Multiple Myeloma Genomics – A Concise Review

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The aim of this review is to summarize the current knowledge of genomic information in multiple myeloma. Multiple myeloma is a genetically complex plasma cell neoplasm that evolves from pre-malignant stages following genomic evolution leading to the proliferation of malignant plasma cells and the production of monoclonal immunoglobulin. The outcomes of patients with myeloma have dramatically improved over the past decade with the introduction of novel agents. Nevertheless, the disease is considered incurable and displays considerable heterogeneity in clinical presentation, course and survival. This heterogeneity can often be traced to cytogenetic abnormalities in the malignant clone. Accordingly, a large body of literature has examined the impact of genomics on myeloma and risk stratification based on cytogenetics has been adopted. In this review, we will focus on the cytogenetics of multiple myeloma and the prognostic significance as well as possible predictive implications. We will briefly review the existing methodologies relevant to myeloma but explore in greater depth the more novel molecular tools as applied to this disease. **Conclusion.** The field of genomics in multiple myeloma is rapidly evolving however more translational research is needed to accurately use genomic data as a tool of precision medicine.

Introduction

Multiple myeloma (MM) is a clonal malignancy of terminally differentiated plasma cell representing the second most common hematological malignancy (10% of all hematological malignancies) after non-Hodgkin lymphoma with a globally marked increase in incident cases over that past 25 years (1, 2). This genetically complex disease develops in a multistep process that evolves from pre-malignant disease states such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) following primary genetic events including chromosomal translocations involving the immunoglobulin heavy-chain genes

(IGH) and aneuploidy. Subsequently, secondary genetics events including copy number abnormalities, DNA hypomethylation and acquired mutations lead to tumor progression (3, 4). Genetic events detected at the MGUS stage are considered primary events involved in tumor development and events present at the MM stages that were absent in MGUS are thought to be secondary events leading to tumor progression (4, 5).

Since the early 2000s we have observed an accelerated growth of knowledge pertaining to genomic and molecular characterization of MM evolving from metaphase karyotyping and Fluorescent In Situ Hybridization (FISH) to more high-throughput technologies such as gene expression profil-

ing (GEP) and next generation sequencing The advances in genomic techniques has led to a better appreciation of the underlying genetic abnormalities of multiple myeloma not only at the chromosomal level but at the single gene level showing that multiple myeloma is not a single disease but a collection of diseases with a common clinical phenotype (3). Moreover, myeloma displays significant clonal heterogeneity which is also characterized by different clones having different genomic abnormalities which can impact presentation and drug sensitivity (6). The myeloma plasma cells for the most part reside in the bone marrow but they can also be seen in the peripheral blood and other extramedullary sites. However, it is noteworthy that most of the genomic work has focused on the bone marrow compartment although some investigators have examined the biology of extramedullary disease (7) as well as the genomic characterization of the disease by the means of circulating tumor DNA analysis aiming to accommodate the clonal heterogeneity and multifocal nature of the disease (spatial heterogeneity) however most of this studies are limited by small sample sizes and the lack of consensus about a platform capable of identifying existing and new subclones (8, 9). Accordingly, this complex genomic landscape is not yet fully elucidated.

The focus of this review is to summarize the current knowledge of genomic information in MM. For the sake of brevity, we will not focus on already establish methodologies such as metaphase cytogenetics and FISH but rather explore emerging data with new molecular techniques. In addition, we will not review the genomics of other plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, amyloidosis, osteosclerotic myeloma or plasma cell leukemia.

Genetic Alterations

Using metaphase cytogenetics and FISH, the primary genetic abnormalities in MM include translocations and trisomies commonly involving odd-numbered chromosomes which are each noted in about 40% of patients with some overlap (10, 11). The primary translocations (>90%) in MM usually involve the immunoglobulin heavy chain (IgH) gene locus on chromosome 14 (14q32.33) and one of several partner chromosomes including chromosomes 4, 6, 11, 14, and 20 (Table 1). Less common chromosomes partners include chromosome 12 and 8. Primary trisomies typically involve the odd-numbered chromosomes 3, 5, 7, 9, 11, 15, 19 and/or 21 leading to a hyperdiploid karyotype (4, 10-13). In one series, harboring of trisomy 3 or trisomy 5 has significantly better overall survival whereas trisomy 21 was associated with worse outcome (14). Secondary genomic events include chromosomal translocations (MYC), copy number variations and single-nucleotide variants. Monosomy of chromosome 13 and del 13q are the most common secondary cytogenetic abnormalities in MM being detected in 35-40% and 6-10% of patients respectively (12, 15). Early reports suggested that monosomy 13 or deletion 13q was associated with worse outcome. However, more recent data in patients treated with bortezomib and/or lenalidomide, the impact of this abnormality is no longer prognostic (16) and it appears that this historical link between del 13q is a surrogate of its association with high risk cytogenetics lesions. Other abnormalities commonly observed in MM include del 1p, gain 1q, del 17p, and monosomy 17 (3, 10) (Table 1).

The presence of t(4;14) observed in ~15% of patients with MM results in deregulation of the expression of fibroblast growth factor (FGFR3) and multiple myeloma SET (MMSET) and is associated with adverse

Table 1. Genomic Alterations in Multiple Myeloma[*]

Genomic Event	Genes Involved	Frequency in MM[†] (%)	Prognostic Value
Primary Abnormalities			
Trisomies	Odd-numbered chromosomes: 3, 5, 7, 9, 11, 15, 19 or 21	~45	Favorable[‡]
Translocations	t(11;14): CCND1	15	Neutral
	t(4;14): FGR3/MMSET	15	Adverse
	t(6;14): CCND3	2	Neutral
	t(14;16): MAF	5	Adverse
	t(14;20): MAFB	1	Adverse
Secondary Abnormalities			
Chromosome gains	1q: MCL1, CKS1B, ANP32E or BCL9	40	Adverse
	8q: MYC	15	Neutral
	11q: CCND1	15	Neutral
Chromosome losses	1p: CDKN2C or FAM46C	30	Adverse
	12p: CD27	15	Adverse
	14q: TRAF3	10	Not determined
	16q: CYDL or WWOX	30	Neutral
	17p:TP53	10	Adverse
	13q: RB1, DIS3, mir15a or mir16.1	40	Neutral
Translocations	Affecting MYC: t(8;14), t(8;11)	15	Adverse

[*]Adapted from Manier S, et al. and Kumar SK (4, 12); [†]Multiple myeloma; [‡]Trisomy 21 may be associated with worse outcome.

prognosis with poor PFS and OS in different clinical settings (4, 17, 18). It's worth to mention that despite the poor prognosis associated with t(4;14) it appears that early treatment of such patients with a proteasome inhibitor may result in survival improvement (19). In terms of prognosis, the most important chromosome arm alteration given its associated aggressive clinical course, poor overall survival and development of extramedullary disease is the monoallelic deletion of 17p13 (locus of tumor suppressor gene *p53*) (20, 21). Additional chromosomal changes modulate the outcome of patients with t(4;14) and del(17p) which accounts for the degree of heterogeneity observed in the survival of these high risk patients. OS is impacted in patients harboring t(4;14) when associated with del(13q14), del(1p32) and chromosomal structural changes (>30). Del(1p32) has been also associated

with worsening prognosis in patient with del(17p) (22). Most recently Walker et al (23) in a genome-wide analysis of the largest set (1273 NDMM patients) of molecular and clinical data established to date from NDMM, as part of the Myeloma Genome Project, have identified genetic drivers that adversely impact prognosis. Multivariate analysis identified biallelic inactivation of TP53 and gain or amplification of 1q as being associated with poor PFS (15.4 months) and OS (20.7 months).

Importantly, genetic alterations are further modulated by clinical parameters such as the international staging system (ISS) and serum lactate dehydrogenase (LDH) to impact prognosis. Accordingly, patients with t(4;14) and ISS1 and normal LDH are expected to fare better than patients with the t(4;14) and ISS3 for example. This is the basis of the revised ISS (17). Based on the revised

ISS, cytogenetic abnormalities considered to be associated with high risk disease include deletion 17p, t(4;14) and t(14;16).

While there is overall agreement about the prognostic impact of cytogenetic abnormalities in myeloma used to define high risk, it remains unclear whether these abnormalities represent predictive biomarkers. Of the abnormalities detected by FISH, only t(11;14) has the potential to be used as a predictive marker. As such, myeloma patients harboring the t(11;14) have a single agent response rate of nearly 40% with the bcl2 inhibitor venetoclax, whereas patients without this translocations are unlikely to respond (24-26).

Gene Expression Profiling

High-throughput genomic tools such as gene expression profiling (GEP) have been extensively investigated with the goal of predicting patient's outcomes. An initial attempt of molecular classification of MM using GEP identified 5 recurrent translocations, specific trisomies, and expression of cyclin D genes conforming 8 subgroups (11q13, 6p21, 4p16, MAF, D1, D1+D2, and D2) based on cyclin D gene expression and various 14q32 recurrent translocations (27). On the basis of gene expression profiling studies, several subgroups of multiple myeloma have been identified, which further reflects the genetic heterogeneity of the disease.

In the past years, plasma cell gene-expression signatures designed to specifically identify patients with poor outcome have been developed by several groups including the University of Arkansas for Medical Science (UAMS), Intergroupe Francophone du Myélome (IFM), Skyline 92-HOVON and others (28-30). The UAMS group identified a 70-gene signature by GEP to molecularly define high-risk disease under the treatment platform of Total Therapy 2 (TT2) suggesting that altered transcriptional regulation

of genes (nearly half of which map to chromosome 1) may contribute to disease progression. Subsequent multivariate analysis revealed that a 17-gene subset could predict outcomes as well as the 70-gene model (28). Logistic regression analysis of the 70-gene score in relation to event free and overall survival data from UAMS TT2/3 series was performed and published in 2016 showing that the 70-gene prognostic risk score is continuously associated with increased risk of 5-year relapse and death (31). Importantly, these GEP signatures were externally validated in datasets including patients treated on various clinical trials and showing continued prognostic significance (32).

An attempt to combine biological and clinical parameters as a prognostic tool was published by Kuiper R, et al (33). Using clinical data of 4750 patients (from the HO65/GMMG-HD4, UAMS-TT2, UAMS-TT3, MRC-IX, assessment of proteasome inhibition for extending remissions (APEX), and IFM trials) the value of 20 existing risk markers was evaluated. Other than FISH and ISS, gene expression classifiers were used (EMC92, UAMS17, UAMS70, UAMS80, IFM15, MRC-IX6, HM19 and GPI50) showing that combining GEP and ISS data is useful to identify low and high risk MM. Overall while several GEP-based signatures have been developed, there is no consensus on which platform and signature is best and most clinical risk stratification still relies on standard karyotypic analysis and FISH (32). The UAMS has also developed an 80 gene signature (GEP80) by performing GEP analysis in a training set of 142 UAMS-TT3A patients which was subsequently validated in 128 patients in the UAMS-TT3B. The GEP80 signature showed insights into novel mechanisms of resistance to bortezomib with the potential of helping predict response to the agent (34). In addition, while those GEP signature may be prognostic it is unclear if they are predictive and affect the choice of therapy.

Molecular Information from DNA Sequencing

Next-generation sequencing has shown a lack of a universal driver mutation in multiple myeloma, and the presence of coexistent subclones of malignant plasma cells with some degree of overlap (3). Investigators have reported on results of various DNA-based high-throughput technologies better known as next generation sequencing (NGS) including whole-genome sequencing (WGS) and whole-exome sequencing (WES) to distinguish polymorphisms and characterize the biology of MM. In all studies (summarized in Table 2), a heteroge-

Table 2. Landmark Studies in Multiple Myeloma Genomics

Author	Technique(s)	Mutated Gene	Potentially Actionable
Walker et al. (19)	WES*	KRAS	MEK inhibitor
		NRAS	MEK inhibitor
		TP53	PRIMA-1 analog
		DIS3	-
		FAM46C	-
		TRAF3	-
		BRAF	BRAF kinase inhibitor
		RB1	-
		CYLD	-
		IRF4	-
		MAX	-
		HIST1H1E	-
		EGR1	-
		LTB	-
		FGFR3	Masitinib
Lohr et al. (18)	WES*	KRAS	MEK inhibitor
	WGS†	NRAS	MEK inhibitor
		TP53	PRIMA-1 analog
		DIS3	-
		FAM46C	-
		BRAF	BRAF kinase inhibitor
		TRAF3	-
		RB1	-
		CYLD	-
		PRDM1	-
		ACTG1	-
Chapman et al. (17)	WES*	NRAS	MEK inhibitor
	WGS†	KRAS	MEK inhibitor
		FAM46C	-
		DIS3	-
		TP53	PRIMA-1 analog
		CCND1	CDK inhibitor
		PNRC1	-
		ALOX12B	-
		HLA-A	-
		MAGED1	-

*Whole exome sequencing; †Whole genome sequencing.

neous mutational landscape was observed and while clonal heterogeneity is an established feature in MM, the subclonal evolution associated with disease progression has not been well explored.

Chapman et al. (35) reported the first results of next generation sequencing in samples of patients with MM. They studied 38 MM patients (WGS in 22 pts, WES in 15 pts and 1 patient sample analyzed by both approaches). This study identified 10 statistically significant protein-coding mutations in MM including NRAS, KRAS, FAM46C, DIS3, TP53, CCND1, PNRC1, ALOX12B, HLA-A and MAGED1 but at a low frequency. One of the thirty eight patients harbored a BRAF kinase mutation leading to the genotyping of an additional 161 MM patients and found BRAF mutations in 7 patients (4%). The gene set mutation spectrum included genes involved the nuclear factor Kappa B (NF-κB) pathway, histone methylation, protein translation, and homeostasis.

In 2014, a study by Lohr et al. (36) was designed to address some of the limitations of the Chapman et al study (35) that was only powered to detect commonly mutated genes and didn't examine copy number alterations or clonal heterogeneity due to the small sample size and modest sequence coverage. Parallel sequencing of paired tumor/normal samples from 203 MM patients showed that eleven genes were recurrently mutated including KRAS, NRAS, TP53, FAM46C, DIS3, BRAF, TRAF3, PRDM1, CYLD, RB1 and ACTG1. Among the 11 significantly mutated genes were five genes (KRAS, NRAS, FAM46C, DIS3 and TP53) previously identified by Chapman et al. (35). The previously tested gene set hypotheses including the mutations of genes in the NF-kB pathway, histone-modifying enzymes and the coagulation cascade retained statistical significance across all 203 patients (p<0.05) when tested as individual hypotheses.

The largest comprehensive molecular analysis was reported by Walker et al. (20) that performed WES in 463 patients enrolled in a phase III trial (National Cancer Research Institute Myeloma XI Trial) identifying 15 significantly mutated genes: IRF4, KRAS, NRAS, MAX, HIST1H1E, RB1, EGR1, TP53, TRAF3, FAM46C, DIS3, BRAF, LTB, CYLD, and FGFR3. In this cohort the RAS/MAPK pathway was the most frequently mutated pathway (KRAS: 21.2%, NRAS: 19.4%, BRAF: 6.7%) making up a total of 43.2%. Moreover, mutational activation of the NF-kB pathway genes were identified in 17% of cases. In this study FGFR3 was found to be mutated solely in the t(4;14) group and the transcriptional regulator EGR1 mutation in the hyperdiploid samples.

Interestingly, the only recurrent mutations that significantly affect survival outcomes are those observed in TP53. The coexistence of del 17p, and *TP53* mutations (25-40% of patients harboring del 17p) appears to cumulatively increase the risk of poor outcomes highlighting the hierarchical interaction between abnormalities of different types (4, 12, 21). Most chromosome 17 deletions are hemizygous and are observed in around 10% of patients with newly diagnosed MM however, the frequency increases up to 80% in advanced disease. The TP53 gene is located within a minimally deleted region on 17p13 and functions as a transcriptional regulator influencing cell-cycle arrest, DNA repair, and apoptosis in response to DNA damage (4, 21, 37).

These sequencing studies have examined the mutational landscape in MM showing that despite genetic heterogeneity the most frequently mutated genes belong to a limited number of pathways (Table 3) as well as the lack of a universal driver mutation and the presence of coexistent subclones. More importantly, in the current era of personalized medicine when physicians aim to tailor the appropriate therapy to each patient on the

Table 3. Frequently Mutated Genes in Multiple Myeloma[*]

Gene	Frequency (%)	Function
KRAS	20-25	MAPK signaling pathway (cell survival and growth)
NRAS	23-25	MAPK signaling pathway (cell survival and growth)
TP53	8-15	Tumor suppressor involved in response to DNA damage and apoptosis
DIS3	11	Exosome endoribonuclease
FAM46C	~11	Unclear
BRAF	6-15	MAPK signaling pathway (cell survival and growth)
TRAF3	3-6	NF-κB signaling pathway (cell survival and proliferation)
ROBO1	2-5	Transmembrane receptor involved cell growth though crosstalk with MET signaling
CYLD	2-3	NF-κB signaling pathway (cell survival and proliferation)
EGR1	4-6	Transcription factor
SP140	5-7	Antigen-response mechanisms in mature B cells
FAT3	4-7	Cadherin superfamily member (cell adhesion)
CCND1	3	Cell cycle progression

[*]From Kumar SK (12).

basis of genomic data, the identification of driver mutations in MM is promising especially for those patients harboring actionable mutations/pathways. To date however, the only evidence of precision medicine is related to BRAF mutation found in about 4% of patients and case reports had noted response with the BRAF inhibitor, vemurafenib (38, 39).

Clonal Evolution and Subclonality

Despite being characterized by the secretion of a unique monoclonal protein in the majority of patients, a degree of heterogeneity is observed at the molecular level, which suggests a Darwinian evolution of MM (35, 36, 6, 40). This heterogeneity is observed as soon as the monoclonal gammopathy of undetermined significance stage, meaning that immortalized plasma cells diverge very early in their evolution (40, 41). Keats et al. have examined the genomic changes over time in 28 patients with multiple myeloma (42). They noted that about a third of the patients (especially low risk hyperdiploid patients) had stable genome over time. The rest of the patients had clonal changes characterized by either clonal heterogeneity at diagnosis or linear evolution. Of interest, patients with high risk cytogenetics had more genomic changes and only one high risk patient had genomic stability. The same authors studied the clonal dynamics of 1 patient with t(4;14) at 7 time points and noted the clonal dynamics in the face of treatment selection.

Next generation sequencing has shown a lack of universal driver mutation, presence of coexistent subclones and oligoclonality in MM which leads to various type of evolution of the disease over time (3, 40). Clonal evolution in multiple myeloma before and after therapy can follow several patterns including branching clonal development, subclonal shift, linear clonal pattern and clonal stability (4). In patients with branching clonal evolution (estimated 30% of patients), one or more subclones appear at a later time point, whereas others subclones have disappeared. In patients with a subclonal shift, the subclones at diagnosis are also present at relapse, but the frequency of the subclones has changed throughout the disease course and one clone has become more dominant than another. In patients with a linear clonal
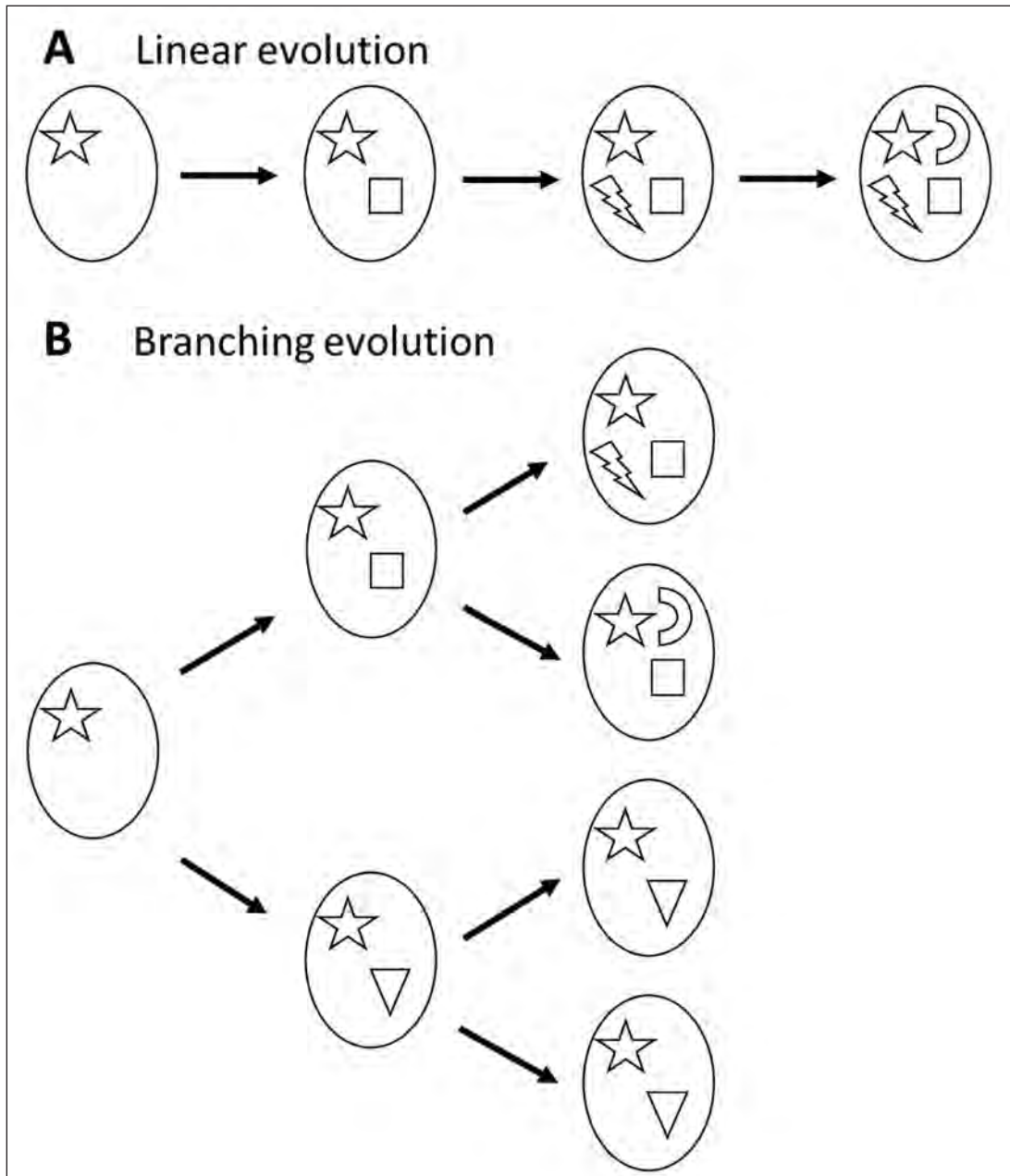
Figure 1. Myeloma is characterized by two types of subclonal evolution (A) a linear one with acquisition of novel mutations over time in the clone and (B) a branching evolution where subclones diverge with subclonal acquisition of novel mutations. From Robiou du Pont S (40).

evolution (~40% of patients), a new sub-clone has emerged between diagnosis and relapse, which was absent at diagnosis (40). In patients with clonal stability (approxi-mately 30% of patients) the same composi-tion of clonal and subclonal heterogeneity is found before and after treatment suggesting that all subclones are affected by therapy and will repopulate equivalently (4) (Figure 1). As noted by Keats et al. this may be more

commonly noted in patients with low risk disease.

The therapeutic implications of clonal heterogeneity and clonal evolution are key areas in multiple myeloma and may have therapeutic implications as previously noted by Fakhri et al. (41) including subclone drug resistant allowing future dominance, targeted therapy of the main clone to maximize effectiveness, combination therapy to overcome branching clonal evolution and therapy recycling based on reemergence of clone(s). Targeted agents will more than likely have to be combined with standard-of-care agents, and such regimens might need to be adjusted over time based on the evolving clonal architecture, while maintaining the broadly active backbone combinations (12).

Summary

The availability of more affordable and high throughput genomic tools has led to an improved understanding of the genomic landscape of multiple myeloma. While the complexity and heterogeneity of the disease continue to make personalized medicine a challenge for myeloma patients, it is our opinion that this genomic revolution will undoubtedly lead to precision medicine in myeloma in the near future. Importantly, in addition to an improved understanding of tumor genomics, an in-depth assessment of the tumor microenvironment (including the immune microenvironment) and the host are needed to more completely characterize the disease, identify new targets and develop better therapies for myeloma patients.

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