Review

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Genetic Alterations in Multiple Myeloma: Implications for Prognosis and Advances in Diagnostic Approaches

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Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells, leading to organ damage and symptoms summarized by the acronym CRAB (calcium elevation, renal insufficiency, anemia, and bone lesions). The disease can also present with extramedullary involvement, which signifies a more aggressive course and may affect various organs such as the skin, liver, kidneys, and central nervous system. MM progresses from precursor stages like monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), which differ in their risk of progression to active disease. Genetic alterations—including chromosomal translocations, deletions, amplifications, and point mutations—are central to pathogenesis and may influence prognosis and therapeutic response in MM. This review explores the genetic changes that drive MM progression, their prognostic implications, and the role of advanced diagnostic technologies in improving risk stratification and guiding personalized treatment. In particular, we examine key genetic alterations such as t(4;14), del(17p), and cellular myelocytomatosis oncogene (c-MYC) amplification, and their influence on treatment outcomes. The review also highlights recent advancements in diagnostic techniques, including next-generation sequencing (NGS), fluorescence *in situ* hybridization (FISH), and polymerase chain reaction (PCR), which are transforming MM management through more precise and targeted therapeutic strategies. The integration of these diagnostic tools promises to enhance personalized treatment approaches, leading to improved outcomes and survival by tailoring therapies to each patient's genetic profile.

Keywords: multiple myeloma; genetic alterations; diagnostic technologies; prognostic implications

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the presence of abnormal clonal plasma cells. It accounts for approximately 1% of all malignant neoplasms. The global incidence of MM is currently estimated at 160,000 cases annually, with a mortality of about 106,000. Its incidence increases with age, peaking in the seventh decade of life. The average age at diagnosis is approximately 65 years [1]. Clinical symptoms can vary among patients but are typically summarized by the acronym CRAB (calcium elevation, renal insufficiency, anemia, and bone lesions), which stands for elevated Calcium, Renal insufficiency, Anemia, and Bone lesions [2]. Approximately 2% of patients present with extramedullary disease at diagnosis, typically involving the skin and soft tissues, while about 8% develop it later in the disease course, affecting organs such as the liver, kidneys, lymph nodes, central nervous system (CNS), breast, pleura, and pericardium [3]. Extramedullary disease represents a more aggressive form of MM, characterized by the ability of malignant plasma cells to invade and proliferate outside the bone marrow. MM develops from two asymptomatic premalignant stages: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). These conditions are marked by clonal plasma cell proliferation in the bone marrow without signs of organ damage. The diagnostic criteria include the presence of a monoclonal (M) protein in the serum (MGUS <3 g/dL; SMM ≥ 3 g/dL), bone marrow plasma cell percentage ($<10\%$ for MGUS; $\geq 10\%$ for SMM), and the absence of anemia, hypercalcemia, lytic bone lesions, or renal failure attributable to plasma cell proliferation [2]. The risk of progression to active MM differs significantly between these two premalignant stages: approximately 1% per year for MGUS and 10–20% per year for SMM [4,5].

Occupational exposure to chemicals such as benzene, coal dust, or wood dust—common in industries

Table 1. Chromosomal abnormalities in multiple myeloma and their prognostic significance [8].

Chromosomal abnormality	Prognostic significance
t(11;14) (11q13; 14q32)	Favorable. More responsive to therapies such as venetoclax [16].
t(4;14) (4p16; 14q32)	Poor. Associated with reduced response to autologous stem cell transplantation [9].
1q Amplification	Poor. Linked to rapid disease progression [10–12].
5q Amplification	Favorable. Associated with better prognosis; often seen with hyperdiploidy involving chromosomes 5, 9, and 15 [11].
1p Deletion	Poor. Associated with unfavorable outcomes [12].
12p Deletion	Poor. Considered an adverse prognostic factor [13].
13q Deletion	Poor. Observed in ~50% of MM cases and linked to poor prognosis [12].
TRAF3 Deletion	Favorable. Found in ~15% of MM cases; may affect response to bortezomib [14].
16q Deletion	Poor. Detected in ~40% of MM patients; associated with adverse outcomes [10,17].
TP53 Deletion (17p)	Very poor. Targets a tumor suppressor gene, associated with poor clinical outcomes and therapy resistance [15].

MM, multiple myeloma; TRAF3, TNF receptor-associated factor 3; TP53, tumor protein p53.

like petroleum production, machinery manufacturing, and carpentry—has been associated with an increased risk of developing MM.

Although its precise etiology remains unclear, epidemiological studies have identified several lifestyle and environmental factors that may contribute to disease onset.

Risk Factors for MM

This section examines the influence of these risk factors on MM development, with an emphasis on recent findings and underlying mechanisms [6].

Obesity is a significant modifiable risk factor for MM:

- Body Mass Index (BMI): An elevated BMI is correlated with a higher risk of MM. Adipose tissue secretes pro-inflammatory cytokines and adipokines, such as interleukin-6 (IL-6), which can support the proliferation and survival of plasma cells.
- Dietary Patterns: Diets high in processed foods and low in fruits and vegetables may contribute to obesity and systemic inflammation, thereby indirectly increasing the risk of MM. In contrast, diets rich in antioxidants and anti-inflammatory components may offer protective effects, although further research is needed to confirm these associations [7].

Chromosomal abnormalities are crucial to identify, as they significantly influence prognosis, therapeutic response, and overall survival in MM. The main cytogenetic abnormalities observed in MM include trisomies, immunoglobulin heavy chain (IgH) translocations, deletions, and amplifications (Table 1, Ref. [8–17]).

Genetic Alterations

Genetic alterations commonly associated with MM can be broadly categorized into translocations, deletions, amplifications, and point mutations [18,19]. Among these, some of the most frequently studied alterations are as follows.

Translocations

Chromosomal translocations are hallmark genetic abnormalities in MM. A prominent example is the t(4;14) translocation, which results in the fusion of the fibroblast growth factor receptor 3 (*FGFR3*) gene on chromosome 4 with the multiple myeloma SET domain (*MMSET*) gene on chromosome 14. This alteration is frequently observed in high-risk MM and is associated with poor prognosis. Patients harboring the t(4;14) translocation typically exhibit shorter overall survival and reduced responsiveness to conventional therapies.

Another significant translocation is t(11;14), which involves the cyclin D1 (*CCND1*) gene. While often found in cases with a hyperdiploid karyotype and generally linked to a more indolent disease course, t(11;14) is also associated with an increased risk of disease progression if not adequately treated [16].

Hyperdiploidy

The term hyperdiploidy refers to an increase in the number of chromosomes. In MM, hyperdiploidy (HRD) is one of the fundamental cytogenetic categories used to classify chromosomal abnormalities. It occurs in approximately 50% of MM cases and is generally associated with a favorable prognosis [11].

Hyperdiploid MM is characterized by the gain of whole chromosomes, resulting in trisomies—particularly of odd-numbered chromosomes. The most commonly affected chromosomes include 3, 5, 7, 9, 11, 15, 19, and 21. The karyotype typically ranges from 48 to 75 chromosomes [11].

Deletions

Deletions of specific chromosomal regions also play a crucial role in the pathogenesis and progression of MM. One of the most common genetic abnormalities is the del(13q) deletion, involving the loss of a segment of chromosome 13. This alteration is associated with a poorer prognosis, as it correlates with an increased risk of relapse and shorter progression-free survival (PFS).

Another significant deletion is del(17p), which results in the loss of the tumor protein p53 (TP53) gene, a key tumor suppressor. Loss of TP53 function is one of the most aggressive markers in MM, as it compromises DNA damage repair mechanisms and contributes to resistance to standard therapies [15].

Amplifications

Amplifications of the cellular myelocytomatosis oncogene (*c-MYC*) gene represent another important genetic alteration in MM [20]. c-MYC is involved in regulating cell cycle progression, and its amplification is commonly associated with aggressive disease. Patients with c-MYC amplification often exhibit a high tumor burden, rapid disease progression, and a poor prognosis. Moreover, this alteration is linked to resistance to conventional therapies and reduced treatment responses [20].

Point Mutations

Point mutations in genes such as Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma rat sarcoma viral oncogene homolog (NRAS), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) have also been identified in MM, though they are less prevalent than translocations or deletions. These mutations disrupt normal cell signaling pathways and contribute to tumorigenesis. Specifically, KRAS and NRAS mutations have been associated with poor clinical outcomes and therapeutic resistance, particularly to proteasome inhibitors [21].

Prognostic Implications of Genetic Alterations

The genetic alterations observed in MM are not only central to disease pathogenesis but also have profound implications for prognosis and treatment strategy [22].

- High-risk genetic alterations—such as t(4;14), del(17p), and c-MYC amplification—are associated with unfavorable outcomes, including shorter overall survival, higher relapse rates, and limited response to conventional treatments. These alterations often indicate a more aggressive disease course that may warrant intensive or experimental therapies.
- Intermediate-risk alterations, including t(11;14) and del(13q), are typically associated with a more moderate disease progression. Nonetheless, they present ongoing challenges in disease management and may require personalized treatment approaches and vigilant monitoring.
- Low-risk alterations, such as certain hyperdiploid karyotypes and mutations associated with indolent disease forms, generally indicate a favorable prognosis. These patients tend to experience longer progression-free survival and respond better to standard therapies.

Primary cytogenetic abnormalities detected in the early stages of MM include trisomies, most commonly involving chromosomes 5, 7, 9, 11, 13, and 15, as well as translocations of the immunoglobulin heavy chain (*IgH*) gene locus. As the disease progresses, secondary genetic alterations frequently emerge, including del(17p) or monosomy 17, del(13q) or monosomy 13, del(1p), and 1p gain. These abnormalities are associated with poor overall survival, early development of drug resistance and relapse, as well as the emergence of extramedullary disease [23].

The majority of primary translocations in MM, accounting for over 90%, involve the immunoglobulin heavy chain (IgH) gene locus located on chromosome 14 (14q32.33) and various partner chromosomes, including chromosomes 4, 6, 11, 14, and 20.

Translocations involving the IGH locus (14q32) are considered primary cytogenetic abnormalities in MM and have variable prognostic significance and therapeutic implications depending on the partner chromosome. The most commonly involved partner loci include 11q13 (CCND1), 4p16 (FGFR3/MMSET), 16q23 (MAF), and 20q11 (MAFB).

- The t(11;14) translocation is the most frequent in MM and is generally considered a favorable prognostic marker in the absence of other high-risk genetic abnormalities [24].
- In contrast, the t(4;14) translocation is associated with a poor prognosis [25].
- The t(14;16) translocation correlates with reduced overall survival [26], while the t(14;20) translocation is similarly linked to inferior survival outcomes in MM patients [27,28].

Extramedullary myeloma is a rare manifestation of the disease that arises from the dissemination of clonal plasma cells from the bone marrow, which subsequently colonize extra-osseous tissues or circulate in the peripheral blood [29,30]. This form of myeloma is associated with a particularly poor prognosis due to its aggressive clinical behavior and resistance to conventional therapies.

The most common cytogenetic abnormalities in MM include numerical alterations, with chromosome 1 being the most frequently affected through both amplification and deletion [31]. Instability of chromosome 1 is strongly associated with a poor prognosis in MM [32].

In contrast, amplification of 5q has been reported as a favorable prognostic factor [33]. Moreover, a combined gain of chromosomes 5, 9, and 15 has been shown to offer high sensitivity and specificity for prognostic assessment in MM [11].

Deletion of chromosome 12 is considered an unfavorable prognostic marker [13]. Similarly, loss of chromosome 13 is commonly observed in MM and is associated with poor clinical outcomes [34]. Additionally, deletion of the *DIS3* gene—frequently mutated in MM—has been linked to adverse prognosis [35,36].

Deletions of the TNF receptor-associated factor 3 (*TRAF3*) gene located on 14q may also influence response

Table 2. International staging system (ISS) for multiple myeloma.

Stage	VALUES (sβ2M = Serum β2 microglobulin; ALB = serum albumin)
I	Sβ2M <3.5 mg/L; serum albumin ≥3.5 g/dL
II	Sβ2M <3.5 mg/L; serum albumin <3.5 g/dL; or sβ2M 3.5 to 5.5 mg/L, irrespective of serum albumin
III	Sβ2M >5.5 mg/L

to bortezomib, a proteasome inhibitor used in MM therapy [37]. Finally, loss of the 16q arm is associated with particularly adverse clinical outcomes [38].

Classification Systems and Predictive Markers

The clinical course of MM is highly heterogeneous, highlighting the need for a simple and reliable staging system that can be applied globally for patient classification and risk stratification. In 2005, the International Staging System (ISS) was introduced. This system incorporates several clinical and biochemical parameters, including serum β2-microglobulin (Sβ2M), serum albumin, platelet count, serum creatinine, and age, which were identified as strong predictors of overall survival [39].

The ISS primarily uses the combination of Sβ2M and serum albumin to stratify patients into three prognostic stages (Table 2):

- Stage I: Sβ2M <3.5 mg/L and serum albumin ≥3.5 g/dL (median survival: 62 months);
- Stage II: Neither Stage I nor Stage III (median survival: 44 months);
- Stage III: Sβ2M ≥5.5 mg/L (median survival: 29 months).

Elevated levels of serum β2-microglobulin indicate increased tumor burden and impaired renal function, while decreased serum albumin is typically attributed to the effects of inflammatory cytokines produced by the myelomatous microenvironment. Another important prognostic serum marker is lactate dehydrogenase (LDH), which reflects high cellular proliferation and the presence of extraosseous or extramedullary disease.

The integration of genetic risk, assessed via fluorescence *in situ* hybridization (FISH), with LDH levels led to the development of the Revised International Staging System (R-ISS). This system refines patient stratification and classifies individuals into three stages based on both biochemical and cytogenetic factors (Table 3) [15,40]:

- Stage I: Sβ2M <3.5 mg/L, serum albumin ≥3.5 g/dL, standard-risk chromosomal abnormalities (CA) by FISH, and normal LDH;
- Stage II: Does not meet criteria for either Stage I or Stage III;
- Stage III: Sβ2M ≥5.5 mg/L and either high-risk CA by FISH or elevated LDH.

Table 3. Revised international staging system (R-ISS) for multiple myeloma.

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

iFISH, interphase fluorescence *in situ* hybridization; LDH, lactate dehydrogenase.

It has been demonstrated that 1q amplification is associated with a poor prognosis and is found in approximately 40% of newly diagnosed multiple myeloma (NDMM) cases [41,42].

To improve prognostic accuracy, a new classification system—the Second Revision of the International Staging System (R2-ISS)—was introduced. This system incorporates the ISS, LDH levels, and cytogenetic abnormalities, including del(17p), t(4;14), and 1q gain/amplification. The R2-ISS provides a straightforward scoring system that enhances the stratification of intermediate-risk NDMM patients. Based on cumulative scores, patients are grouped into four categories: R2-ISS low, intermediate-low, intermediate-high, and high risk [26].

Laboratory Techniques to Detect Chromosomal Abnormalities

Standard techniques used to investigate chromosomal abnormalities in MM include conventional cytogenetics (karyotyping) and fluorescence *in situ* hybridization (FISH) [43]. Karyotyping relies on Giemsa banding but is successful in only about 30% of cases due to the low proliferative capacity or mitotic index of myeloma cells (Table 4) [44,45].

Although FISH is more sensitive and specific for detecting targeted chromosomal abnormalities, it is limited by high costs and technical constraints, which prevent the simultaneous screening of all lesions.

Next-generation sequencing (NGS) has significantly advanced our ability to detect genomic alterations in MM. NGS not only identifies a wide spectrum of genetic muta-

Table 4. Comparison of diagnostic techniques for chromosomal abnormalities.

Technique	What it detects	Sensitivity	Cost	Time to result	Limitations
FISH	Translocations (e.g., t(11;14), t(4;14))	Moderate to High	High	Hours to Days	Limited in screening all lesions
NGS	Genomic Aberrations (e.g., point mutations, minimal residual disease)	Very High (one cell in a million)	High	Days	Expensive, requires expertise
MLPA	Copy Number Variations (CNVs)	Moderate	Moderate	24 Hours	Cannot detect balanced translocations
Digital MLPA	MLPA+NGS (combines the advantages of both)	Very High	High	24–48 Hours	Requires a combination of both technologies

NGS, next-generation sequencing; MLPA, multiplex ligation-dependent probe amplification.

tions and structural variations but also enables the detection of minimal residual disease (MRD) with a sensitivity as high as one malignant cell in a million, which is critical for accurate disease monitoring.

Another useful method is multiplex ligation-dependent probe amplification (MLPA), a PCR-based technique that enables the simultaneous amplification of approximately 50 genomic targets in a single reaction [46–48]. MLPA is particularly effective for detecting copy number variations (CNVs) but is not suitable for identifying balanced translocations. The assay requires about 50 ng of DNA extracted from bone marrow samples and delivers results in approximately 24 hours. However, MLPA may miss abnormalities in small subclones, so sample enrichment with CD138+ plasma cells is recommended to improve sensitivity [23,49–52].

A newer technique, known as digital MLPA, combines MLPA with NGS to allow the parallel analysis of up to 1000 probes in a single reaction, offering greater resolution and efficiency.

A deeper understanding of tumor genomics is essential for fully characterizing the biological behavior of MM, identifying novel therapeutic targets, and guiding the development of more effective treatment strategies [53,54].

Recent Advances in Diagnostic Technologies

In recent years, diagnostic technologies in MM have made significant progress, enabling more accurate, sensitive, and comprehensive detection of genetic alterations (Table 5). These advances not only improve the identification of relevant mutations but also support personalized treatment strategies for MM patients.

Next-Generation Sequencing (NGS)

NGS has revolutionized the detection of genetic mutations in MM [55,56]. It allows for the simultaneous sequencing of multiple genes at high resolution, offering detailed insight into the disease's genetic landscape. Compared to traditional methods, NGS can detect rare mutations, uncover novel alterations, and provide a comprehensive view of tumor heterogeneity.

- Impact on Diagnosis: NGS identifies point mutations, copy number variations, and gene fusions—many of which may be missed by other techniques. By sequencing either the entire exome or targeted gene panels (e.g., those involved in cell cycle regulation or apoptosis), clinicians can gain deeper insight into MM pathogenesis and detect precursor conditions like MGUS and SMM before progression to active disease.
- Impact on Personalized Treatment: The genetic data obtained through NGS enables refined risk stratification. For instance, patients with high-risk abnormalities such as t(4;14) or del(17p) can be identified early, guiding the use of more aggressive or targeted therapies. Moreover, NGS may reveal actionable mutations that could respond to specific agents, including proteasome inhibitors, immunomodulatory drugs (IMiDs), or monoclonal antibodies.

Cytogenetic Analysis

Cytogenetic analysis examines chromosomal alterations such as translocations, deletions, and amplifications—hallmarks of MM.

- Impact on Diagnosis: Traditional cytogenetic methods like FISH and karyotyping remain indispensable. FISH, in particular, detects hallmark translocations such as t(4;14), t(11;14), and t(14;16) at the cellular level [57–59]. Cytogenetic analysis also identifies important alterations involving genes like TP53 and c-MYC, associated with aggressive disease phenotypes.
- Impact on Personalized Treatment: Cytogenetic findings directly influence prognosis and treatment decisions. For example, patients with del(17p) or t(4;14) often require more intensive therapy, including high-dose chemotherapy or stem cell transplantation. These insights help classify patients into risk categories, facilitating the use of novel agents tailored to specific chromosomal alterations.

Polymerase Chain Reaction (PCR)

PCR is a sensitive technique used to amplify specific DNA sequences, particularly valuable in detecting minimal residual disease (MRD) and tracking genetic markers in MM.

Table 5. Advances in diagnostic technologies and their impacts on diagnosis and personalized treatment.

Diagnostic technology	Description	Impact on diagnosis	Impact on personalized treatment
Next-Generation Sequencing (NGS) - Provides in-depth analysis of tumor heterogeneity and identifies precursor conditions like MGUS and smoldering MM that may progress to active disease.	A high-resolution sequencing method that simultaneously analyzes multiple genes. - Helps identify novel therapeutic targets (e.g., mutations responsive to proteasome inhibitors, immunomodulatory drugs, or monoclonal antibodies).	- Detects genetic alterations, including point mutations, copy number variations, and gene fusions that are often missed by traditional methods.	- Enables precise risk stratification, identifying high-risk genetic features such as t(4;14) or del(17p).
Cytogenetic Analysis - Identifies chromosome abnormalities and mutations (e.g., TP53, MYC) that indicate more aggressive disease forms.	Examines chromosomes for large-scale genetic alterations (e.g., translocations, deletions, amplifications). - Cytogenetic analysis helps to stratify patients into different risk categories, allowing for tailored treatments and novel agents targeting specific chromosomal abnormalities.	- Vital for detecting chromosomal translocations such as t(4;14), t(11;14), t(14;16) using FISH or karyotyping.	- Guides treatment decisions, especially for patients with high-risk cytogenetic features like del(17p) or t(4;14), who may require aggressive therapies like high-dose chemotherapy or stem cell transplantation.
Polymerase Chain Reaction (PCR) - Identifies genetic mutations such as KRAS or NRAS that could influence disease management.	Amplifies specific DNA sequences to detect minimal residual disease (MRD) and genetic markers. - Enables personalized treatment adjustments (e.g., consolidation or maintenance therapy for MRD-positive patients, and more focused monitoring for MRD-negative patients).	- Detects monoclonal proteins or specific gene rearrangements characteristic of MM (e.g., monoclonal immunoglobulin heavy chain gene rearrangements).	- Essential for MRD monitoring, assessing how well a patient is responding to therapy, and predicting the likelihood of relapse.

MGUS, monoclonal gammopathy of undetermined significance.

- Impact on Diagnosis: PCR detects monoclonal immunoglobulin gene rearrangements, a hallmark of MM, and can also monitor mutations in genes like KRAS and NRAS. These capabilities aid in diagnosis and guide therapeutic decisions.
- Impact on Personalized Treatment: PCR is essential for MRD monitoring, a critical metric for assessing treatment efficacy [60]. By identifying even minimal levels of residual disease, clinicians can modify therapeutic plans—such as initiating maintenance or consolidation therapy in MRD-positive patients, while reducing intensity for MRD-negative cases.

Combining Technologies for a Comprehensive Approach

The integration of NGS, cytogenetic analysis, and PCR represents a significant advancement in MM diagnostics. This multimodal approach provides a detailed and multi-dimensional view of the disease:

- NGS identifies molecular mutations;
- Cytogenetic analysis reveals structural chromosomal abnormalities;
- PCR enables high-sensitivity MRD monitoring.

Together, these technologies enhance risk stratification, inform personalized treatment, and allow for early relapse detection, ultimately leading to improved patient outcomes.

Emerging Genetic Markers and Their Role in Personalized Treatment of Multiple Myeloma

Advancements in the understanding of genetic alterations have significantly transformed the treatment landscape of MM, paving the way for more personalized therapeutic strategies. While traditional therapies, such as chemotherapy, stem cell transplantation, and proteasome inhibitors, remain foundational, precision medicine has introduced approaches tailored to the patient's specific genetic profile. Genetic markers are critical for identifying patients most likely to respond to specific treatments, thereby optimizing therapeutic outcomes. Recent studies have identified several novel mutations, including alterations in DIS3, TP53, and MMSET, all of which are associated with poor clinical outcomes. For instance, DIS3 mutations are linked to disease progression and diminished response to bortezomib, while TP53 mutations correlate with aggressive disease behavior and reduced survival, indicating the need for more intensive treatment in affected patients [61].

Beyond single-gene mutations, chromosomal abnormalities, such as deletions of 17p and 13q, and translocations involving the IgH locus, remain key prognostic markers in MM [62]. More recently, alterations like the t(4;14) translocation and 1p deletions have been associated with treatment resistance, suggesting that patients harboring these abnormalities may benefit from targeted therapeutic approaches [63,64]. The advent of NGS has revolutionized genetic profiling, enabling comprehensive detection of mutations and structural variants that influence drug response. This facilitates risk-adapted treatment, where high-risk patients receive aggressive regimens, and low-risk patients may be managed with less intensive therapies [65,66]. Monoclonal antibodies, such as daratumumab and elotuzumab, targeting surface antigens like CD38 and SLAMF7, have shown promise in MM treatment, especially when guided by molecular profiling. Despite these advances, challenges persist. Genetic heterogeneity among patients and evolving subclonal dynamics complicate treatment planning. Additionally, continued research is needed to refine genetic testing methods and establish standardized treatment algorithms based on specific genetic profiles. As scientific understanding grows, genetic markers are expected to play an increasingly central role in personalized MM therapy, enhancing efficacy while minimizing toxicity [67,68].

Conclusions

Genetic alterations play a fundamental role in the pathogenesis, prognosis, and management of MM. The genetic profile of each patient significantly influences treatment selection and response. For instance, individuals with high-risk genetic features may benefit from intensive combination therapies, including proteasome inhibitors, immunomodulatory drugs (IMiDs), and monoclonal antibodies, whereas patients with low-risk mutations may be appropriately managed with less aggressive approaches and close monitoring. Integrating genetic markers into routine clinical practice has enabled more personalized treatment strategies, improving disease control and survival outcomes. The continuous advancement of NGS technologies has further enhanced mutation detection and prognostic accuracy, supporting early intervention and refined risk stratification. Chromosomal translocations, particularly those involving the IgH locus, and chromosomal instabilities such as del(17p) and del(13q), remain central prognostic indicators. Advanced diagnostic techniques—such as FISH, NGS, MLPA, and digitalMLPA—have markedly improved the sensitivity and accuracy of detecting genomic alterations, including minimal residual disease (MRD). Emerging technologies are improving our understanding of MM across its full spectrum, from asymptomatic precursor stages like MGUS and SMM to aggressive variants such as extramedullary myeloma. The incorporation of genetic information into treatment protocols has the potential to personalize therapy, improve patient outcomes, and adapt interventions based on disease biology. However, challenges remain in fully interpreting the prognostic value of certain alterations and overcoming diagnostic variability. The future of MM treatment lies in the ongoing refinement of ge-

nomic technologies and the integration of targeted therapeutic strategies, aiming to deliver more precise, individualized patient care.

Availability of Data and Materials

Not applicable.

Author Contributions

SM and FG: Conceptualization, Study Design. FC and BD: Data Curation, Investigation. CMLD, PP, AMM, GL, CD, and AC: Formal Analysis, Data Interpretation. FC, BD, and FG: Drafting of the Manuscript. SM, FG, FC, BD, CMLD, PP, AMM, GL, CD, and AC: Critical Revision and Final Approval of the Manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Francesco Gaudio and Stefano Martinotti serve as two of the guest editors of this journal. We declare that Francesco Gaudio and Stefano Martinotti had no involvement in the peer review of this article and has no access to information regarding its peer review.

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