

Toward Precision Medicine for Patients with Multiple Myeloma

Rina Kansal^{1,2,*}

¹Molecular Oncology and Genetics, Diagnostic Laboratories, Versiti Blood Center of Wisconsin, Milwaukee, WI 53233, USA

²Department of Pathology and Anatomical Sciences, The University at Buffalo, Buffalo, NY 14260, USA

*Correspondence should be addressed to Rina Kansal, rinakansal@msn.com

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Abstract

Multiple myeloma (MM), the second most common hematologic malignancy, is a plasma cell neoplasm that arises from a precursor, monoclonal gammopathy of undetermined significance (MGUS), which may or may not be previously diagnosed. Smoldering multiple myeloma (SMM), another precursor of MM, lacks myeloma-defining events and end-organ damage that are diagnostic of MM in the appropriate clinical settings. Newly diagnosed MM (NDMM) is highly heterogeneous genetically and clinically with very variable survival outcomes ranging from a few months to over a decade. Despite this heterogeneity, treatment outcomes have improved significantly in the last two decades, with overall survival improving continuously due to novel classes of drugs approved for treating MM. However, due to the immense heterogeneity, the quest for a cure will almost certainly require individualized patient evaluation and management at every level for every factor influencing patient quality of life and survival, including most importantly determining upfront the progression risks in the precursor states and prognostic risks for progression or relapse in NDMM. Toward that goal, this paper briefly describes, including a historical perspective, current concepts, and recent advances in NDMM for students, researchers, and clinical practitioners. The topics discussed include an overview of the epidemiology, current diagnostic criteria, including for distinguishing MGUS, SMM, and MM, refractory and relapsed MM, staging and prognosis of MM, treatment response criteria, including measurable residual disease evaluation, improvements in survival, current standards for treating NDMM, and disparities and inequities in receiving care in ethnic minority populations for treatment of MM, followed by progress in evaluating the risk of progression in MGUS and SMM, and finally, the genomics of MM, SMM, and MGUS since integrating disease biology in assessing and precisely managing all risk factors and achieving equity in treating all patients would help to achieve that precision medicine goal for a cure.

Keywords: Multiple myeloma, Multiple myeloma epidemiology, Multiple myeloma diagnosis, Multiple myeloma therapy, Smoldering multiple myeloma, Monoclonal gammopathy of undetermined significance, Plasma cell neoplasms, Residual neoplasm, Precision medicine, Genomics

Abbreviations: MM: Multiple Myeloma; SEER: Surveillance, Epidemiology, and End Results; M-proteins: Monoclonal Immunoglobulin Proteins; CRAB: Hypercalcemia, Renal Damage, Anemia, and Bone Lesions; NDMM: Newly Diagnosed Multiple Myeloma; SMM: Smoldering Multiple Myeloma; MGUS: Monoclonal Gammopathy of Undetermined Significance; DL: Deciliter; IgM: Immunoglobulin M; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IMWG: International Myeloma Working Group; PFS: Progression-free Survival; FLC: Free Light Chain; FISH: Fluorescence In situ Hybridization; IgM: Immunoglobulin M; MRI: Magnetic Resonance Imaging; CT: Computerized Tomography; PET-CT: Fludeoxyglucose (F18) Positron Emission Tomography with Computerized Tomography; IgD: Immunoglobulin D; IgE: Immunoglobulin E; AL: Immunoglobulin Light Chain Amyloidosis; AHL: Immunoglobulin Heavy and Light Chain Amyloidosis; AH: Immunoglobulin Heavy Chain Amyloidosis; ISS: International Staging System; LDH: Lactate Dehydrogenase; AHSCT: Autologous Hematopoietic Stem Cell Transplant; R-ISS: Revised International Staging System; OS: Overall Survival; Mo: Months; FU: Follow-up; IFM: Intergroupe Francophone du Myélome; R2-ISS: Second Revised International Staging System; NCCN: National Comprehensive Cancer Network; RDW: Red Blood Cell Distribution Width; MRD: Minimal/Measurable Residual Disease; CR: Complete Response; VGPR: Very Good Partial Response; ASO-PCR: Allele-specific Oligonucleotide Polymerase Chain Reaction; MFC: Multiparameter Flow Cytometry; NGS: Next-generation Sequencing; FDA: Food and Drug Administration; IStopMM: Iceland Screens, Treats, or Prevents Multiple Myeloma; PANGEA: Precursor Asymptomatic Neoplasms by Group Effort Analysis; MAPK: Mitogen-activated Protein Kinase; NF-κB: Nuclear Factor κ-light Chain-enhancer of Activated B cells; APOBEC: Apolipoprotein B mRNA Editing Catalytic polypeptide-like; CoMMpass: Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile; PROMMIS: Prospective Observational Multiple Myeloma Impact Study; IRMMa: Individualized Risk for Multiple Myeloma Model; DSS: Durie-Salmon Staging

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy after lymphomas, affecting predominantly older adults with a median age of 69 years, based on the U.S. Surveillance, Epidemiology, and End Results (SEER) data [1]. MM is a neoplasm of plasma cells that infiltrate the bone marrow and may infiltrate extramedullary tissues, usually accompanied by increased levels of monoclonal immunoglobulin proteins (M-proteins), with the causation of end-organ damage, characterized by hypercalcemia, renal disease, anemia, or bone lesions ("CRAB" features) as the classically described clinical features [2-4]. In the USA, 35,780 new cases of MM, including 19,520 males and 16,260 females, and 12,540 deaths due to this disease, including in 7,020 males and 5,520 females are estimated to occur in 2024 [5]. The incidence per 100,000 U.S. persons of all ethnicities is higher in males at 8.7 than in females at 5.9, with the highest rates in non-Hispanic black males and females at 17.1 and 13.0, respectively [1]. In 2022, the global prevalence and incidence of MM were ~540,000 and 187,952, respectively, with 121,388 deaths [6]. The worldwide age-standardized incidence rates were the highest in the North American, Northern, Western, and Southern European, Australian, and New Zealand regions at 3.2-7.0 per 100,000 males and 2.5-6.2 per 100,000 females [6]. The global incidence is increasing and associated with a higher prevalence of physical inactivity, overweight, obesity, and diabetes [7]. In the last two decades, much has been learned about this unique hematologic malignancy, with progressive, continuous, and ongoing advances in patient survival. Still, there are unmet needs, and a cure is not yet apparent. The purpose of this review is to briefly describe significant advances in MM that have led to improvements in survival, including a brief description of the current diagnostic criteria of MM and its precursor conditions, staging, and prognosis of newly diagnosed MM (NDMM), treatment response criteria, including minimal or measurable residual disease (MRD) assessment, progress in the evaluation of the risk of progression of precursor states to active MM, and recent advances in the genomics of NDMM and smoldering multiple myeloma (SMM), which still need to be used routinely for determining prognostic risk in NDMM and progression risk in precursor states to enable precise identification of all patients for individualized risk-adapted clinical management and treatment regimens.

Monoclonal Gammopathy of Undetermined Significance (MGUS), Smoldering Multiple Myeloma (SMM), and Active Multiple Myeloma (MM)

Multiple myeloma consistently evolves from a precursor condition, monoclonal gammopathy of unknown significance (MGUS) [8], but the converse is not true. MGUS, as defined by the presence of fewer than 3 grams/deciliter (dL) of serum M-proteins, absent urinary M-proteins, or moderate amounts of light chains in the urine, the absence of any end-organ

damage, and fewer than 10% plasma cells in the bone marrow [9], progresses to MM, Waldenstrom's macroglobulinemia or light chain amyloidosis at the rate of 1% per year, notably, with a greater risk of death due to causes other than progression to plasma cell neoplasms [2,9,10]. Two types of MGUS, non-immunoglobulin M (non-IgM) MGUS, and light chain MGUS are caused by monoclonal plasma cells, and these types of MGUS are precursors for MM [8]. In contrast, IgM MGUS is caused by lymphoplasmacytoid cells, and this type of MGUS may progress to Waldenstrom's macroglobulinemia or immunoglobulin-related amyloidosis [11].

The second precursor neoplasm, SMM, was defined by the International Myeloma Working Group (IMWG) in 2003 [12] by the presence of $\geq 3\%$ serum M-proteins, or $\geq 10\%$ plasma cells in the bone marrow, in the absence of any end-organ damage [12]. In 2007, a study of 276 patients with SMM showed the following risks of progression to MM with end-organ damage or amyloidosis: 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year for the subsequent 10 years, with a cumulative 73% risk of progression at 15 years [13,14]. Of these 276 patients, only six (2%) had bone marrow plasmacytosis of $>60\%$, and these six patients had a median progression-free survival (PFS) of 7.7 months, with disease progression or death in 83% [15]. A free light chain (FLC) ratio of >8 or <0.125 in the serum of patients with SMM showed a $>50\%$ risk of progression to active disease [16]. The IMWG consensus guidelines for monitoring MGUS and SMM were published in 2010 [17].

A similarly high risk of progression was shown to be present in small percentages of patients having $\geq 60\%$ bone marrow plasma cells in three additional cohorts of SMM during 2011-2013, with 95% of those high-risk patients progressing to active MM within 2 years: (1) 3.2% ($n = 21$) of 655 patients with a median time to progression of 7 months [15]; (2) 12.5% ($n = 12$) of 96 patients, also with a highly abnormal FLC ratio of ≥ 100 or $\leq 1/100$ in the serum, progressing in less than 18 months [18]; and (3) in 4% ($n = 6$) of 135 patients in the third cohort [19]. In another study, an FLC ratio of >100 in the serum of 90 patients with SMM showed a 79% risk of progression to active MM or light-chain amyloidosis [20].

Further, in 2007, the Spanish group showed a high proportion (95%) of immunophenotypically aberrant plasma cells among total bone marrow plasma cells by multiparametric flow cytometric immunophenotypic analysis to have a significant risk of progression in both precursor states, MGUS and SMM [21]. In conjunction with a reduction from normal levels of one or two uninvolved immunoglobulins (termed immunoparesis), the presence of 95% aberrant plasma cells based on the analysis of CD38, CD138, CD19, CD45, and CD56 expression, showed a 72% risk of progression of SMM to active MM [21]. Based on these features, the Spanish Myeloma group showed delayed progression of high-risk SMM by early treatment with lenalidomide, and dexamethasone compared with observation in a randomized phase 3 clinical

trial published in 2013 [22]. In another study investigating radiologic imaging, the presence of >1 focal lesion detected by whole-body magnetic resonance imaging in 149 patients with SMM predicted disease progression to active MM [23].

Genetically, the neoplastic cells in MM are considered to harbor either chromosomal hyperdiploidy or chromosomal translocations involving the immunoglobulin heavy chain gene locus at 14q32 [24]. These abnormalities are considered primary genetic events that are also present in the earlier stage of MGUS. They are insufficient to cause MM, which requires additional secondary genetic abnormalities such as copy number changes, DNA hypomethylation, and acquired mutations to occur in the plasma cell (a post-germinal center mature B-cell) that had acquired a primary genetic abnormality while transiting the follicular germinal center or had inherited genetic variation [24]. The neoplastic plasma cells in MM are thought to derive from self-renewing myeloma-propagating cells due to interactions in the bone marrow niche causing the transformation of plasma cells to neoplastic myeloma cells [24].

The current diagnostic criteria for MM and its precursor neoplasms were developed by the IMWG in 2014 [11], as an update from the previous 2003 [12] and 2010 [17] criteria, to include very high-risk SMM as a type of active MM to enable treatment of those patients [11,25]. In addition to 10% clonal bone marrow plasma cells or a biopsy-proven bony or extramedullary plasmacytoma, the 2014 IMWG diagnostic criteria of MM required any one or more of myeloma-defining events, which then started to include any of the following additional biomarkers, referred to as “SLiM” in addition to the above-mentioned CRAB features, for “SLiM-CRAB” criteria [11]:

- (1) Bone marrow plasmacytosis $\geq 60\%$ (“S” for “sixty” in SLiM),
- (2) Serum FLC involved: uninvolved ratio ≥ 100 (“Li” for “light chain” in SLiM), and
- (3) More than one focal lesion on MRI studies, with each focal lesion being $>5\text{mm}$ in size (“M” in SLiM) [11].

The 2014 IMWG group defined SMM to require the following two criteria [11]: (1) serum M-protein (IgG or IgA) $\geq 30\text{ g/L}$ or urinary M-protein $\geq 500\text{ mg}$ per 24 hours; or clonal bone marrow plasma cells 10% to 60%; or both; and (2) the absence of myeloma-defining events or amyloidosis [11].

SMM was further characterized for risk of progression to active MM by a retrospective single-institution Mayo Clinic study that identified 400 patients based on the 2014 IMWG criteria [26]. In that study, three readily determined variables, i.e., bone marrow plasma cells $>20\%$, serum M-protein $>2\text{g/dL}$, and an abnormal serum FLC ratio >20 , were considered to predict a 50% risk of progression at 2 years, if two or more factors were present [26]. In 2020, the IMWG confirmed this risk stratification model often termed “20/2/20” in an

international retrospective study of 1,996 patients with SMM from 75 centers in 23 countries [27]. This risk model uses readily available clinical values to estimate tumor burden and can be applied in low-resource settings. Findings identified by fluorescence in situ hybridization (FISH), present in only a subset of their studied patients, could improve the risk model, and the IMWG authors noted that prospective studies would be needed to determine the clinical validity of incorporating cytogenetics and genomics data in identifying more precise risk of progression [27].

Figure 1 depicts the differential diagnosis of non-IgM MGUS and SMM, which are precursors of active MM, with active MM, which must be treated. The presence of any of the CRAB features of end-organ damage or myeloma-defining biomarkers (often termed SLiM-CRAB as explained above) must be absent in MGUS and SMM. The presence of any of the CRAB or SLiM-CRAB features, in conjunction with either 10% or greater clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma or both indicates a diagnosis of active MM, which requires treatment. The IMWG diagnostic criteria are used universally and have been included in the World Health Organization diagnostic pathology classification [28] and the parallel International Consensus classification of hematolymphoid neoplasms [29]. Since plasma cells are post-germinal center B cells, multiple myeloma is also termed plasma cell myeloma and is classified among lymphoid neoplasms arising from B cells [28,29].

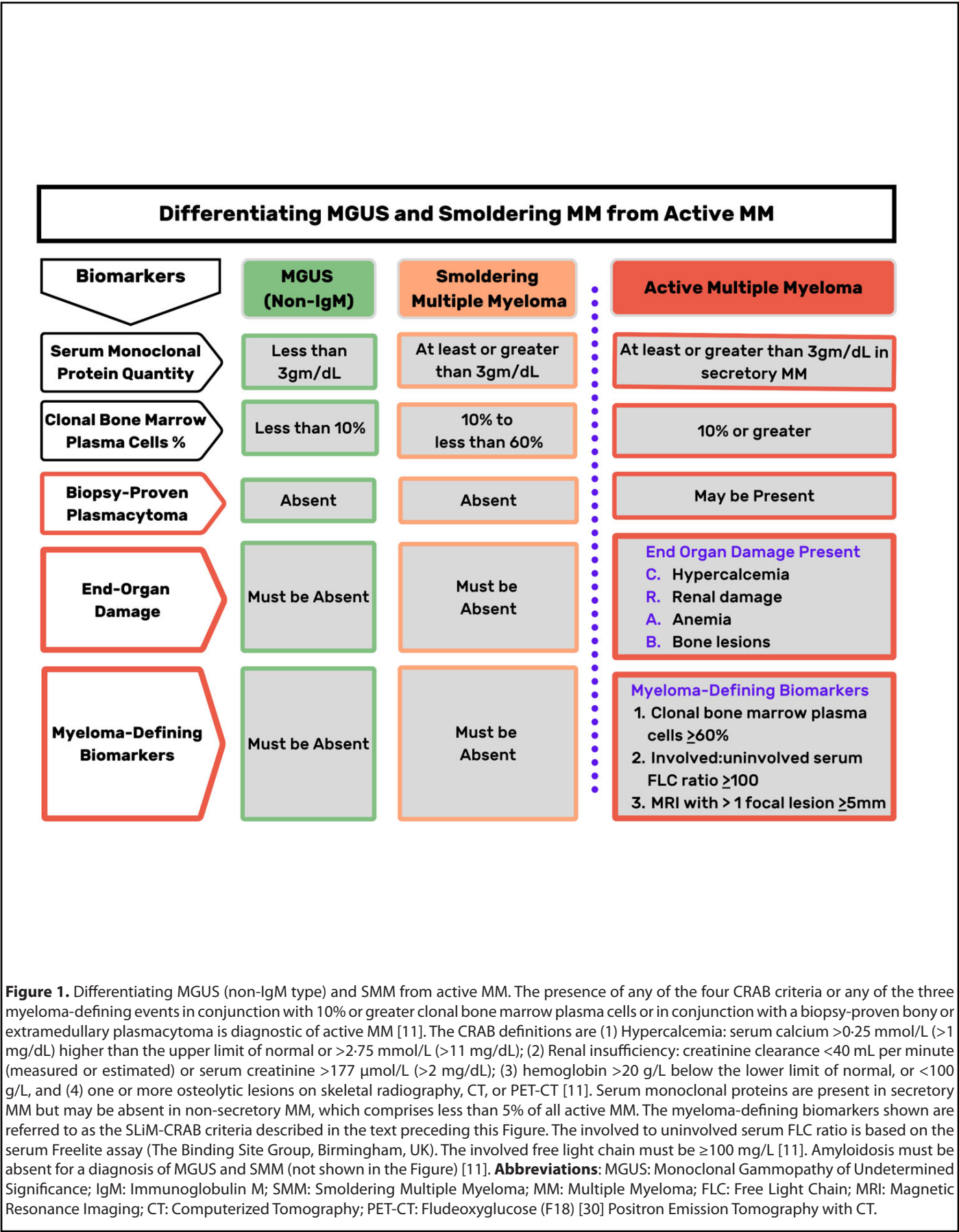
Figure 2 shows the defining criteria for the diagnosis of the three types of MGUS, based on IMWG criteria [11]. The evaluation of the risks of progression of non-IgM MGUS and light chain MGUS to active disease is described in a subsequent section.

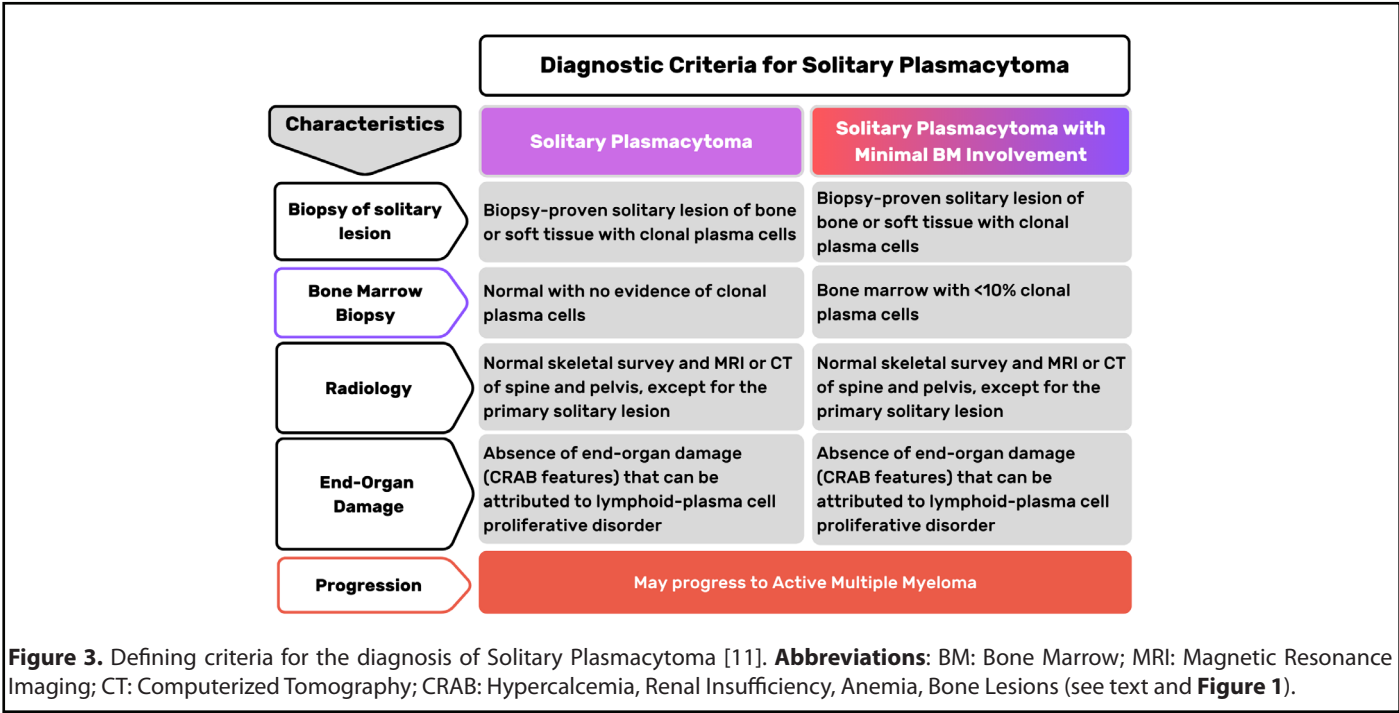
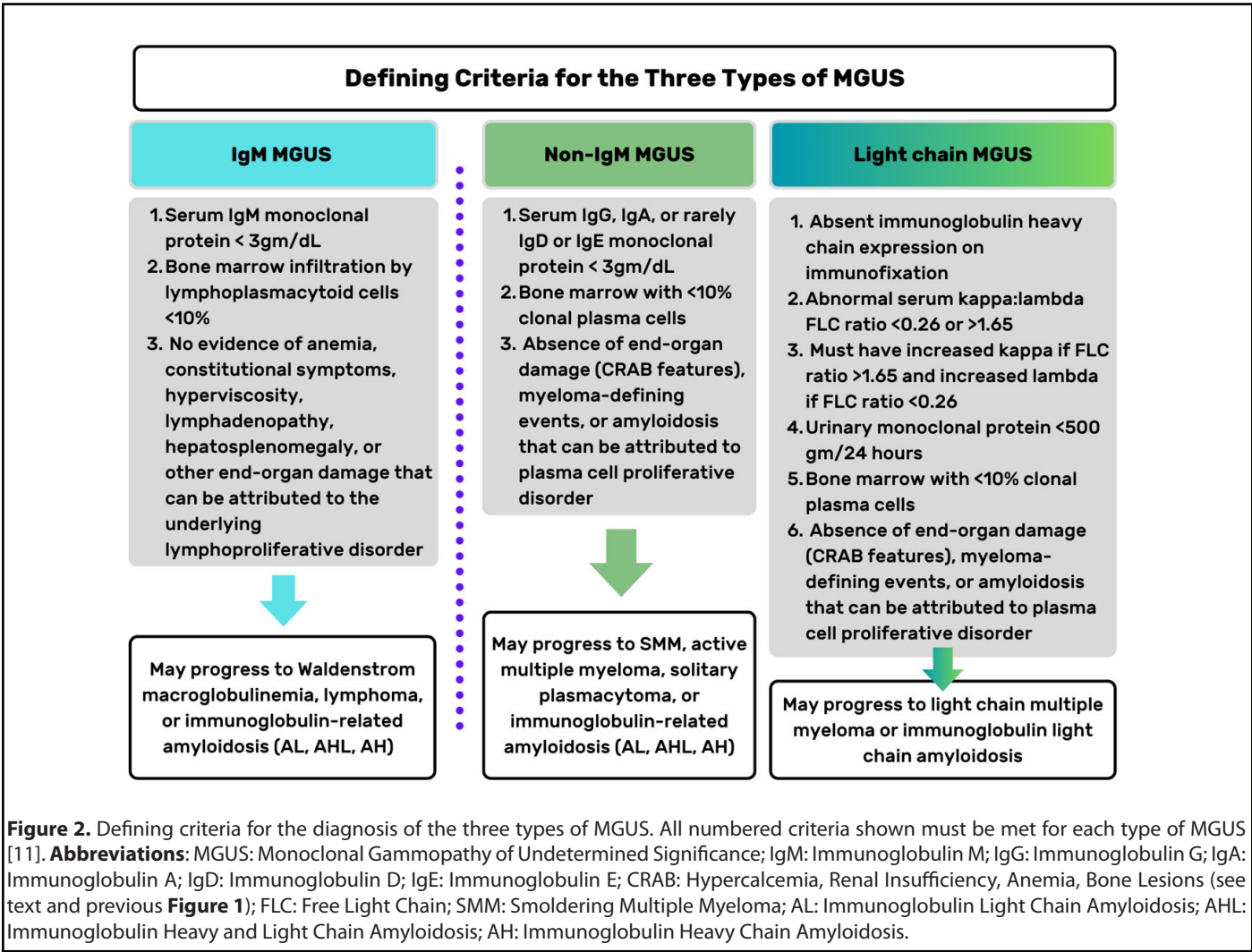
Figure 3 shows the defining criteria for solitary plasmacytoma with and without minimal bone marrow involvement.

Plasma cell leukemia is currently defined by the presence of 5% or greater circulating plasma cells in the peripheral blood smear of a patient diagnosed with multiple myeloma, according to an IMWG consensus in 2021 [31]. The earlier diagnostic criteria for this leukemia required the presence of $>20\%$ circulating plasma cells and an absolute circulating plasma cell count of $2 \times 10^9/\text{L}$ [32]. Plasma cell leukemia may be primary, i.e., present at the time of MM diagnosis, or secondary, i.e., present in relapsed or refractory MM in a patient with a previous diagnosis of MM [31]. Patients with MM having increased circulating plasma cells are expected to have poor overall survival and progression-free survival [33].

Refractory and Relapsed Multiple Myeloma: International Myeloma Working Group Definitions

Refractory and relapsed multiple myeloma were defined by the IMWG [34] to design clinical trials using novel drugs [35]. According to the IMWG definitions, refractory myeloma





refers to the refractoriness of the disease to treatment, which can occur after primary (or initial) treatment or after salvage therapy. Refractory myeloma is identified by non-responsiveness, i.e., failure to achieve a minimal response, or by progressive disease while on therapy or within 60 days of the last therapy [34]. Refractory myeloma may be “relapsed and refractory,” which occurs after relapse during salvage therapy, or it may be “primary refractory myeloma,” in which case the patient does not ever achieve a minimal response or better with any therapy [34].

In contrast, relapsed (or recurrent) myeloma is defined as myeloma that progresses after being previously treated but it does not meet the criteria for relapsed and refractory myeloma or primary refractory myeloma described above [34]. These IMWG definitions are used for the current treatments [36] and clinical trials (reviewed in [37]) for patients with relapsed or refractory MM.

Staging and Prognosis of Newly Diagnosed Multiple Myeloma

An accurate assessment of prognostic risk at diagnosis of disease is critically important for patients and their treating clinicians. Multiple myeloma is a very heterogeneous disease, and clinical outcomes are variable with some patients considered as high-risk having worse outcomes than others in the same risk group [38]. The improved survival rates have been seen primarily in MM considered to have standard risk [39]. Even some patients considered as standard-risk MM may show early relapses or refractory disease or inferior outcomes compared to other patients with standard-risk MM, indicating that there is heterogeneity in the risk within the defined risk categories [39-41]. The term “functional high-risk myeloma” has been used for those patients who do not fall into a high-risk group at diagnosis by the current criteria but are recognized as high-risk after failure of front-line therapy, including relapse within 18 months of treatment initiation or 12 months of frontline autologous stem cell transplantation [42].

Historically, a clinical staging system for MM was first developed by Durie and Salmon in 1975, based on four variables: hemoglobin, serum calcium level, bone lesions on X-ray, and serum and urine M-protein levels, which provided three risk groups based on the tumor (myeloma) cell mass [43], shown as stages I-III in (**Table 1**). In 1990, serum β_2 -microglobulin was identified as the most powerful predictor of prognosis in MM [44]. This simple laboratory value, representing a disease factor, in conjunction with the serum albumin level (a patient factor), comprised the two variables required by the International Staging System (ISS) in 2005 to separate three prognostic risk groups [45], also shown in (**Table 1**). A subsequent comparison of the two staging systems in 2009 showed that the ISS was not prognostically reliable in patients treated by transplantation indicating that additional variables were required for prognostic risk stratification [46].

In 2010, a German study showed the independent prognostic significance of cytogenetic abnormalities in MM patients who underwent autologous stem cell transplantation [47]. In 2011, an IMWG consensus panel considered the following abnormalities to be high-risk in MM: high serum β_2 microglobulin, low serum albumin, and chromosomal 13 or 13q deletion, t(4;14), and del(17p), if detected by chromosomal banding analysis, and t(4;14), t(14;16), and del(17p) if detected by FISH [48].

In 2012, the UK Medical Research Council group identified the following cytogenetic abnormalities to have adverse prognostic risk independent of the ISS: +1q21, del(17p13) and immunoglobulin heavy chain gene translocations t(4;14), t(14;16) and t(14;20) [49]. They defined risk groups based on the number of adverse cytogenetics abnormalities: (1) no adverse cytogenetics as favorable, (2) one adverse genetic lesion as intermediate, and (3) >1 adverse lesion as high-risk [49]. They also identified an ultra-high-risk group by combining >1 adverse genetics with the ISS stage II or III, thus improving risk stratification [49]. A combined genetic-ISS model, including patient age, improved prognostic risk stratification in an international collaborative IMWG study in 2013 [50]. Based on these previous studies [47,49,50], the IMWG consensus on risk stratification was published in 2014 [51]. The Mayo Clinic guidelines [52] for risk stratification, published in 2013 [52], were based primarily on cytogenetics findings, as follows: (1) high-risk: del(17p), t(14;16), and t(14;20) by FISH, (2) intermediate-risk: t(4;14) by FISH, cytogenetic deletion 13, hypodiploidy, and (3) standard-risk: all other abnormalities, including t(11;14) and t(6;14) by FISH [52]. A high-risk gene expression profiling signature was included in the Mayo Clinic guidelines for high-risk and plasma cell labeling index $\geq 3\%$ for intermediate-risk groups, but the guidelines stated that these tests would be unavailable to most clinicians and were not recommended [52]. A 92-gene expression profiling signature was developed in 2012 for use in clinical trials; the authors emphasized that this signature had not been developed to evaluate risk in a single individual patient and was meant to be used in groups of at least 25 patients [53].

Subsequently, three independent variables were found to identify a risk of death due to early progression in patients treated with an autologous hematopoietic stem cell transplant (AH SCT): elevated serum lactate dehydrogenase (LDH), ISS stage 3, and adverse cytogenetics t(4;14), del(17p), or both genetic abnormalities [54]. The above-described laboratory values and cytogenetic abnormalities were evaluated in patient-level data and incorporated into the Revised ISS (R-ISS) in 2015 [55]. As shown in **Table 1**, the R-ISS created three stages I, II, and III, defined by the ISS stage, serum LDH, and the presence of high-risk or standard-risk cytogenetic abnormalities by FISH. However, the R-ISS identified only 9.5% of patients in stage III (highest risk in the system) with the maximum percentage being 61.9% for the intermediate stage II, for whom there were no inclusive definitions, except

Table 1. Multiple myeloma staging systems and prognostic risk stratification schemes published from 1975 to 2015.				
Staging System		Criteria		
Name	Patients studied	Stage I	Stage II	Stage III
Durie-Salmon Staging System, published in 1975 [43]	N = 71 (41 men; 30 women) with multiple myeloma with follow-up available; median age 62 years (range 35-81 years)	Requires all following values: 1. Hemoglobin <10 g/dL, and 2. Serum calcium <12 mg/dL, and 3. Normal X-ray bone structure or solitary plasmacytoma, and 4. Low monoclonal protein production: (a) Serum IgG <5 g/dL (b) Serum IgA <3 g/dL (c) Urine light chain monoclonal component on electrophoresis <4 g/24 h	Not stage I or III	Requires one or more of the following values: 1. Hemoglobin <8.5 g/ dL, or 2. Serum calcium >12 mg/ dL, or 3. Advanced lytic bone lesions, or 4. High monoclonal protein production (a) Serum IgG >7 g/dL (b) Serum IgA >5 g/dL (c) Urine light chain monoclonal component on electrophoresis >12 g/24 h
		Subclassification: A = Relatively normal renal function (serum creatinine value <2.0 mg/dL); B = Abnormal renal function (serum creatinine value >2.0 mg/dL)		
International Staging System (ISS), published in 2005 [45]	N= 10,750 (57% male), median age 60 years, with untreated symptomatic MM from 17 institutions in North America, Europe, and Asia	Serum β 2 microglobulin <3.5 mg/L, and Serum albumin $\geq$ 3.5 g/dL	Not stage I or III; Stage II has two categories: serum β 2M <3.5 mg/L but serum albumin <3.5 g/dL; or serum β 2M 3.5 to <5.5 mg/L with any level of serum albumin	Serum β 2 microglobulin $\geq$ 5.5 mg/L
Revised International Staging System (R-ISS), published in 2015 [55]	N= 4445 NDMM; median age 62 (range 82-91) years, from 11 international, multicenter trials from 2005 – 2012; ISS, LDH, and cytogenetics available in 3060 of 4445 patients	1. Stage 1 as per the ISS, and 2. Absent high-risk* (or presence of standard-risk) cytogenetic abnormalities by interphase FISH, and 3. Normal serum LDH level (less than the upper limit of normal)	Not stage I or III by the Revised ISS	1. Stage III by the ISS, and 2. Either (a) a high-risk* cytogenetic abnormality by interphase FISH, or (b) high serum LDH level
		*High risk cytogenetic abnormalities = presence of del(17p), t(4;14), or t(14;16) Standard risk cytogenetic abnormalities = no high-risk cytogenetic abnormality		
		N = 871 (30.6%) of 3060	N = 1894 (61.9%)	N = 295 (9.5%)
	Median OS at 46 mo. median FU	Not reached	83 months	43 months
Abbreviations: ISS: International Staging System; MM: Multiple Myeloma; β 2M: β 2 Microglobulin; NDMM: Newly diagnosed Multiple Myeloma; FISH: Fluorescence In situ Hybridization; LDH: Lactate Dehydrogenase; OS: Overall Survival; Mo: Months; FU: Follow-up.				

not being stratified as ISS stages I or III [55]. Based on the R-ISS, the IMWG guidelines for treating high-risk MM were published in 2016 [56].

In 2019, the Intergroupe Francophone du Myélome (IFM) developed and validated a prognostic index based on the clinical data and results for seven specific cytogenetic abnormalities, (17p), t(4;14), del(1p32), 1q21 gain, trisomy 3,

trisomy 5 (a good prognostic factor), and trisomy 21 in 1,635 patients with NDMM enrolled in four clinical trials between 2000 and 2012 [57]. Bone marrow plasma cells were selected by CD138+ magnetic cell sorting, and only those samples with $\geq$ 70% plasma cells post-sorting were selected for cytogenetic analysis. FISH was performed for t(4;14)(p16;q32), and the other abnormalities were detected by a copy number and single nucleotide polymorphism array platform. If del(17p)

was detected, the percentage of involved plasma cells was determined by an additional *TP53*/CEP17 FISH probe analysis, and del(17p) was included only if present in $\geq 60\%$ of plasma cells [57,58]. Cytogenetics findings alone provided a better separation than the ISS of patients who died from those who survived and were better than the R-ISS in an external validation dataset in correlating the prognosis with the outcome. Three risk groups were identified: low, intermediate, and high. Low risk was present only if del(17p) and t(4;14) were both absent [57]. Less than 35% of patients with t(4;14) but most patients with del(17p) were identified as high-risk [57]. The hazard ratios for death were 6 to 15 times higher in high-risk compared to low-risk patients [57]. The t(14;16) was not included in their analysis since there have been studies showing that the presence of this abnormality does not confer a higher risk (reviewed in [57]); in their study, the risk did not differ due to the presence or absence of the t(14;16) abnormality [57].

Chromosome 1q abnormalities have been studied in MM for at least two decades. Amplification of 1q, representing ≥ 4 or more copies of 1q, and gain of 1q, representing three copies of 1q (two normal copies and one extra copy) have been shown to have a poor prognosis in MM, with the evidence being stronger for amplification of 1q than for gain of 1q (reviewed in [59]). The Second Revised ISS (R2-ISS) published in 2022 was based on 10,483 patients with NDMM enrolled in 16 international, multi-center clinical trials from 2005 to 2016,

with a median follow-up of 75.5 months [60]. Patient-level data were examined in this study for factors required for the R-ISS and gain or amplification of 1q, referred to as 1q+ since separated data for gain or amplification of 1q were unavailable for these patients [60]. The factors that most affected the overall survival (OS) and PFS were the ISS stage, serum LDH, del(17p), t(4;14), and 1q+ [60]. These variables were used in the training set of 2,226 patients to derive an additive risk score, which determined four risk groups shown in **Tables 2A** and **2B** [60]. The intermediate-risk group in the three-stage R-ISS was re-defined by the R2-ISS by defining four risk groups [60].

The biggest strength of this system is that the risk factors are possible to evaluate in most patients, requiring only simple laboratory tests and FISH studies, which are readily available in many institutions worldwide [60]. However, it does not yet include other poor significant prognostic factors as discussed by the authors [60], including the presence of circulating plasma cells [61-66], *TP53* mutations, and extramedullary disease (defined in [67]), and patient factors such as frailty, which could be added to further identify high-risk in NDMM. Red blood cell distribution width (RDW) has been reported as a parameter that is increased in IgA MM and increases with progressive clinical stages of MM, and this value could be incorporated into prognostic models for MM [68]. The risk factors recognized as high-risk in NDMM and relapsed MM by the current U.S. National Comprehensive Cancer Network (NCCN) guidelines are shown in **Figure 4** [69].

Table 2A. Four risk groups in the Second Revised International Staging System (R2-ISS) for newly diagnosed multiple myeloma [60].		
R2-ISS Risk Groups	Total Additive Risk Scores ^a	% (N) of Patients
Low (I)	0	19% (428)
Low-intermediate (II)	0.5-1	31% (686)
Intermediate-high (III)	1.5-2.5	41% (917)
High (IV)	3-5	9% (195)
^a The total additive risk score was derived by adding the risk scores for individual prognostic factors, shown in (Table 2B).		

Table 2B. Individual risk scores and hazard ratios for each risk factor in R2-ISS [60].			
Risk factors	Score Values ^a	Hazard Ratios (95% Confidence Interval)	
		OS	PFS
ISS Stage II	1	1.75 (1.45 - 2.05)	1.43 (1.28 - 1.61)
ISS Stage III	1.5	2.53 (2.13 - 3.01)	1.76 (1.54 - 2.01)
del(17p)	1	1.82 (1.53 - 2.17)	1.43 (1.23 - 1.65)
LDH high	1	1.60 (1.36 - 1.88)	1.37 (1.20 - 1.57)
t(4;14)	1	1.53 (1.29 - 1.81)	1.40 (1.21 - 1.62)
1q+	0.5	1.47 (1.49 - 1.68)	1.33 (1.20 - 1.48)
^a Score values were calculated using overall survival as the outcome and were rounded to the nearest 0.5 [60].			
Abbreviations: ISS: International Staging System; LDH: Lactate Dehydrogenase; OS: Overall Survival; PFS: Progression-free Survival; 1q+: Gain or Amplification of Chromosome 1q			

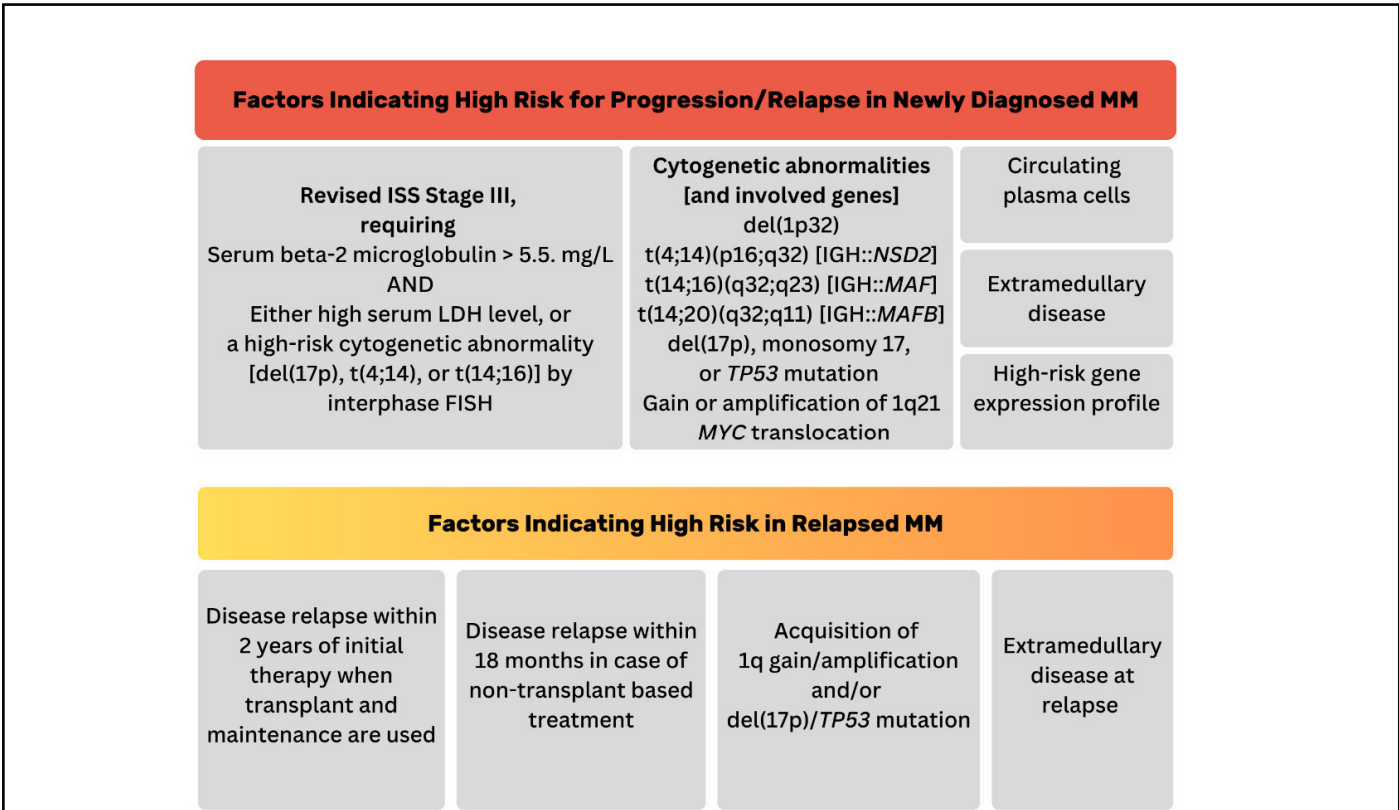


Figure 4. Factors recognized as high-risk for progression or relapse in patients with newly diagnosed MM and relapsed MM; this Figure is adapted from the NCCN guidelines version 4.2024 [69]. Chromosomal 1q gain/amplification alone is not considered high-risk in NDMM [69]. The presence of 5% or more circulating plasma cells is defined as plasma cell leukemia [69]. **Abbreviations:** MM: Multiple Myeloma; LDH: Lactate Dehydrogenase; FISH: Fluorescence In situ Hybridization.

Treatment Response Criteria in Multiple Myeloma, Including Minimal/Measurable Residual Disease (MRD) Evaluation

The first uniform criteria for treatment responses in MM were developed by the European Group for Blood and Bone Marrow Transplant in 1998 [70]. In 2006, the IMWG updated these criteria due to the need to compare precisely the effects of new therapies in clinical trials and use in the clinic for individual patients, with the following definitions [71]:

- (1) "Complete response" (CR) required <5% bone marrow plasma cells, negative immunofixation in serum and urine, and disappearance of any soft tissue plasmacytomas.
- (2) "Stringent CR" required CR plus normal serum FLC ratio and the absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence to evaluate the κ : λ ratio (with an abnormal κ : λ ratio being >4:1 or <1:2 based on ≥ 100 plasma cells).
- (3) "Very good partial response" (VGPR) with serum and urine M-protein detectable by immunofixation but not by electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein <100 mg per 24 hours; and

- (4) Partial response with 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 90% or <200 mg per 24 hours.

A serum FLC assay was added to evaluate treatment responses in patients with non-secretory and oligo-secretory disease [71].

In 2006 [71], "measurable disease" was defined by serum and urine M-protein and serum FLC levels, requiring the measurement of any one or more of the following three parameters: (1) serum M-protein ≥ 1 g/dL (≥ 10 gm/L), (2) urine M-protein ≥ 200 mg/24 hours, and (3) involved serum free light level ≥ 10 mg/dL (≥ 100 mg/L) with an abnormal serum FLC ratio [71]. In 2011, two-to-four-color flow cytometry was added to the response criteria as a technique for determining the κ : λ ratio for stringent CR; "immunophenotypic CR" was defined as stringent CR plus the absence of phenotypically aberrant (clonal) plasma cells in the bone marrow with a minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry with > 4 colors, and "molecular CR" was defined as CR plus negative allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) with a detection sensitivity of 1 in 10^5 cells [34].

A decade ago, the treatments using newer therapies for multiple myeloma led to an urgent need to measure deeper responses to treatment that could detect residual disease with higher sensitivities than the traditional methods of measuring serum and urine M-proteins. It has been known for more than two decades that flow cytometric immunophenotypic analysis can detect normal plasma cells from neoplastic plasma cells in the same specimen [72,73]. Multiple publications in 2015 by international experts addressed MRD evaluation by multiparameter flow cytometry (MFC) in MM, including the need for a harmonized approach [74], data acquisition [75], data analysis and reporting [76], and quality control [77]. The IMWG consensus criteria for treatment response, published in 2016 [78], added responses to treatment after detecting MRD in bone marrow specimens by high sensitivity MFC (termed next-generation flow) or by next-generation sequencing (NGS) of the immunoglobulin heavy chain gene variable-diversity-junctional (VDJ) region at a minimum sensitivity level of 1 in 10^5 bone marrow cells, and to detect extramedullary disease by sensitive radiologic imaging techniques, which form the current guidelines for MRD assessment in multiple myeloma [69,78].

As per guidelines from the U.S. Food and Drug Administration (FDA), the detection sensitivity of an MRD assay in hematologic malignancies is required to be 10-fold below the clinical decision-making threshold, which means that an assay's analytical sensitivity of detecting 1 abnormal cell in 10^6 cells is required for the clinical decision-making threshold of 1 in 10^5 [79]. Comparing MFC with NGS, both methods can achieve the high sensitivity required for MRD evaluation in multiple myeloma [80-82]. MFC has a significant advantage of an in-built evaluation of the quality of the bone marrow sample being evaluated, since normally occurring bone marrow cells such as B cell precursors (hematogones), nucleated red blood cells, and mast cells can be identified by flow cytometry [76]. Also, normal and neoplastic plasma cells in the bone marrow can be distinguished by MFC, allowing a precise determination of MRD [83]. Although MFC requires a fresh sample with viable cells, the technique has been used worldwide even in developing countries with limited resources, and a diagnostic sample is not necessary [83,84]. In contrast, although NGS can be performed on an archived sample, the technique for MRD evaluation mandates the availability of a quality diagnostic bone marrow sample, ideally less than 48 hours old [74,84] to first establish the diagnostic clone, and high-quality DNA and high total DNA yield are critically required for MRD evaluation by NGS [81]. In addition, if the sample is transported to a reference laboratory for NGS, the cost increases and hemodilution in the sample analyzed for MRD may not be possible to evaluate for. Finally, the choice of method would depend on the instrumentation and expertise available at the institution [82].

Regardless of the selected method, both NGS and MFC depend on a bone marrow biopsy, which is well-known to pathologists for having patchy involvement by neoplastic

plasma cells in MM. Even if the first pull in a bone marrow biopsy is dedicated for MRD analysis by MFC or NGS, that specimen might still not accurately represent the amount of disease even in the bone marrow, and another method must still be used for extramedullary disease assessment. Therefore, for MRD assays to be truly representative of the residual quantity of myeloma disease in the body, including involved extra-medullary and medullary foci, other methods using peripheral blood draws such as analysis of genomic variants in circulating tumor DNA [85] and circulating tumor cells [61] should be seriously considered for further development to be used on a wide scale to evaluate MRD in patients with multiple myeloma.

Improvement In Survival Rates Due to Novel Classes of Drugs

The 5-year survival rates for all patients with MM in the USA improved from 25% in 1975-1977 and 32% in 1995-1997 to 60% in 2013-2019 [5]. The increased survival in the last two decades is primarily due to improved therapies and novel agents. Thalidomide was introduced in clinical trials in MM in the late 1990s and lenalidomide and bortezomib in the early 2000s [86]. A registry-based Swedish study showed a 29% reduction in mortality in younger patients aged <70 years diagnosed in the 1994-2003 period [87]. Subsequently, a patient-level study showed that among patients treated from 1950 to 2005 in Sweden, overall survival improved the most in the 2000-2005 period [88]. This improvement was attributed to the use of high-dose melphalan before autologous hematopoietic stem cell transplantation and novel agents such as thalidomide [87,88].

Improvements in survival in the USA also occurred mainly in younger patients, based on SEER data, with patients aged <50 years showing 5- and 10-year relative survival of 56.7% and 41.3% in 2002-2004 and patients aged 50 to 59 years showing 5- and 10-year relative survival of 48.2% and 28.6% in 2000-2004, but only moderate improvement in ages 60 to 69 years, and no improvement in older patients [89]. In a Mayo Clinic cohort, OS was shown to be significantly improved in patients with MM diagnosed for the first time or with relapse after 2000 and treated with one or more of the novel agents, thalidomide, lenalidomide, bortezomib, compared with patients diagnosed in the 1990s [90]. In 2014, 6-year OS was shown to be improved from 31% to 56% primarily in older patients aged >65 years from 2001-2005 to the 2006-2010 groups of patients at the Mayo Clinic, a specialized institution in the USA [91]. The OS for Spanish patients with MM improved from 1980 to 2020, with median values of 22.4 months in 1980-1990, 37.4 months in 1991-2000, 61.8 months in 2001-2010, and 103.6 months in 2011-2020, attributed mainly to the use of novel agents in frontline therapy [92]. Of note, survival has also improved significantly in the 70-79 and >75 years age groups, as shown in large population-based studies from Germany [93], Norway [94], Sweden, and Denmark [95].

During 2007-2014, there were 128 publications for clinical trials conducted only in the USA for MM [96], reflecting the active clinical research in treating this disease, albeit with the under-representation of the patient populations with greater disease prevalence in the USA [96]. In 2012, lenalidomide as maintenance following autologous hematopoietic stem cell transplantation showed significantly improved progression-free survival (PFS) [97,98] and OS [97]. Also in 2012, carfilzomib was used for frontline treatment in combination with lenalidomide and dexamethasone in patients aged 35-81 years (with 43% >65 years of age) to show exceptional responses [99]. Bortezomib, combined with thalidomide and dexamethasone as induction therapy before, and consolidation therapy after, double AHSTs for NDMM showed a superiority of the triplet regimen including a proteasome inhibitor and an immunomodulatory agent compared with thalidomide and lenalidomide alone [100,101], also confirmed after long-term follow-up [102].

Also in 2014, low-dose lenalidomide and dexamethasone until disease progression in a clinical trial of 1,623 patients with transplant-ineligible MM showed significantly improved PFS, and improved OS, compared with the standard-of-care combination of melphalan, prednisone, and thalidomide [103]. Updated results in 2016 confirmed the OS benefit of low-dose lenalidomide-dexamethasone, including a 14-month improvement in median OS in patients >75 years [104]. Daratumumab, an anti-CD38 human IGGk monoclonal antibody, that kills myeloma cells by antibody-dependent and complement-dependent cytotoxicity, was given breakthrough status [105] and first given accelerated approval in the USA in November 2015 to treat relapsed or refractory MM with $\geq$ three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent (reviewed in [106]) or if refractory to both classes of drugs [107]. In 2016, unprecedented improvements in PFS were shown [108] in patients with relapsed or refractory MM by adding daratumumab to the combination of bortezomib and dexamethasone [109] or lenalidomide and dexamethasone [110]. The SWOG S0777 trial, which started in 2007, showed in 2017 a landmark improvement in OS to 75 months by adding bortezomib to lenalidomide and dexamethasone in NDMM [111,112].

The U.S. NCCN guidelines from April 2024 recommend triplet drug regimens as preferred combinations for frontline therapy in transplant and non-transplant candidates, or a quadruplet drug regimen also including an anti-CD38 agent such as daratumumab in transplant-eligible patients with MM [69]. The newer drug classes include proteasome inhibitors such as bortezomib, carfilzomib, and ixazomib (reviewed in [113,114]), immunomodulatory agents such as thalidomide [115,116], lenalidomide, and pomalidomide (reviewed in [106,116]), often combined with dexamethasone in triplet drug regimens. Despite the advances in therapies with improved survival rates, MM remains incurable, and the disease is characterized by several relapses [117]. The best chances of a sustained deep

therapeutic response are in the frontline treatment of MM since the proportion of patients receiving therapy decreases with each successive line of therapy [118].

In the last decade, the sustained absence of minimal or preferably, measurable residual disease (MRD) at the minimal sensitivity level of detecting one abnormal plasma cell in 100,000 (or 10^5) cells has emerged as an indicator of favorable prognosis in patients with MM [119]. Flow cytometry is the most readily available method worldwide with a fast turnaround time compared to next-generation sequencing to detect MRD [120] with ongoing efforts to harmonize high-sensitivity flow cytometry data analysis internationally to achieve conformity in clinical trials [83]. According to the NCCN guidelines from April 2024, MRD should be evaluated only with a suspected complete response, with MRD evaluation recommended after each stage of treatment [69]. Intense clinical research in the form of clinical trials using different treatment modalities, including anti-CD38 antibodies, chimeric antigen receptor T-cell therapy, and bispecific antibodies, has been conducted by the myeloma community toward curing the disease. Excellent treatment responses including high rates of undetectable MRD (considered as MRD-negativity) have been seen in transplant-eligible NDMM in the phase 3 PERSEUS (daratumumab, bortezomib (V), lenalidomide (R), and dexamethasone (D) vs. VRD) [121] and phase 2 GRIFFIN (Daratumumab-VRD vs. VRD) [122] trials, transplant-ineligible NDMM in the phase 3 MAIA (Daratumumab-RD vs. RD), [123] and phase 3 IMROZ (Isatuximab-VRD vs. VRD) [124] trials, and relapsed or refractory MM [125-131]. The international MM community has been working toward the use of MRD as an endpoint as a surrogate for PFS in clinical trials for patients with MM [119,132-134] since 2009 (discussed in [134]). In April 2024, an oncologic advisory committee of the FDA approved MRD as an endpoint for accelerated approvals in clinical trials for transplant-eligible and transplant-ineligible NDMM and relapsed or refractory MM [135]. This approval is a significant milestone since it will allow a readout of clinical trials earlier than a clinical survival endpoint, and in the future, after being studied at the patient level, MRD evaluation could allow clinical decision-making during the treatment of MM in individual patients.

Disparities and Inequities in Receiving Healthcare in Patients with Multiple Myeloma

Despite the advances in novel therapies available to patients with MM, several barriers preclude access to novel agents, including AHST for treating patients with MM from ethnic minority populations in the USA, which many clinicians have studied in the USA [136-143]. A recent National Cancer Database study of 111,799 patients with MM diagnosed during 2004-2013 and who received AHST as primary treatment, comprising 77.5% non-Hispanic White, 15.1% non-Hispanic Black, 5.2% Hispanic, and 2% non-Hispanic Asian patients, identified socioeconomic factors that affected access to

treatment [136]. Of note, insurance payer status significantly affected the access to an AHSCT for all ethnic groups [136]. In this context, the complex healthcare structure in the USA is described as an important structural barrier to accessing novel treatments [138,144]. In the entire cohort, only 10.6% of all non-Hispanic Black patients received an AHSCT [136]. In another 2008-2014 cohort of 28,450 patients undergoing AHSCT for MM, it was notable that post-transplant outcomes were similar, but there were differences in utilization rates of AHSCT in different ethnic groups [137]. The lowest rate of increase in AHSCT was seen in Hispanic, followed by non-Hispanic Black patients, compared with non-Hispanic White patients [137]. Hispanic and non-Hispanic Black patients are often younger than 60 years, compared to the median age of 69 years for MM, are likely to have advanced-stage disease, and are referred for transplant later than non-Hispanic White patients [137]. Access to novel therapies for MM is delayed in minority populations in the USA, as shown in several studies based on SEER data [139-141]. Globally, factors adversely affecting access to treatment include older age, female sex, and Black, Hispanic, or Asian ethnicity [145].

Progress in Determining the Risk of Progression of MGUS and SMM to Active Multiple Myeloma

It is important to note that the above-described risks of progression from asymptomatic MGUS or SMM to active MM represent an average risk for patient populations. These risks do not apply to the risk of progression in individual patients, as described in an example in 2021 [146]. Also, tumor burden alone cannot predict whether the disease will progress or

how fast the disease will progress. A longitudinal follow-up study in 2019 showed that the risk of progression in MGUS can change quickly from low or intermediate risk to high risk [147]. Of note, among the patients who progressed from MGS to MM, the majority (79%) progressed directly to MM without an intermediate SMM phase [147]. The adverse prognostic indicators for the progression of MGUS included an IgA isotype of the M-protein, $\geq 15\text{g/L}$ M-protein concentration, serum FLC ($\kappa:\lambda$) ratio of <0.1 or >10 , and uninvolved immunoglobulins below the level of normal; adding points based on these variables can stratify progression risk of MGUS into low, intermediate, and high-risk categories [146,147]. **Figure 5** shows these risk factors and low-, intermediate-, and high-risk categories for progression of non-IgM MGUS and light chain MGUS [146,147].

In 2024, the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM), a prospective population-based study developed a multivariable prediction model in 1,043 individuals ≥ 40 years of age with MGUS to predict the risk of SMM, which provided greater benefit than the Mayo Clinic model to decide when to defer a bone marrow biopsy [148]. In the iStopMM study, individuals with SMM had a mean M-protein concentration of 0.62 (range 0.01-3.5) g/dL, and in 73% of persons with SMM, there were 11-20% bone marrow plasma cells [149].

Personalized risks of progression were studied in a multi-site international project in patients with MGUS and SMM with available serial laboratory values in the Precursor Asymptomatic Neoplasms by Group Effort Analysis (PANGEA)

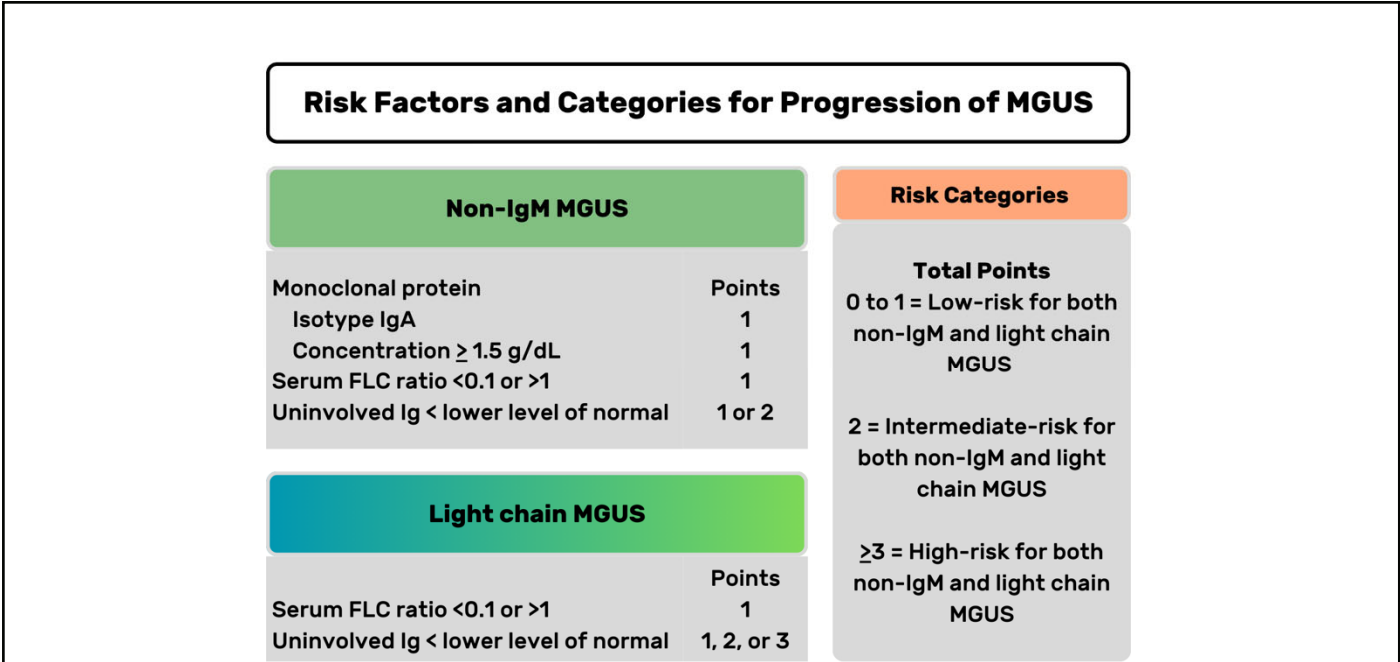


Figure 5. Risk factors and categories for progression of MGUS [146,147]. **Abbreviations:** MGUS: Monoclonal Gammopathy of Undetermined Significance; IgM: Immunoglobulin M, IgA: Immunoglobulin A; FLC: Free Light Chain $\kappa:\lambda$ Ratio; Ig: Immunoglobulins.

model published in 2023 [150]. Patient age, serum FLC ratio, M-protein concentration in g/dL, creatinine concentration in mg/dL, and hemoglobin values over time were used in the model with and without bone marrow plasma cell percentages. Significantly, these models were more accurately predictive for individual patients than the existing models, even in the absence of a bone marrow biopsy using only the other laboratory values, and a freely accessible online user-friendly tool is available for application [150]. Additional cohorts representing the African American population that have a higher prevalence of MGUS (reviewed in [151]), and circulating tumor cells, cell-free DNA, and immune variables, are planned to be studied in this model [150]. Further, at least three randomized clinical trials have shown a survival benefit by starting treatment at the SMM stage [22,152,153]. The reader is referred to the European Myeloma Network consensus statement [154] and the cited review [155] for guidelines and ongoing clinical trials for treating patients with SMM.

What Have We Learned from Genomic Analyses in Multiple Myeloma and Its Precursors That Could Routinely be Applied Clinically to Determine Prognostic Risk?

Genomics in newly diagnosed multiple myeloma

Multiple studies performed in the last two decades using gene expression profiling, copy number arrays, and next-generation sequencing have shown that MM is genetically and clinically heterogeneous (reviewed in [156,157]). The mitogen-activated protein kinase (MAPK) pathway genes *KRAS*, *NRAS*, and *BRAF* are the most frequently mutated in MM, followed by genes in the nuclear factor κ -light chain-enhancer of activated B cells (NF- κ B) pathway [158-160]. However, these mutations had no impact on survival in a large clinical trial in 2015 [158]. In that same clinical trial, mutations in *TP53*, *ATM*, *ATR*, *CCND1* and del(17p), and 1q amplification conferred an adverse impact on OS, while ISS-III, age >70 years, t(4;14), *MYC* translocations, and mutations in *TP53*, *ATM*, *ATR*, and *ZFHX4* were prognostic for PFS [158]. In a study of 1,273 NDMM samples in the Myeloma Genome Project with available clinical, outcome, and exome sequencing data, 63 driver genes with mutations were identified, of which 17 (27%) genes were potentially actionable [161], but only the mutated *TP53* driver gene was an indicator of clinical outcome [162]. The study noted dependencies between oncogenic mutations and translocation subgroups, suggesting that the path to progression from the initial primary initiating events in myeloma is nonrandom [161,162]. Multiple types of driver alterations were identified: (1) mutated genes, (2) chromosomal translocations, (3) chromosomal and segmental losses and gains, (4) loss of heterozygosity, and (5) an APOBEC (Apolipoprotein B mRNA Editing Catalytic polypeptide-like) deaminase [163] mutational signature, which leads to C>T/G>A transitions in specific trinucleotides. Importantly, an

increased number of driver alterations had a poor prognosis [161,162], a concept validated further by the following examples:

In the Myeloma Genome Project, bi-allelic *TP53* inactivation or amplification (≥ 4 copies) of *CKS1B* (chromosomal location 1q21), comprising 6.1% of the cohort identified a higher-risk subgroup within the ISS-III patients with poor survival [164].

The dual combination of t(4;14) and mutated *TP53* showed the shortest OS in another study [165].

A classifier using $\beta 2$ -microglobulin and serum LDH with mRNA levels of APOBEC2, APOBEC3B, and inflammation-related genes *IL11*, *TGFB1*, and *TGFB3* further stratified NDMM patients in the highest R2-ISS risk group [166].

A recent study showed chromosomal 1q21 gain or amplification combined with mutated *KRAS* in patients with NDMM to predict a higher risk of developing extramedullary disease [167].

Importantly, in 2019, complex structural abnormalities, including chromothripsis, defined as “the catastrophic shattering of a chromosome followed by re-ligation in a random order” [168], and a novel replication-based mechanism of templated insertions were identified as major initiating driver events [169]. These genetic events and chromosomal hyperdiploidy occur as early drivers of disease [169]. In contrast, point mutations in genes, genomic duplication, and chromoplexy, defined as “intricately weaved genomic rearrangements occurring in concert” [170], occur later in the disease [169].

In the prospective CoMMpass (Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile) study comprising 1,143 patients with previously untreated NDMM from the USA, Canada, Spain, and Italy diagnosed between 2011 and 2016, high risk was defined by one or more of the following genetic features: del(17p13), t(14;16), t(14;20), t(8;14), and t(4;14) [171]. This study described five hyperdiploid and three non-hyperdiploid subtypes of NDMM, with no difference in outcomes between the hyperdiploid and non-hyperdiploid subtypes. However, any subtype, regardless of hyperdiploid status and having both 1q gain and loss of chromosome 13 showed inferior overall survival than the other subtypes, with 1q gain attributed as the reason for the inferior outcome [171]. The authors of this study [171] emphasized previous findings [158,161,164] in distinguishing between partial and complete loss-of-function in genes such as *TP53* to be clinically important since only a subset of patients with del(17p) detected by conventional cytogenetics analyses are truly high-risk [171].

Further, a 92-gene expression profiling signature that prognosticates NDMM as standard-risk or high-risk for relapse [53], when applied in the Prospective Observational Multiple Myeloma Impact Study (PROMMIS) upgraded or downgraded

the risks assigned clinically to impact clinical decisions [172]. The Multiple Myeloma DREAM challenge, which focused on identifying factors predicting high risk in MM, defined as disease progression or death within 18 months of diagnosis, identified a high expression of the *PHF19* gene, an epigenetic regulator, as having the strongest association with disease progression [173]. In that study, a prognostic model using age, ISS, and gene expression of only two genes, *PHF19* and *MMSET* (or *NSD2*) performed well as compared to other complex, gene expression models with higher numbers of genes [173]. In a large single-cell study using multi-omics, chromosome 1q amplification, *TP53* mutations, and a high expression of *PHF19* were identified as high-risk genetic features associated with relapsed/refractory MM [174].

Genomics in precursor states, MGUS, SMM, and comparison of SMM with NDMM

A whole exome and deep targeted sequencing study of samples from 214 patients with SMM showed that the genetic abnormalities in SMM are already present similar to those in NDMM, except for clinical features that define MM [175]. Structural copy number abnormalities serve as founder events and mutations in gene mutations in cellular pathways lead to disease progression. The following risk factors for progression were identified in this study: *KRAS* and *NRAS* single nucleotide variants, deletion 17p, single nucleotide variants of *TP53* and *ATM* genes, and *MYC* translocations or copy number variations [175].

Interestingly, in another study that compared SMM with MM, *KRAS* mutations in SMM significantly predicted progression to MM, and mutations in *KRAS*, *NRAS*, and *FAM46C* were considered myeloma-defining events [176]. Significantly fewer mutations in the MAPK and NF- κ B pathways were found in cases of SMM, wherein t(11;14) was the most commonly observed translocation in 23% (n=19/82) of SMM cases, with 2.4-4.9% of cases harboring the high-risk translocations, t(4;14), t(6;14), and t(14;16) [176]. About 10% (n = 8/82) of SMM cases showed biallelic inactivation of tumor suppressor genes, *TP53*, *DIS3*, *RB1*, *FAM46C*, and *TRAF3*, which were significantly fewer than similar events seen in MM [176]. *KRAS* mutations and del(6q) were associated with a shorter time to progression, but *MYC* translocations, although identified, were not associated with an adverse prognosis [176]. The number of somatic mutations increased with time in SMM, but the mutational signatures did not change during the progression to multiple myeloma [176].

Further, it was recently shown in both precursor conditions, MGUS and SMM, and cases of MM that there are two types of diseases: a stable disease type that arises later in life and does not progress until decades, and a progressive type that starts earlier in life and progresses early to MM [177]. Significantly, these differences were distinguished despite a low tumor burden characterized by current criteria, but this analysis would require whole genome sequencing [177]. In a smaller genomic analysis of 10 paired samples of SMM and MM, longer and

shorter times for the progression of SMM were seen in 6 and 4 cases, respectively [178]. The collective evidence described above suggests that molecular and genomic analyses could identify high risk in MM and identify cases of SMM with a high risk of progression to MM that cannot be identified by current diagnostic and risk stratification criteria.

An individualized risk prediction model integrating clinical and genomic information

In April 2024, based on comprehensive information including clinical, demographic, genomic, and treatment data in 1,933 patients as a training set and 256 patients as a validation set, the first individualized risk prediction model for NDMM (IRMMA) for PFS and OS was described [179]. The model performed better than the existing ISS models, although the numbers of patients were smaller than those in the R-ISS and R2-ISS. The alterations were correlated with gene expression profiling signatures developed at the University of Arkansas [180]. Twenty genomic features, including 1q21 gain or amplification, del(1p), *TP53* loss, *NSD2* translocations, APOBEC mutational signatures, and copy-number signatures, including chromothripsis, were considered integral for the accuracy of the model. The predictive model is freely available online at the website <https://irmma-risk-calculator.miami.edu/>. Of note, the model was based on information obtained from a single bone marrow biopsy, and anti-CD38 treatments or MRD as treatment responses were not yet included. As stated by the authors, this model's accuracy could be improved in the future by integrating information obtained from a peripheral blood sample and evaluating newer treatment options [179].

Figure 6 is created to depict the concepts of progression risks from MGUS and SMM to MM and prognostic risks in MM.

Conclusions

Among all hematological malignancies, the international multiple myeloma community has led to unprecedented advances in the clinical treatments and outcomes of patients with MM along with advancing our understanding of the pathogenesis of the disease and its precursor conditions by working collaboratively toward a common goal of achieving a cure for their patients. These improvements in outcomes have been achieved despite the immense and unique clinical and genetic heterogeneity in this malignant disease arising from plasma cells. The next steps towards a cure include emphasizing the determination of the most precise risks possible by integrating all known intrinsic patient, disease, and extrinsic factors for determining prognostic risk in NDMM and the risk of progression in its precursors, MGUS and SMM, including medullary and extramedullary disease. Reducing obesity and preventing diabetes could prevent and intercept the progression of neoplastic disease from MGUS to SMM or MM. Eliminating barriers to healthcare equity for all patients regardless of ethnic origin, and socioeconomic and geographic factors would help immensely to implement precision medicine.

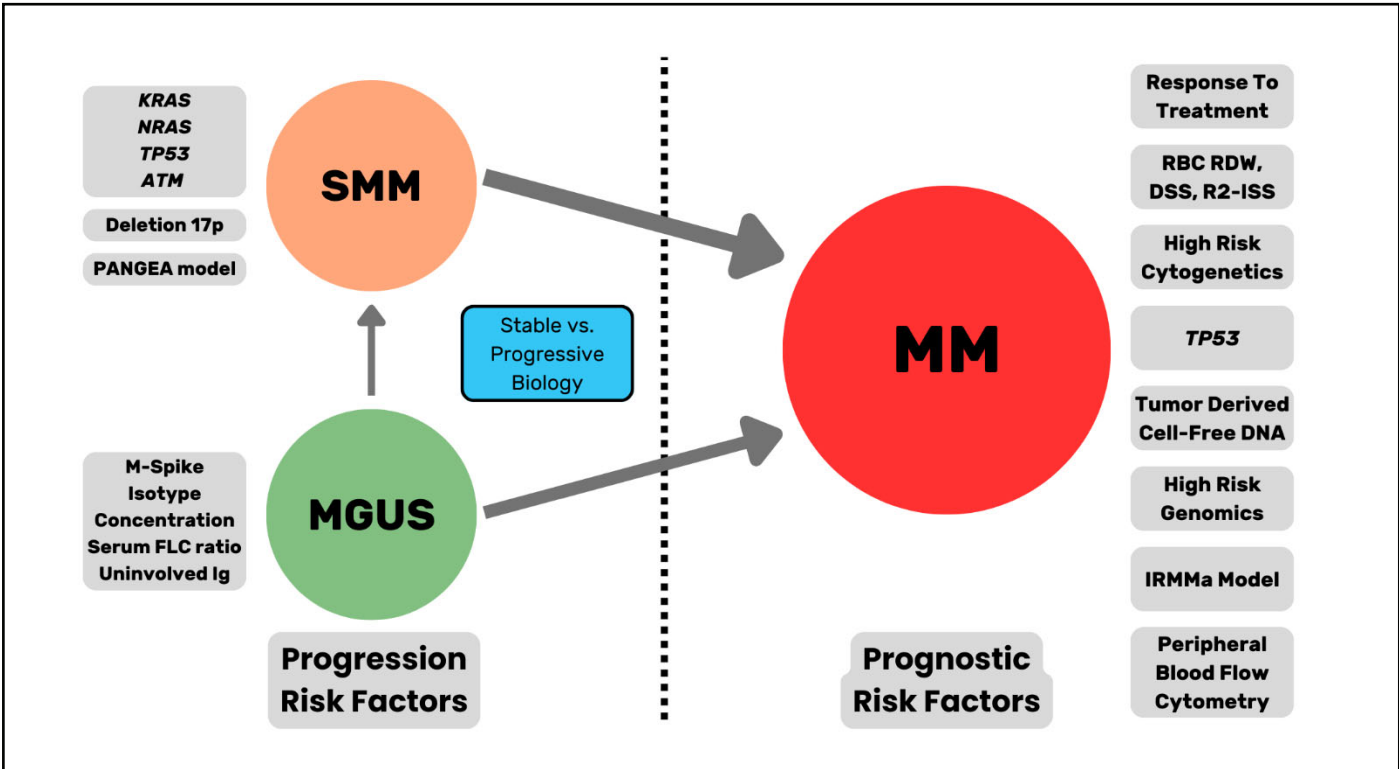


Figure 6 shows the concepts of progression risk in patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) versus prognostic risk in patients with newly diagnosed multiple myeloma (MM). The factors that can determine these risks are shown in separate grey boxes adjacent to the disease states. **Abbreviations:** SMM: Smoldering Multiple Myeloma; MGUS: Monoclonal Gammopathy Of Undetermined Significance; MM: Multiple Myeloma at New Diagnosis; PANGAEA: Precursor Asymptomatic Neoplasms by Group Effort Analysis [150]; M-spike: Monoclonal Protein Spike [146,147]; FLC: Free Light Chain [146,147]; Ig: Immunoglobins [146,147]; RBC RDW: Red Blood Cell Distribution Width; DSS: Durie-Salmon Staging [43]; R2-ISS: The Second Revision of the International Staging System [60]; IRMMa: Individualized Risk for Multiple Myeloma Model [179].

Also, given the heterogeneity in the biology of MM, including stable and progressive disease biology, and the need to do a bone marrow biopsy to determine MRD and requiring accessibility to high-sensitivity MFC or NGS for MRD evaluation, it would be of value to be able to specify in the future which patients with which specific risk parameters should be evaluated for MRD to be able to make scientifically-based decisions about changing, continuing, or discontinuing therapies based on MRD values. Questions related to MRD assessment that need to be answered include: (1) Does an undetectable MRD value, at whichever level of sensitivity (1 in 10⁴, 10⁵, or 10⁶ cells) available, predict that the disease will not relapse in patients with high-risk myeloma? (2) Similarly, will a detectable or positive MRD value matter in patients with low-risk or standard-risk myeloma? Answers to these questions will help guide the use of MRD when it would be valuable to the management of the patient.

Conflicts of Interest

None.

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References

1. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2024 Apr 17. [cited 2024 Jun 17]. Available from: <https://seer.cancer.gov/statistics-network/explorer/>. Data source(s): SEER Incidence Data, November 2023 Submission (1975-2021), SEER 22 registries.
2. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004 Oct 28;351(18):1860-73.
3. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011 Mar 17;364(11):1046-60.
4. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 2022 Feb 1;327(5):464-77.
5. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024 Jan-Feb;74(1):12-49.
6. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L,

- et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2024. Available from: <https://gco.iarc.who.int/today>, accessed June 17, 2024.
7. Huang J, Chan SC, Lok V, Zhang L, Lucero-Prisno DE 3rd, Xu W, et al. Non-communicable Disease Global Health Research Group, Association of Pacific Rim Universities. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. *Lancet Haematol.* 2022 Sep;9(9):e670-7.
 8. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009 May 28;113(22):5412-7.
 9. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002 Feb 21;346(8):564-9.
 10. Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Kumar S, Cerhan JR, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med.* 2018 Jan 18;378(3):241-9.
 11. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014 Nov;15(12):e538-48.
 12. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol.* 2003 Jun;121(5):749-57. PMID: 12780789.
 13. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med.* 2007 Jun 21;356(25):2582-90.
 14. Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: emphasis on risk factors for progression. *Br J Haematol.* 2007 Dec;139(5):730-43.
 15. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. *N Engl J Med.* 2011 Aug 4;365(5):474-5.
 16. Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood.* 2008 Jan 15;111(2):785-9.
 17. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. International Myeloma Working Group. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia.* 2010 Jun;24(6):1121-7.
 18. Kastiris E, Terpos E, Mouloupoulos L, Spyropoulou-Vlachou M, Kanellias N, Eleftherakis-Papaikovou E, et al. Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. *Leukemia.* 2013 Apr;27(4):947-53.
 19. Waxman AJ, Mick R, Garfall AL, Cohen A, Vogl DT, Stadtmauer EA, et al. Classifying ultra-high risk smoldering myeloma. *Leukemia.* 2015 Mar;29(3):751-3.
 20. Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. *Leukemia.* 2013 Apr;27(4):941-6.
 21. Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, de Coca AG, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood.* 2007 Oct 1;110(7):2586-92.
 22. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, López Corral L, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med.* 2013 Aug 1;369(5):438-47.
 23. Hillengass J, Fechtner K, Weber MA, Bäuerle T, Ayyaz S, Heiss C, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol.* 2010 Mar 20;28(9):1606-10.
 24. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer.* 2012 Apr 12;12(5):335-48.
 25. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. *Am Soc Clin Oncol Educ Book.* 2016;35:e418-23.
 26. Lakshman A, Rajkumar SV, Buadi FK, Binder M, Gertz MA, Lacy MQ, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. *Blood Cancer J.* 2018 Jun 12;8(6):59.
 27. Mateos MV, Kumar S, Dimopoulos MA, González-Calle V, Kastiris E, Hajek R, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J.* 2020 Oct 16;10(10):102.
 28. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms (Published Erratum in *Leukemia* 2023 Sep;37(9):1944-51). *Leukemia.* 2022 Jul;36(7):1720-48.
 29. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee (Published Erratum in *Blood* 2023 Jan 26;141(4):437). *Blood.* 2022 Sep 15;140(11):1229-53.
 30. Ashraf MA, Goyal A. Fludeoxyglucose (18F). 2023 Aug 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

31. Fernández de Larrea C, Kyle R, Rosiñol L, Paiva B, Engelhardt M, Usmani S, et al. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. *Blood Cancer J.* 2021 Dec 2;11(12):192.
32. Fernández de Larrea C, Kyle RA, Durie BG, Ludwig H, Usmani S, Vesole DH, et al.; International Myeloma Working Group. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. *Leukemia.* 2013 Apr;27(4):780-91.
33. Li Q, Ai L, Zuo L, Li J, Zhao F, Xu A, et al. Circulating plasma cells as a predictive biomarker in Multiple myeloma: an updated systematic review and meta-analysis. *Ann Med.* 2024 Dec;56(1):2338604.
34. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. International Myeloma Workshop Consensus Panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood.* 2011 May 5;117(18):4691-5.
35. Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson P, et al. Clinically relevant end points and new drug approvals for myeloma. *Leukemia.* 2008 Feb;22(2):231-9.
36. Kastiris E, Terpos E, Dimopoulos MA. How I treat relapsed multiple myeloma. *Blood.* 2022 May 12;139(19):2904-17.
37. Tanenbaum B, Miett T, Patel SA. The emerging therapeutic landscape of relapsed/refractory multiple myeloma. *Ann Hematol.* 2023 Jan;102(1):1-11.
38. Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, et al. Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma. *J Clin Oncol.* 2020 Jun 10;38(17):1928-37.
39. Davies FE, Pawlyn C, Usmani SZ, San-Miguel JF, Einsele H, Boyle EM, et al. Perspectives on the Risk-Stratified Treatment of Multiple Myeloma. *Blood Cancer Discov.* 2022 Jul 6;3(4):273-84.
40. Majithia N, Rajkumar SV, Lacy MQ, Buadi FK, Dispenzieri A, Gertz MA, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia.* 2016 Nov;30(11):2208-13.
41. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Early relapse after single auto-SCT for multiple myeloma is a major predictor of survival in the era of novel agents. *Bone Marrow Transplant.* 2015 Feb;50(2):204-8.
42. Banerjee R, Cicero KI, Lee SS, Cowan AJ. Definers and drivers of functional high-risk multiple myeloma: insights from genomic, transcriptomic, and immune profiling. *Front Oncol.* 2023 Oct 2;13:1240966.
43. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer.* 1975 Sep;36(3):842-54.
44. Durie BG, Stock-Novack D, Salmon SE, Finley P, Beckord J, Crowley J, et al. Prognostic value of pretreatment serum beta 2 microglobulin in myeloma: a Southwest Oncology Group Study. *Blood.* 1990 Feb 15;75(4):823-30.
45. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. *J Clin Oncol.* 2005 May 20;23(15):3412-20.
46. Hari PN, Zhang MJ, Roy V, Pérez WS, Bashey A, To LB, et al. Is the International Staging System superior to the Durie-Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. *Leukemia.* 2009 Aug;23(8):1528-34.
47. Neben K, Jauch A, Bertsch U, Heiss C, Hielscher T, Seckinger A, et al. Combining information regarding chromosomal aberrations t(4;14) and del(17p13) with the International Staging System classification allows stratification of myeloma patients undergoing autologous stem cell transplantation. *Haematologica.* 2010 Jul;95(7):1150-7.
48. Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, et al. International Myeloma Workshop Consensus Panel 2. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood.* 2011 May 5;117(18):4696-700.
49. Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, et al. NCRI Haematology Oncology Studies Group. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. *Leukemia.* 2012 Feb;26(2):349-55.
50. Avet-Loiseau H, Durie BG, Cavo M, Attal M, Gutierrez N, Haessler J, et al. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. *Leukemia.* 2013 Mar;27(3):711-7.
51. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia.* 2014 Feb;28(2):269-77.
52. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc.* 2013 Apr;88(4):360-76.
53. Kuiper R, Broyl A, de Knecht Y, van Vliet MH, van Beers EH, van der Holt B, et al. A gene expression signature for high-risk multiple myeloma. *Leukemia.* 2012 Nov;26(11):2406-13.
54. Moreau P, Cavo M, Sonneveld P, Rosinol L, Attal M, Pezzi A, et al. Combination of international scoring system 3, high lactate dehydrogenase, and t(4;14) and/or del(17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. *J Clin Oncol.* 2014 Jul 10;32(20):2173-80.

55. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol.* 2015 Sep 10;33(26):2863-9.
56. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood.* 2016 Jun 16;127(24):2955-62.
57. Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien ML, Royer B, et al. Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma. *J Clin Oncol.* 2019 Jul 1;37(19):1657-65.
58. Thakurta A, Ortiz M, Bleuca P, Towfic F, Corre J, Serbina NV, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. *Blood.* 2019 Mar 14;133(11):1217-21.
59. Schmidt TM, Fonseca R, Usmani SZ. Chromosome 1q21 abnormalities in multiple myeloma. *Blood Cancer J.* 2021 Apr 29;11(4):83.
60. D'Agostino M, Cairns DA, Lahuerta JJ, Wester R, Bertsch U, Waage A, et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project. *J Clin Oncol.* 2022 Oct 10;40(29):3406-18.
61. Tembhare PR, Sriram H, Khanka T, Gawai S, Bagal B, Ghogale SG, et al. Circulating tumor plasma cells and peripheral blood measurable residual disease assessment in multiple myeloma patients not planned for upfront transplant. *Hemasphere.* 2024 Apr 1;8(4):e63.
62. Kostopoulos IV, Ntanasis-Stathopoulos I, Rousakis P, Eleutherakis-Papaïakovou E, Panteli C, Malandrakis P, et al. Circulating Plasma Cells in Newly Diagnosed Multiple Myeloma: Prognostic and More. *J Clin Oncol.* 2023 Jan 20;41(3):708-10.
63. Chakraborty R, Lentzsch S. Circulating Tumor Cell Burden as a Component of Staging in Multiple Myeloma: Ready for Prime Time? *J Clin Oncol.* 2022 Sep 20;40(27):3099-102.
64. Hofste Op Bruinink D, Kuiper R, van Duin M, Cupedo T, van der Velden VHJ, Hoogenboezem R, et al. Identification of High-Risk Multiple Myeloma With a Plasma Cell Leukemia-Like Transcriptomic Profile. *J Clin Oncol.* 2022 Sep 20;40(27):3132-50.
65. Garcés JJ, Cedena MT, Puig N, Burgos L, Perez JJ, Cordon L, et al. Circulating Tumor Cells for the Staging of Patients With Newly Diagnosed Transplant-Eligible Multiple Myeloma. *J Clin Oncol.* 2022 Sep 20;40(27):3151-61.
66. Bertamini L, Oliva S, Rota-Scalabrini D, Paris L, Morè S, Corradini P, et al. High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma. *J Clin Oncol.* 2022 Sep 20;40(27):3120-31.
67. Rosiñol L, Beksac M, Zamagni E, Van de Donk NWCJ, Anderson KC, Badros A, et al. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. *Br J Haematol.* 2021 Aug;194(3):496-507.
68. Carlisi M, Presti RL, Plano F, Mancuso S, Siragusa S, Caimi G. Changes in RDW according to prognostic predictors in newly diagnosed multiple myeloma. *Sci Rep.* 2024 Feb 3;14(1):2832.
69. National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®). NCCN Guidelines Version 4.2024. Multiple Myeloma. Version 4.2024 — April 26, 2024. Available at <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1445>. Accessed June 15, 2024.
70. Bladé J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol.* 1998 Sep;102(5):1115-23.
71. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia.* 2006 Sep;20(9):1467-73 (Erratum in *Leukemia.* 2007 May;21(5):1134).
72. Rawstron AC, Davies FE, DasGupta R, Ashcroft AJ, Patmore R, Drayson MT, et al. Flow cytometric disease monitoring in multiple myeloma: the relationship between normal and neoplastic plasma cells predicts outcome after transplantation. *Blood.* 2002 Nov 1;100(9):3095-100.
73. San Miguel JF, Almeida J, Mateo G, Bladé J, López-Berges C, Caballero D, et al. Immunophenotypic evaluation of the plasma cell compartment in multiple myeloma: a tool for comparing the efficacy of different treatment strategies and predicting outcome. *Blood.* 2002 Mar 1;99(5):1853-6.
74. Rawstron AC, Paiva B, Stetler-Stevenson M. Assessment of minimal residual disease in myeloma and the need for a consensus approach. *Cytometry B Clin Cytom.* 2016 Jan;90(1):21-5.
75. Stetler-Stevenson M, Paiva B, Stoolman L, Lin P, Jorgensen JL, Orfao A, et al. Consensus guidelines for myeloma minimal residual disease sample staining and data acquisition. *Cytometry B Clin Cytom.* 2016 Jan;90(1):26-30.
76. Arroz M, Came N, Lin P, Chen W, Yuan C, Lagoo A, et al. Consensus guidelines on plasma cell myeloma minimal residual disease analysis and reporting. *Cytometry B Clin Cytom.* 2016 Jan;90(1):31-9.
77. Oldaker TA, Wallace PK, Barnett D. Flow cytometry quality requirements for monitoring of minimal disease in plasma cell myeloma. *Cytometry B Clin Cytom.* 2016 Jan;90(1):40-6.
78. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016 Aug;17(8):e328-46.
79. U.S. Food and Drug Administration. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual

- Disease in Development of Drug and Biological Products for Treatment. January 2020 (accessed August 1, 2024). Available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and>
80. Medina A, Puig N, Flores-Montero J, Jimenez C, Sarasquete ME, García-Alvarez M, et al. Comparison of next-generation sequencing (NGS) and next-generation flow (NGF) for minimal residual disease (MRD) assessment in multiple myeloma. *Blood Cancer J.* 2020 Oct 30;10(10):108.
81. Ho C, Syed M, Roshal M, Petrova-Drus K, Mounq C, Yao J, et al. Routine Evaluation of Minimal Residual Disease in Myeloma Using Next-Generation Sequencing Clonality Testing: Feasibility, Challenges, and Direct Comparison with High-Sensitivity Flow Cytometry. *J Mol Diagn.* 2021 Feb;23(2):181-99.
82. Medina A, Jiménez C, Puig N, Sarasquete ME, Flores-Montero J, García-Álvarez M, et al. Interlaboratory Analytical Validation of a Next-Generation Sequencing Strategy for Clonotypic Assessment and Minimal Residual Disease Monitoring in Multiple Myeloma. *Arch Pathol Lab Med.* 2022 Jul 1;146(7):862-71.
83. Soh KT, Came N, Otteson GE, Jevremovic D, Shi M, Olteanu H, et al. Evaluation of multiple myeloma measurable residual disease by high sensitivity flow cytometry: An international harmonized approach for data analysis. *Cytometry B Clin Cytom.* 2022 Mar;102(2):88-106.
84. Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R, et al. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia.* 2021 Jan;35(1):18-30.
85. Dhakal B, Sharma S, Balcioglu M, Shchegrova S, Malhotra M, Zimmermann B, et al. Assessment of Molecular Residual Disease Using Circulating Tumor DNA to Identify Multiple Myeloma Patients at High Risk of Relapse. *Front Oncol.* 2022 Feb 2;12:786451.
86. Ghobrial IM, Anderson KC. The road to cure in multiple myeloma. *Blood* 2008;111(5):2503.
87. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol.* 2007 May 20;25(15):1993-9.
88. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol.* 2010 Feb 10;28(5):830-4.
89. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood.* 2008 Mar 1;111(5):2521-6.
90. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood.* 2008 Mar 1;111(5):2516-20.
91. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia.* 2014 May;28(5):1122-8.
92. Puertas B, González-Calle V, Sobejano-Fuertes E, Escalante F, Queizán JA, Báñez A, et al. Novel Agents as Main Drivers for Continued Improvement in Survival in Multiple Myeloma. *Cancers (Basel).* 2023 Mar 2;15(5):1558.
93. Eisfeld C, Kajüter H, Möller L, Wellmann I, Shumilov E, Stang A. Time trends in survival and causes of death in multiple myeloma: a population-based study from Germany. *BMC Cancer.* 2023 Apr 6;23(1):317.
94. Langseth ØO, Myklebust TÅ, Johannesen TB, Hjertner Ø, Waage A. Incidence and survival of multiple myeloma: a population-based study of 10 524 patients diagnosed 1982-2017. *Br J Haematol.* 2020 Nov;191(3):418-25.
95. Moore KLF, Turesson I, Genell A, Klausen TW, Knut-Bojanowska D, Redder L, et al. Improved survival in myeloma patients-a nationwide registry study of 4,647 patients ≥75 years treated in Denmark and Sweden. *Haematologica.* 2023 Jun 1;108(6):1640-51.
96. Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. *Leuk Lymphoma.* 2016 Dec;57(12):2827-32.
97. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012 May 10;366(19):1770-81.
98. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012 May 10;366(19):1782-91.
99. Jakubowiak AJ, Dytfield D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood.* 2012 Aug 30;120(9):1801-9.
100. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. GIMEMA Italian Myeloma Network. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet.* 2010 Dec 18;376(9758):2075-85.
101. Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood.* 2012 Jul 5;120(1):9-19.

102. Tacchetti P, Pantani L, Patriarca F, Petrucci MT, Zamagni E, Dozza L, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto Italian Myeloma Network). Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): long-term follow-up analysis of a randomised phase 3, open-label study. *Lancet Haematol.* 2020 Dec;7(12):e861-73.
103. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. FIRST Trial Team. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med.* 2014 Sep 4;371(10):906-17.
104. Hulin C, Belch A, Shustik C, Petrucci MT, Dührsen U, Lu J, et al. Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and Thalidomide in the Randomized, Phase III FIRST Trial. *J Clin Oncol.* 2016 Oct 20;34(30):3609-17.
105. Laubach JP, Tai YT, Richardson PG, Anderson KC. Daratumumab granted breakthrough drug status. *Expert Opin Investig Drugs.* 2014 Apr;23(4):445-52.
106. Holstein SA, McCarthy PL. Immunomodulatory Drugs in Multiple Myeloma: Mechanisms of Action and Clinical Experience. *Drugs.* 2017 Apr;77(5):505-20.
107. U.S. Food and Drug Administration. Daratumumab (DARZALEX). Available at <https://www.fda.gov/drugs/resources-information-approved-drugs/daratumumab-darzalex>. Accessed July 31, 2024.
108. Rajkumar SV, Kyle RA. Progress in Myeloma - A Monoclonal Breakthrough. *N Engl J Med.* 2016 Oct 6;375(14):1390-2.
109. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. CASTOR Investigators. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016 Aug 25;375(8):754-66.
110. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. POLLUX Investigators. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016 Oct 6;375(14):1319-31.
111. Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet.* 2017 Feb 4;389(10068):519-27.
112. Killock D. Haematological cancer: Landmark survival achieved in MM. *Nat Rev Clin Oncol.* 2017 Mar;14(3):139.
113. Teicher BA, Tomaszewski JE. Proteasome inhibitors. *Biochem Pharmacol.* 2015 Jul 1;96(1):1-9.
114. Montefusco V, Mussetti A, Salas MQ, Martinelli G, Cerchione C. Old and new generation proteasome inhibitors in multiple myeloma. *Panminerva Med.* 2020 Dec;62(4):193-206.
115. Morgan GJ, Davies FE. Role of thalidomide in the treatment of patients with multiple myeloma. *Crit Rev Oncol Hematol.* 2013 Oct;88 Suppl 1:S14-22.
116. Niesvizky R. Immunomodulatory agents changing the landscape of multiple myeloma treatment. *Crit Rev Oncol Hematol.* 2013 Oct;88 Suppl 1:S1-4.
117. Moreau P, Touzeau C. Multiple myeloma: from front-line to relapsed therapies. *Am Soc Clin Oncol Educ Book.* 2015:e504-11.
118. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol.* 2016 Oct;175(2):252-64.
119. Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv.* 2020 Dec 8;4(23):5988-99.
120. Soh KT, Wallace PK. Evaluation of measurable residual disease in multiple myeloma by multiparametric flow cytometry: Current paradigm, guidelines, and future applications. *Int J Lab Hematol.* 2021 Jul;43 Suppl 1:43-53.
121. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. PERSEUS Trial Investigators. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2024 Jan 25;390(4):301-13.
122. Voorhees PM, Sborov DW, Laubach J, Kaufman JL, Reeves B, Rodriguez C, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol.* 2023 Oct;10(10):e825-37.
123. Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021 Nov;22(11):1582-96.
124. Facon T, Dimopoulos MA, Leleu XP, Beksac M, Pour L, Hájek R, et al. IMROZ Study Group. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2024 Jun 3.
125. Dimopoulos MA, Terpos E, Boccadoro M, Delimpasi S, Beksac M, Katodritou E, et al. APOLLO Trial Investigators. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021 Jun;22(6):801-12.
126. Moreau P, Dimopoulos MA, Mikhael J, Yong K, Capra M, Facon T, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet.* 2021 Jun 19;397(10292):2361-71.
127. Usmani SZ, Quach H, Mateos MV, Landgren O, Leleu X, Siegel D, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes

- from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol.* 2022 Jan;23(1):65-76.
128. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2022 Aug 11;387(6):495-505.
129. Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk NWCJ, Rodríguez-Otero P, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med.* 2022 Dec 15;387(24):2232-44.
130. Rodríguez-Otero P, Ailawadhi S, Arnulf B, Patel K, Cavo M, Nooka AK, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2023 Mar 16;388(11):1002-14.
131. San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med.* 2023 Jul 27;389(4):335-47.
132. Cavo M, San-Miguel J, Usmani SZ, Weisel K, Dimopoulos MA, Avet-Loiseau H, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood.* 2022 Feb 10;139(6):835-44.
133. Avet-Loiseau H, Ludwig H, Landgren O, Paiva B, Morris C, Yang H, et al. Minimal Residual Disease Status as a Surrogate Endpoint for Progression-free Survival in Newly Diagnosed Multiple Myeloma Studies: A Meta-analysis. *Clin Lymphoma Myeloma Leuk.* 2020 Jan;20(1):e30-7.
134. Landgren O, Prior TJ, Masterson T, Heuck C, Bueno OF, Dash AB, et al. EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical end point for multiple myeloma. *Blood.* 2024 Jul 25;144(4):359-67.
135. Johnson V. ODAC Supports MRD Endpoint in Accelerated Approval for Multiple Myeloma. May 3, 2024 (accessed May 7, 2024). Available at <https://www.cgtlive.com/view/odac-supports-mrd-endpoint-accelerated-approval-multiple-myeloma>
136. Ailawadhi S, Adu Y, Frank RD, Das S, Hodge DO, Fernandez A, et al. Factors determining utilization of stem cell transplant for initial therapy of multiple myeloma by patient race: exploring intra-racial healthcare disparities. *Blood Cancer J.* 2024 May 28;14(1):86.
137. Schriber JR, Hari PN, Ahn KW, Fei M, Costa LJ, Kharfan-Dabaja MA, et al. Hispanics have the lowest stem cell transplant utilization rate for autologous hematopoietic cell transplantation for multiple myeloma in the United States: A CIBMTR report. *Cancer.* 2017 Aug 15;123(16):3141-9.
138. Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. *Cancer.* 2017 May 1;123(9):1590-96.
139. Fiala MA, Wildes TM, Vij R. Racial Disparities in the Utilization of Novel Agents for Frontline Treatment of Multiple Myeloma. *Clin Lymphoma Myeloma Leuk.* 2020 Oct;20(10):647-51.
140. Ailawadhi S, Parikh K, Abouzaid S, Zhou Z, Tang W, Clancy Z, et al. Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis. *Blood Adv.* 2019 Oct 22;3(20):2986-94.
141. Costa LJ, Huang JX, Hari PN. Disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. *Biol Blood Marrow Transplant.* 2015 Apr;21(4):701-6.
142. Fillmore NR, Yellapragada SV, Ifeora C, Mehta A, Cirstea D, White PS, et al. With equal access, African American patients have superior survival compared to white patients with multiple myeloma: a VA study. *Blood.* 2019 Jun 13;133(24):2615-8.
143. Bhutani M, Blue BJ, Cole C, Badros AZ, Usmani SZ, Nooka AK, et al. Addressing the disparities: the approach to the African American patient with multiple myeloma. *Blood Cancer J.* 2023 Dec 18;13(1):189.
144. Cook JM. Racial disparities in multiple myeloma and access to stem cell transplantation. *Blood Cancer J.* 2024 Jul 22;14(1):120.
145. Mateos MV, Ailawadhi S, Costa LJ, Grant SJ, Kumar L, Mohty M, et al. Global disparities in patients with multiple myeloma: a rapid evidence assessment. *Blood Cancer J.* 2023 Jul 18;13(1):109.
146. Landgren O. Advances in MGUS diagnosis, risk stratification, and management: introducing myeloma-defining genomic events. *Hematology Am Soc Hematol Educ Program.* 2021 Dec 10;2021(1):662-72.
147. Landgren O, Hofmann JN, McShane CM, Santo L, Hultcrantz M, Korde N, et al. Association of Immune Marker Changes With Progression of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma. *JAMA Oncol.* 2019 Sep 1;5(9):1293-301.
148. Eythorsson E, Rognvaldsson S, Thorsteinsdottir S, Einarsson Long T, Reed ER, Sigurdardottir GA, et al. Development of a Multivariable Model to Predict the Need for Bone Marrow Sampling in Persons With Monoclonal Gammopathy of Undetermined Significance: A Cohort Study Nested in a Clinical Trial. *Ann Intern Med.* 2024 Apr;177(4):449-57.
149. Thorsteinsdóttir S, Gíslason GK, Aspelund T, Rögnvaldsson S, Óskarsson JB, Sigurðardóttir GÁ, et al. Prevalence of smoldering multiple myeloma based on nationwide screening. *Nat Med.* 2023 Feb;29(2):467-72.
150. Cowan A, Ferrari F, Freeman SS, Redd R, El-Khoury H, Perry J, et al. Personalised progression prediction in patients with monoclonal gammopathy of undetermined significance or smouldering multiple myeloma (PANGEA): a retrospective, multicohort study. *Lancet Haematol.* 2023 Mar;10(3):e203-12.
151. Marinac CR, Ghobrial IM, Birmann BM, Soiffer J, Rebbeck TR. Dissecting racial disparities in multiple myeloma. *Blood Cancer J.* 2020 Feb 17;10(2):19.
152. Lonial S, Jacobus S, Fonseca R, Weiss M, Kumar S, Orlowski RZ, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol.* 2020 Apr 10;38(11):1126-37.
153. Landgren CO, Chari A, Cohen YC, Spencer A, Voorhees P, Estell JA, et al. Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS). *Leukemia.* 2020 Jul;34(7):1840-52.

154. Musto P, Engelhardt M, Caers J, Bolli N, Kaiser M, Van de Donk N, et al. 2021 European Myeloma Network review and consensus statement on smoldering multiple myeloma: how to distinguish (and manage) Dr. Jekyll and Mr. Hyde. *Haematologica.* 2021 Nov 1;106(11):2799-812.
155. Thorsteinsdottir S, Kristinsson SY. The consultant's guide to smoldering multiple myeloma. *Hematology Am Soc Hematol Educ Program.* 2022 Dec 9;2022(1):551-9.
156. Maura F, Rustad EH, Boyle EM, Morgan GJ. Reconstructing the evolutionary history of multiple myeloma. *Best Pract Res Clin Haematol.* 2020 Mar;33(1):101145.
157. Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol.* 2017 Feb;14(2):100-13.
158. Walker BA, Boyle EM, Wardell CP, Murison A, Begum DB, Dahir NM, et al. Mutational Spectrum, Copy Number Changes, and Outcome: Results of a Sequencing Study of Patients With Newly Diagnosed Myeloma. *J Clin Oncol.* 2015 Nov 20;33(33):3911-20.
159. Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P, Lawrence MS, Auclair D, et al. Multiple Myeloma Research Consortium; Getz G, Golub TR. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell.* 2014 Jan 13;25(1):91-101.
160. Bolli N, Avet-Loiseau H, Wedge DC, Van Loo P, Alexandrov LB, Martincorena I, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun.* 2014;5:2997.
161. Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies FE, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood.* 2018 Aug 9;132(6):587-97.
162. Bergsagel PL, Kuehl WM. Detailing the genomic landscape of myeloma. *Blood.* 2018 Aug 9;132(6):554-5.
163. Salter JD, Bennett RP, Smith HC. The APOBEC Protein Family: United by Structure, Divergent in Function. *Trends Biochem Sci.* 2016 Jul;41(7):578-94.
164. Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies F, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia.* 2019 Jan;33(1):159-70.
165. Bolli N, Biancon G, Moarii M, Gimondi S, Li Y, de Philippis C, et al. Analysis of the genomic landscape of multiple myeloma highlights novel prognostic markers and disease subgroups. *Leukemia.* 2018 Dec;32(12):2604-16.
166. Grasedieck S, Panahi A, Jarvis MC, Borzooee F, Harris RS, Larijani M, et al. Redefining high risk multiple myeloma with an APOBEC/ Inflammation-based classifier. *Leukemia.* 2024 May;38(5):1172-7.
167. Jelinek T, Zihala D, Sevcikova T, Anilkumar Sithara A, Kapustova V, Sahinbegovic H, et al. Beyond the marrow: insights from comprehensive next-generation sequencing of extramedullary multiple myeloma tumors. *Leukemia.* 2024 Jun;38(6):1323-33.
168. Shoshani O, Brunner SF, Yaeger R, Ly P, Nechemia-Arbely Y, Kim DH, et al. Chromothripsis drives the evolution of gene amplification in cancer. *Nature.* 2021 Mar;591(7848):137-41.
169. Maura F, Bolli N, Angelopoulos N, Dawson KJ, Leongamornlert D, Martincorena I, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. *Nat Commun.* 2019 Aug 23;10(1):3835.
170. Shen MM. Chromoplexy: a new category of complex rearrangements in the cancer genome. *Cancer Cell.* 2013 May 13;23(5):567-9.
171. Skerget S, Penaherrera D, Chari A, Jagannath S, Siegel DS, Vij R, et al. Comprehensive molecular profiling of multiple myeloma identifies refined copy number and expression subtypes. *Nat Genet.* 2024 Aug 19.
172. Biran N, Dhakal B, Lentzsch S, Siegel D, Usmani SZ, Rossi A, et al. Gene expression profiling impacts treatment decision making in newly diagnosed multiple myeloma patients in the prospective PROMMIS trial. *EJHaem.* 2021 May 11;2(3):375-84.
173. Mason MJ, Schinke C, Eng CLP, Towfic F, Gruber F, Dervan A, et al. Multiple Myeloma DREAM Challenge reveals epigenetic regulator PHF19 as marker of aggressive disease. *Leukemia.* 2020 Jul;34(7):1866-74.
174. Johnson TS, Sudha P, Liu E, Becker N, Robertson S, Blaney P, et al. 1q amplification and PHF19 expressing high-risk cells are associated with relapsed/refractory multiple myeloma. *Nat Commun.* 2024 May 16;15(1):4144.
175. Bustoros M, Sklavenitis-Pistofidis R, Park J, Redd R, Zhitomirsky B, Dunford AJ, et al. Genomic Profiling of Smoldering Multiple Myeloma Identifies Patients at a High Risk of Disease Progression. *J Clin Oncol.* 2020 Jul 20;38(21):2380-9.
176. Boyle EM, Deshpande S, Tytarenko R, Ashby C, Wang Y, Bauer MA, et al. The molecular make up of smoldering myeloma highlights the evolutionary pathways leading to multiple myeloma. *Nat Commun.* 2021 Jan 12;12(1):293.
177. Oben B, Froyen G, Maclachlan KH, Leongamornlert D, Abascal F, Zheng-Lin B, et al. Whole-genome sequencing reveals progressive versus stable myeloma precursor conditions as two distinct entities. *Nat Commun.* 2021 Mar 25;12(1):1861.
178. Bolli N, Maura F, Minvielle S, Gloznik D, Szalat R, Fullam A, et al. Genomic patterns of progression in smoldering multiple myeloma. *Nat Commun.* 2018 Aug 22;9(1):3363.
179. Maura F, Rajanna AR, Ziccheddu B, Poos AM, Derkach A, Maclachlan K, et al. Genomic Classification and Individualized Prognosis in Multiple Myeloma. *J Clin Oncol.* 2024 Apr 10;42(11):1229-40.
180. Weinhold N, Heuck CJ, Rosenthal A, Thanendrarajan S, Stein CK, Van Rhee F, et al. Clinical value of molecular subtyping multiple myeloma using gene expression profiling. *Leukemia.* 2016 Feb;30(2):423-30.