): Detected by fluorescence in situ hybridization (FISH), a technique that uses fluorescent chemical probes to bind to specific DNA sequences on chromosomes, revealing structural differences. The high-risk chromosomal abnormalities assessed are del(17p), t(4;14), and t(14;16).

R-ISS Myeloma Stages and Criteria

These revised indicators form a more powerful prognostic index:



Stage	Criteria
I	Sβ2M < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard-risk chromosomal abnormalities (CA) by iFISH Normal LDH
II	Not R-ISS stage I or III
III	Sβ2M ≥ 5.5 mg/L and either High-risk CA by FISH OR High LDH

While the R-ISS incorporates genetic risk markers, it does not always reflect real-world outcomes or current treatment standards — such as triplet and quad

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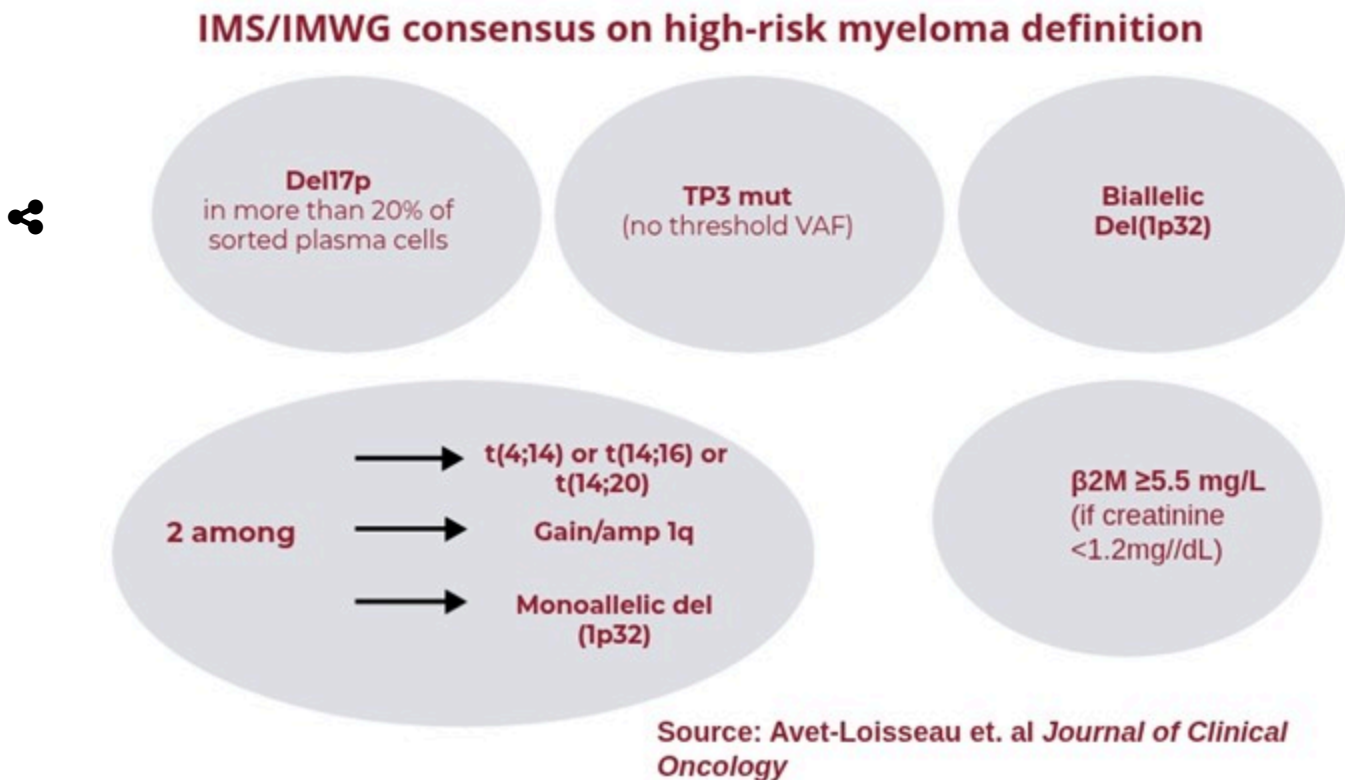
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framework incorporates the most recent research data and advances in treatment, offering a more modern and biologically informed approach to risk stratification.

Its primary purpose is to guide clinical decisions around treatment intensity, treatment duration, and clinical trial enrollment. Patients are divided into two groups: Standard-Risk and High-Risk.

IMWG-IMS Classification Criteria

There are five ways of being defined as high-risk, as outlined by this diagram:



Understanding Treatment Response

While [staging and risk stratification \(/node/1071\)](/node/1071) guide initial treatment decisions, monitoring treatment response is equally important for [managing myeloma time. \(/node/12890/\)](/node/12890/)

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Remission is often maintained long term with continuous or maintenance therapy. However, because myeloma is a relapsing disease, most patients will eventually experience disease progression requiring new treatment approaches.

Other Factors That Influence Outcomes

Staging and risk stratification are important clinical tools, but several additional factors can influence a patient's prognosis and treatment options:

Age: The most common age range at diagnosis is 65–74. Frailty and co-morbidities in older patients may limit access to certain treatment options and reduce tolerance for side effects.

Kidney function: Healthier kidneys and lower creatinine levels are associated with better outcomes. Monoclonal immunoglobulin can impair kidney function, making it harder for the kidneys to filter creatinine from the blood. Elevated creatinine can worsen prognosis and restrict treatment choices.

Overall health: Existing conditions such as diabetes or heart disease affect both myeloma outcomes and tolerance to treatment.

Response to therapy: Myeloma that does not respond to treatment or only responds for a short period of time — even in the absence of high-risk chromosomal abnormalities — indicates "functional" high-risk disease and carries a poor prognosis.

Extramedullary disease (EMD) - although myeloma originates in the bone marrow, it can grow in other tissues and is termed "extramedullary" (meaning outside the marrow). This can be associated with more aggressive myeloma

Plasma Cell Leukemia (PCL) - myeloma cells (cancerous plasma cells) are typically found in the bone marrow. Yet, in some cases, they can be found in the peripheral blood. This is also associated with a more aggressive form of myeloma.

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tools to guide clinical thinking — not deterministic predictions of individual outcomes.

Get More Information From the International Myeloma Foundation

If you are looking for resources and support, you can trust the IMF. We publish articles and videos to ensure you have as much information as possible, and we can help you [find a local support group \(/patient-caregiver-information\)](/patient-caregiver-information) . For support resources, patients with high-risk multiple myeloma can contact the IMF's virtual high-risk multiple myeloma support group at HRMM@imfsupport.org (<mailto:HRMM@imfsupport.org>) .

What's Next?



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