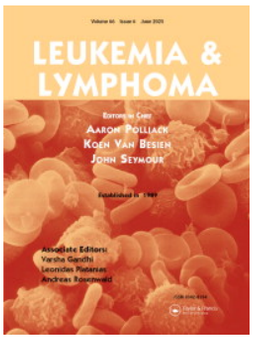

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: www.tandfonline.com/journals/ilal20

Familial aspects of multiple myeloma and Waldenström macroglobulinemia: understanding the predisposition in relatives and the importance of early diagnosis

Neta Sternbach & Morie A. Gertz

To cite this article: Neta Sternbach & Morie A. Gertz (13 Jun 2025): Familial aspects of multiple myeloma and Waldenström macroglobulinemia: understanding the predisposition in relatives and the importance of early diagnosis, Leukemia & Lymphoma, DOI: 10.1080/10428194.2025.2516256

To link to this article: https://doi.org/10.1080/10428194.2025.2516256

Published online: 13 Jun 2025.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2025.2516256

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Familial aspects of multiple myeloma and Waldenström macroglobulinemia: understanding the predisposition in relatives and the importance of early diagnosis

Neta Sternbach[a] and Morie A. Gertz[b]

[a]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah-Tikva, Israel; [b]Division of Hematology, Mayo Clinic, Rochester, MN, USA

ABSTRACT

Multiple myeloma (MM) and Waldenström macroglobulinemia (WM) are B-cell malignancies with emerging evidence of familial predisposition. While most cases are sporadic, recent genomic studies have identified germline mutations and polygenic risk factors that contribute to familial clustering. This review synthesizes current data on inherited susceptibility to MM and WM, focusing on germline variants, polygenic risk scores, and familial patterns. We evaluate the functional relevance of implicated genes and explore biological mechanisms including DNA repair, telomere maintenance, and immune regulation. Germline variants in DNA repair genes (e.g. BRCA1/2, TP53), immune regulators (e.g. TNFRSF13B, TREX1), and telomere-related pathways (e.g. POT1, TERT) have been associated with familial cases. Polygenic inheritance also plays a significant role, with risk loci influencing plasma cell survival and transformation. These findings have direct implications for risk assessment, early diagnosis, and surveillance in at-risk relatives.

ARTICLE HISTORY
Received 28 April 2025
Revised 27 May 2025
Accepted 1 June 2025

KEYWORDS
Neoplasia; myeloma; macroglobulinemia; familial cancer; cancer screening

Introduction

Multiple myeloma (MM) and Waldenström macroglobulinemia (WM) are both B-cell-derived hematologic malignancies with complex pathophysiologies and incurable courses. While most cases are considered sporadic, growing evidence suggests a familial component in a subset of patients. Population-based studies have consistently shown an increased risk of MM and WM among first-degree relatives of affected individuals, indicating that inherited factors contribute significantly to disease susceptibility.

The risk of MM in first-degree relatives has been reported to be 2–4 times higher than in the general population [1–3], with even stronger associations observed in specific populations, such as African Americans (OR = 5.52) as compared to European Americans (OR = 1.26) [4]. WM, though rarer, demonstrates one of the highest familial clustering rates among hematologic malignancies, with up to a 20-fold increased risk in relatives of affected individuals [5]. A pooled analysis from the International Multiple Myeloma Consortium confirmed that MM risk is elevated not only in individuals with a first-degree relative with MM, but also in those with a family history of any lympho-hematopoietic malignancy, supporting the role of shared genetic or immunologic susceptibility across B-cell malignancies [6]. These familial aggregations are not explained solely by shared environmental factors, and recent genetic studies support a heritable basis involving both high-penetrance pathogenic variants and common low-risk alleles.

The underlying mechanisms for this predisposition are multiple and incompletely understood. Identified germline mutations implicate pathways involved in DNA repair (e.g. BRCA1/2, TP53, PMS2) [7–9], immune regulation (e.g. TNFRSF13B) [10], and telomere maintenance (e.g. POT1, TERT) [7,10]. Additional studies have suggested a polygenic inheritance pattern [10–12], further complicating risk prediction and surveillance strategies.

Recognizing familial risk is of growing importance in clinical hematology, particularly as genomic testing becomes more accessible and targeted therapies evolve. Early identification of at-risk individuals – especially those with a family history of MM, WM, or

CONTACT Morie A. Gertz gertz.morie@mayo.edu Division of Hematology, Mayo Clinic, Rochester, MN, USA

precursor conditions like MGUS – may offer an opportunity for tailored surveillance and preemptive intervention. In this review, we summarize the current evidence on familial predisposition to MM and WM, explore potential biological mechanisms, and discuss the clinical implications of early diagnosis in at-risk relatives.

Genetic and familial risk

Recent genetic studies have expanded our understanding of the inherited predisposition in MM. Germline variants have been identified in a wide range of genes involved in DNA repair, immune regulation, and cancer susceptibility. Martins Rodrigues et al. found pathogenic germline variants (PGVs) in 9.1% of sporadic and 18% of familial MM cases, implicating genes such as DIS3, EP300, KDM1A, USP45, BRCA1/2, CHEK2, and TP53 [8].

Thibaud et al. identified PGVs in *BRCA1* and *BRCA2* that were significantly enriched in patients with MM compared to healthy controls, particularly among those with a personal or family history of cancer. In a subset of *BRCA2* carriers, somatic loss of heterozygosity (LOH) was observed, supporting the functional relevance of these variants through a classic two-hit mechanism. PGV carriers, especially those with high- or moderate-penetrance autosomal dominant variants (classified as PGV-A), were more likely to present at a younger age and to report prior malignancies. Importantly, PGV-A carriers demonstrated significantly improved progression-free survival (PFS) following high-dose melphalan and autologous stem cell transplantation (HDM-ASCT), highlighting a potential predictive value for treatment response. In contrast, carriers of autosomal recessive (PGV-B) or low-penetrance founder variants (PGV-C) also showed increased rates of cancer history but were not associated with enrichment in MM or PFS benefit, suggesting distinct clinical implications across PGV subtypes [9].

In WM, although no single high-penetrance gene has been consistently implicated, exome sequencing of affected pedigrees has revealed likely pathogenic variants in TREX1, SAMHD1, POT1, RECQL4, PMS2, and TP53, all involved in DNA repair, telomere maintenance, or immune regulation. Affected members in each pedigree shared a median of 18 rare deleterious variants, although overlap between families was minimal suggesting that WM susceptibility may reflect complex and heterogeneous germline architectures [7]. Additional support for inherited predisposition in WM comes from exome sequencing of affected families, where recurrent germline variants in LAPTM5 (c403t) and HCLS1 (g496a) were enriched in familial cases and shown to be functionally relevant to the tumor clone, suggesting a potential causal role in disease development [13]. McMaster reported frequent coaggregation of WM with other B-cell lymphoproliferative disorders, autoimmune conditions (e.g. Hashimoto's thyroiditis, rheumatoid arthritis), and particularly IgM MGUS, which may progress to WM at higher rates in familial settings. Genetic investigations revealed a high degree of heterogeneity, with evidence for both high-penetrance rare variants and common low-penetrance polymorphisms, as well as diverse inheritance patterns. Moreover, family-based observations provided early insights into potential environmental contributions, underscoring a multifactorial model of disease predisposition involving gene–environment interactions [14].

The polygenic component of MM susceptibility has also gained recognition. Bodnar et al. synthesized data from GWAS, familial clustering, and candidate gene analyses, highlighting both rare high-penetrance germline variants (e.g. BRCA2, CDKN2A, DIS3, and KDM1A) and common susceptibility loci that converge on critical pathways such as DNA repair, telomere maintenance, cell cycle regulation, immune modulation, and chromatin remodeling [15]. A large genome-wide association study (GWAS) by Went et al. identified 35 risk loci for MM, 12 of which were novel. Through Mendelian randomization and fine-mapping, they demonstrated two key mechanisms underlying inherited risk: longer telomere length and increased levels of B-cell maturation antigen (BCMA) and interleukin-5 receptor alpha (IL5RA), both of which support B-cell proliferation and plasma cell survival [10]. In a landmark study of 38 familial MM cases, Halvarsson et al. provided the first direct evidence supporting a polygenic etiology in familial MM. Using SNP array genotyping and polygenic risk scoring based on 16 GWAS-identified susceptibility loci, they demonstrated a significant enrichment of common MM risk alleles in familial cases compared to both sporadic MM cases and population controls. Mixture modeling estimated that approximately one-third of familial MM cases were attributable to this polygenic enrichment, with the remainder likely resulting from rare high-penetrance variants or shared environmental factors. Notably, overrepresented loci included *CCAT1* and *ELL2*, the latter is involved in plasma cell differentiation and immunoglobulin secretion. These findings support a model in which inherited MM risk in a subset of families arises from the additive effect of common, low-penetrance variants, underscoring the relevance of polygenic risk stratification in familial MM [11].

Altogether, these findings suggest that familial predisposition to MM and WM arises from a combination of rare, high-penetrance germline variants and more common, lower-risk alleles. The growing identification of these genetic risk factors highlights the potential of genetic testing in families with clustering of plasma cell dyscrasias and supports the development of individualized surveillance strategies. Key germline genes implicated in MM and WM are summarized in Table 1, odds ratios and frequencies of each mutation are summarized it Table 2.

Mechanistic insights

The biological mechanisms underlying inherited susceptibility to MM and WM are multifactorial and involve dysfunction in key cellular processes such as DNA repair, immune surveillance, telomere maintenance, and plasma cell signaling. Many of the germline variants identified in familial cases converge on these pathways, providing a biologically plausible basis for disease predisposition.

One of the most consistently implicated processes is defective DNA repair. Germline variants in canonical DNA damage response genes – including BRCA1, BRCA2, TP53, ATM, CHEK2, and PMS2 – have been identified in both MM and WM cohorts [7–9]. These genes are crucial for maintaining genomic stability, and loss-of-function mutations can lead to accumulation of somatic mutations, clonal plasma cell expansion, and ultimately malignant transformation. BRCA1 and BRCA2 are key regulators of homologous recombination, a high-fidelity DNA repair pathway. Loss-of-function mutations in these genes impair double-strand break repair, leading to genomic instability and increased susceptibility to malignant transformation. In MM, this dysfunction may be compounded by somatic loss of the wild-type allele, particularly for BRCA2, and confers enhanced sensitivity to DNA-damaging agents like melphalan. TP53 is a master regulator of cell cycle and apoptosis. Even heterozygous or mosaic TP53 mutations may impair genomic surveillance and promote survival of aberrant B cells. Somatic TP53 mutations are associated with progression and poor prognosis in WM, suggesting germline variants could predispose to early transformation. PMS2 is part of the mismatch repair (MMR) system. Deficiency causes microsatellite instability and accumulation of mutations, potentially contributing to clonal evolution.

Another mechanism is telomere maintenance, which appears particularly relevant in WM. Pemov et al. reported rare deleterious germline variants in POT1, a gene essential for telomere protection and length regulation, as well as in RECQL4, a RecQ helicase, participates in DNA replication and repair. Its dysfunction leads to chromosomal instability and is implicated in syndromes with elevated cancer risk [7]. Additionally, a GWAS identified inherited long telomere length as a causal risk factor for MM [10]. This suggests that extended cellular lifespan due to impaired telomere attrition may create a permissive environment for plasma cell transformation.

Immune system dysregulation also plays a critical role in both disorders. Variants in TNFRSF13B, which encodes TACI (a key receptor in B-cell maturation and immunoglobulin class switching), were shown to increase MM risk via a gain-of-function mechanism that promotes excessive B-cell proliferation [10]. Similarly,

Table 1. Overview of key germline genes implicated in multiple myeloma and Waldenström macroglobulinemia.

Gene(s)	Disease association	Function/pathway	Clinical implication
BRCA1, BRCA2	MM	DNA repair, cancer susceptibility	Enriched in MM, particularly in familial cases; associated with younger age at diagnosis and improved progression-free survival following HDM-ASCT
TP53	MM and WM	Tumor suppressor; DNA damage response	Shared across MM and WM pedigrees; associated with broader cancer susceptibility
CHEK2	MM	Checkpoint kinase; DNA repair	Enriched in familial MM
DIS3, EP300, KDM1A, USP45	MM	RNA processing, chromatin remodeling	Identified in familial MM cases
TREX1, SAMHD1, POT1, RECQL4, PMS2	WM	DNA repair, telomere maintenance, immune regulation	Likely pathogenic variants identified in WM-affected pedigrees; minimal overlap between families suggests genetic heterogeneity
LAPTM5 (c.403T), HCLS1 (g.496A)	WM	Immune signaling; B-cell activation	Recurrent variants enriched in familial WM; functionally implicated in tumor biology
IL5RA, TNFRSF13B (BCMA)	MM	B-cell and plasma cell survival	Elevated protein levels causally linked to MM risk via Mendelian randomization; support B-cell proliferation
Multiple loci (e.g. TERC, POT1, STN1)	MM	Telomere maintenance; B-cell proliferation	Genome-wide association studies identified 35 risk loci, including 12 novel loci; support a polygenic risk model for MM susceptibility

MM: multiple myeloma; WM: Waldenström macroglobulinemia; HDM-ASCT: high-dose melphalan and autologous stem cell transplantation.

Table 2. Odds ratios, frequencies, and FDR values for recurrently mutated germline variants in familial multiple myeloma and Waldenström macroglobulinemia.

Gene	Odds ratio (OR) / Frequency	False discovery rate (FDR)	Disease association	Reference
BRCA2	7.0 (2.8–15.3)	<0.001	MM	Thibaud et al. [9]
	~3–4%	0.023		Martins Rodrigues et al. [8]
	1.57 (95%CI: 1.3–1.9)			Went et al. [10]
BRCA1	3.9 (4.6–8.3)	<0.01	MM	Thibaud et al. [9]
CHEK2	~1.5–2%	0.045	MM	Martins Rodrigues et al. [8]
KDM1A	~1.2%	0.045	MM	Martins Rodrigues et al. [8]
ATM	~1.5%	0.069	MM	Martins Rodrigues et al. [8]
POT1	Rare, 1 carrier	0.069	MM	Martins Rodrigues et al. [8]
	1.10	1.1–1.2		Went et al. [10]
TP53	3.4	Not significant	MM	Thibaud et al. [9]
	Rare	0.116	MM	Martins Rodrigues et al. [8]
PALB2	2.5 (0.5–9.9)	Not significant	MM	Thibaud et al. [9]
LAPTM5	Familial: 8%; sporadic: 0.5%	Not reported	WM	Roccaro et al. [13]
HCLS1	Familial: 8%; sporadic: 0.5%	Not reported	WM	Roccaro et al. [13]
TNFRSF13B	1.3 (95%CI: 1.2–1.4)		MM	Went et al. [10]
TREX1, SAMHD1	Identified in pedigrees	No significant gene-level FDR	WM	Pemov et al. [7]

MM: multiple myeloma; WM: Waldenström macroglobulinemia.
FDR thresholds: <0.05 = statistically significant, 0.05–0.15 = suggestive, and >0.15 = not significant enrichment.

in WM pedigrees, variants in TREX1 and SAMHD1 – both of which regulate the innate immune response to endogenous nucleic acids – were associated with disease clustering, supporting the role of aberrant immune signaling in predisposition. TREX1 encodes a 3′–5′ exonuclease that degrades cytoplasmic DNA to prevent chronic immune activation. Its dysfunction leads to accumulation of DNA fragments that trigger type I interferon responses. SAMHD1 hydrolyzes deoxynucleoside triphosphates (dNTPs) and plays a dual role: regulating DNA replication and repair, and suppressing interferon signaling by controlling cytosolic DNA burden. These genes intersect with the STING and NF-κB pathways – both of which are linked to MYD88 signaling, a central oncogenic driver in WM [7,13]. LAPTM5 may contribute to WM via NF-κB activation [13].

Furthermore, polygenic and network analyses have revealed broader pathways of relevance. In a study focused on rare non-coding germline variants, Niazi et al. conducted a comprehensive analysis of rare non-coding germline variants in familial MM and identified a significant enrichment of variants affecting genes involved in the MAPK signaling pathway. These included upstream, 5′ UTR, and 3′ UTR regulatory regions of key genes such as *ERBB3*, *ERBB4*, *FGFR1*, *PIK3R1*, *CAMK2D*, and *PSMC6*, many of which are implicated in plasma cell proliferation, survival, and resistance to proteasome inhibitors. The findings reinforce the role of MAPK signaling as a critical mechanism in MM pathogenesis and suggest that inherited non-coding variation in this pathway may contribute to familial disease susceptibility [12].

In summary, current mechanistic insights underscore that inherited susceptibility to MM and WM involves multiple cellular processes – especially those maintaining genomic integrity, regulating B-cell homeostasis, and fine-tuning immune responses. As new technologies enable deeper genetic interrogation, it is likely that even more interconnected mechanisms will be revealed.

A diagram of the mechanisms of genetic predisposition in MM and WM is shown in Figure 1.

Clinical implications and early diagnosis

A key clinical question raised by emerging genetic data is whether screening should be initiated in selected populations to detect familial MM or WM at a premalignant stage. While no formal guidelines from major societies currently recommend routine surveillance of asymptomatic individuals, growing evidence supports the implementation of risk-adapted screening strategies, particularly in first-degree relatives of affected patients.

The identification of familial clustering and germline predisposition in MM and WM has important clinical consequences, particularly in the areas of risk assessment, early diagnosis, and personalized patient management.

One of the most pressing implications is the need for tailored surveillance strategies in families with multiple affected individuals. While current guidelines for screening asymptomatic first-degree relatives are lacking, evidence suggests that a significant subset of relatives harbor premalignant conditions such as MGUS [4].

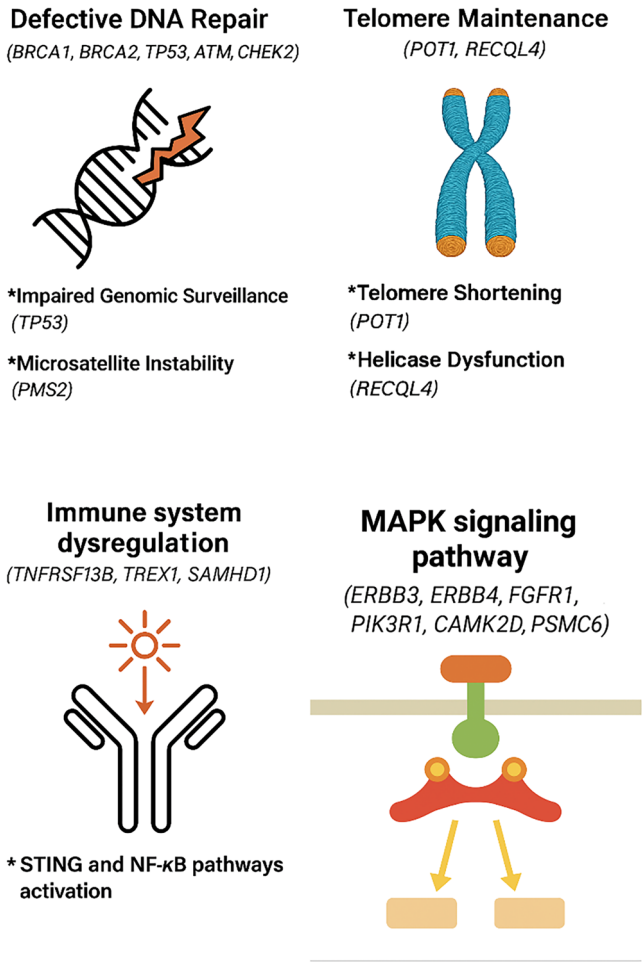

Figure 1. Mechanisms of genetic predisposition in multiple myeloma and Waldenström macroglobulinemia.

Given the well-characterized progression from MGUS to MM, particularly in familial cases, early detection in these individuals could enable risk stratification and closer monitoring, potentially preventing progression to overt disease. Population-based data from Langseth et al. however, suggest that the increased familial risk for MM is largely confined to first-degree relatives; second-degree relatives did not exhibit a significant increase in MM incidence, and no evidence of genetic anticipation was observed in affected parent-offspring pairs. These findings underscore the importance of directing screening and genetic counseling efforts primarily toward first-degree relatives in affected families [16].

Moreover, the presence of PGVs can guide clinical decision-making beyond screening. For example, Thibaud et al. demonstrated that MM patients with BRCA1/2 PGVs had better outcomes following high-dose melphalan and autologous stem cell transplant (ASCT), suggesting that knowledge of germline status could inform treatment planning [9]. Similarly, identifying mutations in DNA repair genes may support consideration of PARP inhibitors or other targeted approaches in future trials.

In WM, the very high familial risk suggests that genetic counseling and longitudinal monitoring should be more routinely considered, especially in families with multiple affected members or early-onset disease [7]. Although no specific guidelines exist for WM surveillance, early identification of IgM-MGUS, lymphoplasmacytic infiltration, or clonal B-cells in at-risk individuals could allow for earlier therapeutic intervention and clinical trial enrollment. Familial studies have also been instrumental in delineating the phenotypic spectrum of WM, including the establishment of IgM-MGUS as a precursor condition and the justification for broader population-based investigations of WM heritability [17].

Interestingly, recent large-scale cohort data suggest that a family history of plasma cell disorders may confer a survival advantage in patients with MGUS, MM, and systemic AL amyloidosis. In a study of over 25,000 patients, Visram et al. found that familial cases had significantly improved overall survival across all three

conditions, even after adjusting for baseline variables [18]. This unexpected finding may reflect earlier diagnosis or more frequent monitoring in individuals with family awareness, but it also reinforces the importance of taking a detailed family history during routine hematologic evaluation.

There are also implications for family planning and genetic counseling. As next-generation sequencing becomes more widely available in oncology clinics, incidental findings of germline mutations in MM/WM-related genes are likely to increase. This emphasizes the importance of pretest counseling, particularly in patients with strong family histories, to address the psychological, ethical, and clinical impact of such findings [7,8].

Importantly, many of these insights are not yet integrated into routine clinical care. The field lacks formal guidelines for genetic screening, counseling, and early diagnosis in relatives of MM and WM patients. Nevertheless, the accumulating evidence provides a strong rationale to move toward proactive surveillance and precision prevention in high-risk families. The promise study (https://www.enroll.promisestudy.org/about) is currently enrolling individuals with a first-degree relative with MM or other hematologic malignancy with a goal of screening 30,000 individual volunteers in an effort to identify 3000 patients with monoclonal gammopathies for long-term monitoring. First-degree relatives of patients with MGUS, smoldering myeloma or macroglobulinemia are all eligible. The iStopMM study includes a specific focus on the role of family history in MM and related diseases. To date over 75,000 blood samples have been collected. The study is investigating whether family history is associated with an increased risk of MGUS, and its progression to active myeloma. The research also explores whether a family history of MM is linked to an increased risk of other hematologic malignancies (https://istopmm.com).

Proposed evaluation strategies for relatives at increased genetic risk of MM and WM are listed in Table 3.

Table 3. Proposed evaluation strategies for relatives at increased genetic risk of multiple myeloma and Waldenström macroglobulinemia.

Population	Recommended Evaluation	Frequency
First-degree relatives of MM patients	SPEP, immunofixation, FLC assay	Baseline + every 2–3 years
First-degree relatives of WM patients	Serum IgM testing; consider bone marrow biopsy if IgM-MGUS or lymphadenopathy present	Baseline + annually if IgM elevation
Relatives of PGV carriers (e.g. BRCA1/2, TP53)	Genetic counseling and targeted germline testing	Once, with follow-up as needed
Families with ≥2 affected members	Consider whole exome or genome sequencing in a research setting	Case-by-case; consider registry enrollment

MM: multiple myeloma; WM: Waldenström macroglobulinemia; SPEP: serum protein electrophoresis; FLC: free light chain; CBC: complete blood count; PGV: pathogenic germline variant; IgM: immunoglobulin M; MGUS: monoclonal gammopathy of undetermined significance.

Future directions

As the understanding of familial predisposition to MM and WM continues to evolve, several critical opportunities for advancing research and clinical care have emerged.

First, there is a growing need for standardized guidelines for genetic screening and surveillance in individuals with a family history of MM or WM. Current practice varies widely, and many at-risk individuals remain undiagnosed until disease onset. Future efforts should focus on the development of evidence-based algorithms that incorporate family history, germline findings, and precursor conditions [4,7]. Bodnar et al. further emphasize the importance of establishing uniform family history tools and risk assessment frameworks to support consistent clinical decision-making [15].

Second, the use of whole genome and exome sequencing in research of high-risk families has the potential to uncover novel pathogenic variants and polygenic patterns of inheritance. Longitudinal studies incorporating sequencing, immune profiling, and clonal evolution tracking could significantly enhance our ability to predict progression from MGUS or IgM-MGUS to overt disease [8,10].

Third, the integration of polygenic risk scores (PRSs) into clinical risk models may offer a path forward in stratifying asymptomatic relatives. PRS aggregates the cumulative effect of multiple low-penetrance susceptibility variants. In a recent study, Canzian et al. developed and validated a PRS based on 23 genome-wide significant loci associated with MM risk. Individuals in the highest PRS quintile had a 3.44-fold increased risk of MM compared to those in the lowest quintile. Although the current discriminatory power of the PRS is modest (AUC ~0.64), it may hold greater predictive value in enriched populations, such as first-degree relatives of MM patients or individuals with MGUS. The authors suggest that future integration of PRS with clinical and environmental risk factors could enable individualized risk stratification and guide surveillance intensity. As additional susceptibility loci are discovered, the utility of PRS-based approaches in familial MM and related disorders is likely to grow, supporting their potential role in future screening paradigms [19].

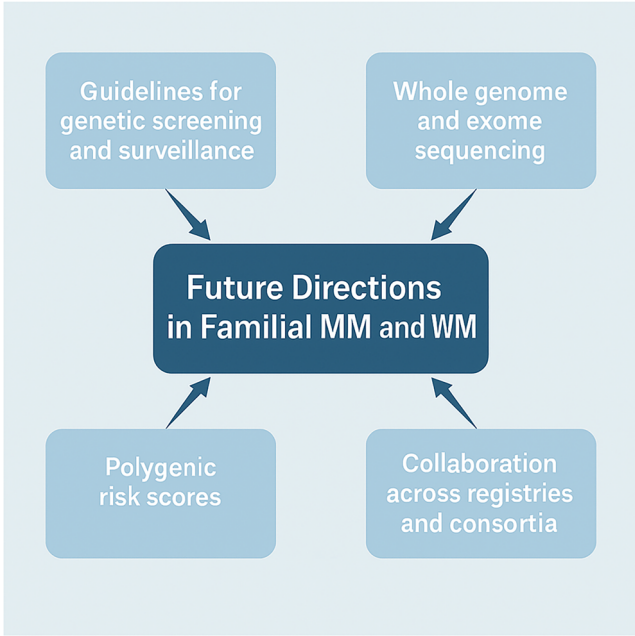

Figure 2. Future directions in familial multiple myeloma and Waldenström macroglobulinemia.

From a therapeutic perspective, future clinical trials should consider stratifying patients based on germline mutation status. As seen with BRCA1/2 mutations in other cancers, patients with DNA repair deficiencies may respond differently to alkylating agents, immunotherapies, or PARP inhibitors [9]. Trial designs that account for these inherited differences will be essential for optimizing personalized treatment.

Finally, enhanced collaboration across registries and international consortia is crucial. Given the rarity of familial MM and WM, large datasets are needed to power statistically robust discoveries. Initiatives that link genomic, clinical, and environmental data will be key to understanding the full spectrum of predisposition and translating this knowledge into practice.

In summary, future research should prioritize multi-dimensional risk modeling, prospective cohort studies, and the development of family-centered care pathways. These efforts will enable a shift from reactive to proactive management in individuals at risk for MM and WM. Future directions in familial MM and WM are summarized in Figure 2.

Conclusions

Familial predisposition to MM and WM represents a clinically relevant, genetically diverse spectrum of risk that encompasses both rare pathogenic variants and polygenic contributions. Advancements in germline testing and genomic profiling have illuminated the biological mechanisms underlying this susceptibility, particularly in DNA repair, immune regulation, and telomere biology. These insights have begun to reshape our approach to risk assessment and early detection in at-risk relatives, although formal screening guidelines remain lacking. As prospective studies such as PROMISE and iStopMM mature, they are expected to inform evidence-based strategies for surveillance and precision prevention. Moving forward, integrating genetic counseling, PRSs, and longitudinal monitoring into routine hematologic care may help mitigate disease burden through earlier diagnosis and tailored interventions.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Morie A. Gertz http://orcid.org/0000-0002-3853-5196

References

[1] Alexander DD, Mink PJ, Adami H-O, et al. Multiple myeloma: a review of the epidemiologic literature. Int J Cancer. 2007;120(Suppl. 12):40–61.

[2] Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14 621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. Blood. 2009;114(4):791–795. doi:10.1182/blood-2008-12-191676

[3] VanValkenburg ME, Pruitt GI, Brill IK, et al. Family history of hematologic malignancies and risk of multiple myeloma: differences by race and clinical features. Cancer Causes Control. 2016;27(1):81–91. doi:10.1007/s10552-015-0685-2

[4] Akkus E, Tuncalı T, Beksac M. Familial multiple myeloma: insights from epidemiology and underlying germline genetic predisposition to the clinic. Clin Lymphoma Myeloma Leuk. 2025;25(6):e411–e416.

[5] Kristinsson SY, Björkholm M, Goldin LR, et al. Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia patients: a population-based study in Sweden. Blood. 2008;112(8):3052–3056. doi:10.1182/blood-2008-06-162768

[6] Schinasi LH, Brown EE, Camp NJ, et al. Multiple myeloma and family history of lymphohaematopoietic cancers: results from the International Multiple Myeloma Consortium. Br J Haematol. 2016;175(1):87–101. doi:10.1111/bjh.14199

[7] Pemov A, Kim J, Luo W, et al. The landscape of rare genetic variants in familial Waldenström macroglobulinemia. Blood Neoplasia. 2024;1(2):100013. doi:10.1016/j.bneo.2024.100013

[8] Martins Rodrigues F, Jasielec J, Perpich M, et al. Germline predisposition in multiple myeloma. iScience. 2025;28(1):111620. doi:10.1016/j.isci.2024.111620

[9] Thibaud S, Subaran RL, Newman S, et al. Multiple myeloma risk and outcomes are associated with pathogenic germline variants in DNA repair genes. Blood Cancer Discov. 2024;5(6):428–441. doi:10.1158/2643-3230.BCD-23-0208

[10] Went M, Duran-Lozano L, Halldorsson GH, et al. Deciphering the genetics and mechanisms of predisposition to multiple myeloma. Nat Commun. 2024;15(1):6644. doi:10.1038/s41467-024-50932-7

[11] Halvarsson B-M, Wihlborg A-K, Ali M, et al. Direct evidence for a polygenic etiology in familial multiple myeloma. Blood Adv. 2017;1(10):619–623. doi:10.1182/bloodadvances.2016003111

[12] Niazi Y, Paramasivam N, Blocka J, et al. Investigation of rare non-coding variants in familial multiple myeloma. Cells. 2022;12(1):96. doi:10.3390/cells12010096

[13] Roccaro AM, Sacco A, Shi J, et al. Exome sequencing reveals recurrent germ line variants in patients with familial Waldenström macroglobulinemia. Blood. 2016;127(21):2598–2606. doi:10.1182/blood-2015-11-680199

[14] McMaster ML. Familial Waldenström macroglobulinemia: families informing populations. Hematol Oncol Clin North Am. 2018;32(5):787–809.

[15] Bodnar S, Brander T, Gold J, et al. FaMMily affairs: dissecting inherited contributions to multiple myeloma risk. Semin Hematol. 2025;62(1):11–19. doi:10.1053/j.seminhematol.2024.11.006

[16] Langseth ØO, Myklebust T, Johannesen TB, et al. Risk of multiple myeloma and other malignancies among first- and second-degree relatives of patients with multiple myeloma: a population-based study. Eur J Haematol. 2022;108(6):486–492. doi:10.1111/ejh.13757

[17] McMaster ML, Berndt SI, Zhang J, et al. Two high-risk susceptibility loci at 6p25.3 and 14q32.13 for Waldenström macroglobulinemia. Nat Commun. 2018;9(1):4182. doi:10.1038/s41467-018-06541-2

[18] Visram A, Vachon C, Baughn LB, et al. Family history of plasma cell disorders is associated with improved survival in MGUS, multiple myeloma, and systemic AL amyloidosis. Leukemia. 2022;36(4):1058–1065. doi:10.1038/s41375-021-01454-4

[19] Canzian F, Piredda C, Macauda A, et al. A polygenic risk score for multiple myeloma risk prediction. Eur J Hum Genet. 2022;30(4):474–479. doi:10.1038/s41431-021-00986-8