

Multiple myeloma: recommendations for next-generation sequencing

Mieloma múltiple: recomendaciones sobre el estudio de secuenciación masiva

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Abstract

Introduction: The integration of laboratory and clinical technologies and knowledge is key to an accurate diagnosis of hematologic neoplasms. Over the past decade, next-generation sequencing (NGS) has enabled the molecular characterization of these diseases, identifying mutations, copy number variations, and recurrent fusion genes. This advancement has driven the update of recommendations for the diagnosis and management of patients with hematologic neoplasms. Recent classifications by the World Health Organization (WHO), the International Consensus Classification (ICC), and the European LeukemiaNet (ELN) highlight the relevance of genetic data, incorporating them into their diagnostic and risk stratification algorithms. In this context, the implementation of targeted NGS panels is recommended for their ability to simultaneously analyze multiple genetic alterations. **Objective:** Although NGS is available in many laboratories, its use is not yet standardized, and there is no clear consensus on the methodology or the genes to be evaluated for each pathology. **Material and method:** The Molecular Biology Group in Hematology (GBMH), in collaboration with a panel of experts, developed this consensus guide. **Results:** Genes of interest were compiled based on their clinical relevance and scientific evidence. **Conclusions:** This guide aims to assist professionals in the use of targeted NGS panels in multiple myeloma.

Keywords: Multiple myeloma. Next-generation sequencing (NGS). Consensus guidelines.

Resumen

Introducción: La integración de tecnologías y conocimientos del laboratorio y la clínica es clave para un diagnóstico preciso de las neoplasias hematológicas. En la última década, la secuenciación masiva (NGS) ha permitido caracterizar el perfil molecular de estas enfermedades, identificando mutaciones, variaciones en el número de copias y genes de fusión recurrentes. Este avance ha impulsado la actualización de las recomendaciones para el diagnóstico y manejo de los pacientes con neoplasias hematológicas. Las clasificaciones recientes de la World Health Organization (WHO), la International Consensus Classification (ICC), y la European LeukemiaNet (ELN) destacan la relevancia de los datos genéticos, incorporándolos a sus algoritmos de diagnóstico y estratificación de riesgo. En este contexto, se recomienda la implementación de paneles de NGS dirigidos por su capacidad para analizar simultáneamente múltiples alteraciones genéticas. **Objetivo:** Aunque el NGS está disponible en muchos laboratorios, su uso no está estandarizado, y no hay un consenso claro sobre la metodología o los genes a evaluar para cada patología. **Materiales y método:** El Grupo de Biología Molecular en Hematología (GBMH), en colaboración con un panel de expertos, desarrolló esta guía de consenso. **Resultados:** Se compiló una lista de genes de interés basados en su relevancia clínica y evidencia científica. **Conclusiones:** Esta guía tiene como objetivo asistir a los profesionales en el uso de paneles de NGS dirigidos en mieloma múltiple.

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*sus Classification (ICC) y la European LeukemiaNet (ELN) destacan la relevancia de los datos genéticos, incorporándolos en sus algoritmos diagnósticos y de estratificación del riesgo. En este contexto, la implementación de paneles dirigidos de NGS se recomienda por su capacidad para analizar múltiples alteraciones genéticas. **Objetivo:** Aunque la NGS está disponible en muchos laboratorios, su uso no está estandarizado y no hay consenso sobre la metodología ni los genes que evaluar en cada enfermedad. **Material y método:** El Grupo de Biología Molecular en Hematología (GBMH), en colaboración con un panel de expertos, elaboró esta guía consensuada. **Resultados:** Se recogen los genes de interés según su relevancia clínica y evidencia científica. **Conclusiones:** Esta guía busca orientar a los profesionales sobre el uso de paneles dirigidos de NGS en el mieloma múltiple.*

Palabras clave: Mieloma múltiple. Secuenciación masiva (NGS). Guías de consenso.

Introduction

Multiple myeloma (MM) is a type of cancer characterized by the infiltration of neoplastic plasma cells in the bone marrow, leading to bone destruction and bone marrow failure. It accounts for 1.8% of all cancers and 18% of hematologic tumors.

MM is a disease characterized by marked proliferative, cytogenetic, and molecular heterogeneity¹. This heterogeneity manifests clinically in different levels of disease aggressiveness. MM patients with a more aggressive form of the disease experience suboptimal responses to some treatments.

The recommendations for initial studies in MM, always performed on bone marrow, include fluorescence in situ hybridization (FISH) studies, always performed on purified CD138+ cells, to detect the following high-risk cytogenetic alterations: del(17p13), gain(1q), del(1p), t(4;14)(p16;q32), and t(14;16)(q32;q23). High-risk cytogenetics is considered in cases where t(4;14), t(14;16), and/or del(17p13) are present in more than 10% of purified plasma cells^{2,3}. It is common to find two or more high-risk cytogenetic alterations in the same patient (multi-hit), which increases cumulative risk. The FISH panel can be expanded at diagnosis if *IGH* is rearranged but is negative for the previous translocations: t(4;14)(p16;q32) and t(14;16)(q32;q23). In this case, t(14;20)(q32;q12) and t(6;14)(p16;q32) are analyzed. At relapse, the diagnostic panel should be repeated, adding analysis of t(11;14)(q13;q32), as it indicates susceptibility to venetoclax-based combination treatments, and t(8;14)(q24;q32), which is common in disease progression and is associated with poor prognosis^{4,5}.

The utility of next-generation sequencing (NGS) studies in MM, particularly aimed at detecting patients resistant to standard treatments or sensitive to specific treatments, is still under investigation. However, prognostically relevant alterations have already been detected that allow identification of high-risk patients. The NGS studies proposed for inclusion in the clinical

care guidelines for MM patients focus on known genomic alterations associated with more aggressive subtypes with frequent suboptimal responses or treatment failures/refractoriness.

The international consensus on the new classification of lymphoid pathology⁶ establishes new recommendations recognizing MM as a genetically heterogeneous disease with 2 differential cytogenetic groups⁶. Approximately 40-50% of cases show recurrent *IGH* translocations with a variety of associated genes, while up to 55% of MM lack *IGH* translocations and are characterized by hyperdiploid, with a small subset falling outside these categories. Alterations in these primary genes are present in precursor cells and persist throughout the course of the disease; they are also associated with a specific prognosis, treatment response, as well as other clinical and phenotypic characteristics, and have a strong correlation with the gene expression profile.

Therefore, MM patients can be formally divided into mutually exclusive diagnostic groups: 1) MM not otherwise specified (NOS), and 2) MM with recurrent genetic abnormalities, including MM with *CCND* family translocations, MM with *MAF* family translocations, MM with *NSD2* translocation, and MM with hyperdiploid. Detection of t(4;14), t(14;16), as well as secondary changes including del(17p), amp1q, and del(1p), identifies high-risk patients.

FISH remains the technique of choice for cytogenetic characterization of myeloma, for which published consensus panels exist⁷. Additional NGS techniques that allow characterization of the mutational profile are particularly interesting given the frequent subclonal evolution and spatial heterogeneity in MM.

Relevant methodological aspects in multiple myeloma

- Timing of study: when establishing the diagnosis and upon treatment failure (either due to relapse or refractoriness to treatment).

Table 1. Study of SNV (single nucleotide variants)/indels in genes of recommended/mandatory study

Reference transcript ID	Gene	Region	Diagnosis	Prognosis	Treatment	Rule out germline origin	Drug resistance	Reference
NM_000051.3	<i>ATM</i>	CDS		X				5
NM_004333.4	<i>BRAF</i>	Exons 6-7,11-15	X		X			20
NM_014953.3	<i>DIS3</i>	CDS	X			X		21
NM_014953.3	<i>KRAS</i>	CDS		X	X			13,18
NM_002524.4	<i>NRAS</i>	Exons 2,3		X	X			18,19
NM_001276761.1	<i>TP53*</i>	CDS	X	X	X	X	X	1,2,5,9,12-16
NM_001178126.1	<i>IGLL5</i>	CDS		X				22
NM_053056.2	<i>CCND1</i>	CDS		X				23
NM_017709.3	<i>TENT5C/ FAM46C</i>	CDS	X					24
NM_001198.3	<i>PRDM1</i>	Exons 4-7		X				17
1NM_145725.2	<i>TRAF3</i>	CDS	X					25
NM_016302.4	<i>CRBN</i>	CDS					X	26

*Only *TP53* is considered mandatory for study in all patients at diagnosis or in relapse/refractoriness.
CDS: coding sequence.

– Studies to be performed: NGS studies are performed at diagnosis, along with FISH studies on the plasma cell population obtained by bone marrow aspiration. Enrichment of CD138+ cells, generally by immunomagnetic methods, should be performed within the first 24 hours after bone marrow extraction. Subsequently, purified cells can be stored in RLT (buffer) at –80 °C or in fetal bovine serum in liquid nitrogen.

The amount of DNA extracted from purified cells can be a limitation for the studies to be performed. FISH studies should be prioritized after purification of CD138+ cells over the rest of the planned studies (NGS panel) in cases where low cellularity is obtained due to poor infiltration, small sample volume (< 2 ml), or other justifying causes.

Studies to be conducted using NGS panels in multiple myeloma

Several types of samples can be used for NGS in MM. These include:

– CD138+ plasma cells from bone marrow aspirate. This is the most common and recommended source. They are purified by CD138 selection, which allows specific study of the tumor clone. Limitation: the

quality of the aspirate may be affected by hemodilution or low cellularity in disease remission.

– Bone marrow without purification (bulk). Used when CD138+ selection is not possible. Limitation: may include DNA from other hematopoietic cells, reducing the sensitivity and specificity of the analysis. The mutation may be detected, but with lower VAF precision.

– Cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA) in plasma. Non-invasive method that allows dynamic monitoring and analysis when bone marrow cannot be obtained. Useful for detecting subclones or emerging mutations in relapses. Limitation: lower sensitivity if tumor burden is low; not yet standardized for systematic use.

After a literature review, the selection of genes and genomic alterations of interest to be performed in all MM patients at diagnosis or in relapse/refractoriness situations was agreed upon by the MM group of the Molecular Biology Group in Hematology (GBMH) and is shown in **table 1**.

The table refers to recommendations for detecting single nucleotide variations (SNVs) and indels (small insertions and deletions). Variants are located in coding regions and splicing zones of genes previously referenced in published works. These genes have been included in panels

used by cooperative groups nationally, such as the Spanish Myeloma Group (GEM-PETHEMA)⁸.

The genes recommended for study, in alphabetical order, are *ATM*, *BRAF*, *CCND1*, *DIS3*, *TENT5C* (*FAM46C*), *IGLL5*, *KRAS*, *NRAS*, *PRDM1*, *TP53*, and *TRAF3* (Table 1). Their selection was based on previously described clinical prognostic impact and their frequency in this pathology⁵. For detection of these variants, there are no other methods with better cost-effectiveness.

Also included as a possible complementary method to FISH cytogenetic studies is the detection of gains or losses of genetic copies of *TP53* (or 17p), 1q/p, or 8q32, by detecting copy number variations (CNVs) using NGS panels developed for this purpose. Although this methodology, unlike FISH, is not yet standardized for cut-off values with clinical significance.

Studies using targeted NGS panels are being evaluated as an alternative to FISH for detecting relevant translocations. Thus, the most frequent translocations typically involve the promoter region of the *IGH* locus (14q32) and cyclin-associated regions (*CCND1* at 11q13, *CCND2* at 12p13, and *CCND3* at 6p21). Translocations affecting *NSD2/FGFR3* (4p16), *MYC* (8q24), and the *MAF* (16q23) and *MAFB* (20q12) genes are also common.

To study these translocations, appropriate probes are chosen that cover the promoter region or upstream of the *IGH* locus, as well as probes that cover both the regions closest to the first exon of the different partners and all remaining exons, invading the 5' and 3' ends of each exon to cover the intronic part where crossover between the chromosomes involved in the translocation may occur. In addition, with the new recommendations, the need to identify *CCND* family translocations, *MAF* family translocations, *NSD2* translocation, as well as the presence of MM with hyperdiploid is confirmed (Tables 2 and 3).

Clinical utility of NGS panel studies in multiple myeloma

– 17p/*TP53* alterations: alterations in the short arm of chromosome 17 include interstitial deletion (17p13.1) or monosomy 17, as well as SNVs/indels in *TP53*. Between 5 and 10% of patients present with 17p deletion at diagnosis and/or mutations in the *TP53* gene, although their incidence increases as the disease progresses, reaching up to 80% in advanced and more aggressive forms of the disease, such as plasma cell leukemia^{1,5,9-12}. Both alterations have a well-defined impact and are associated with poor prognosis^{2,13-15}.

Additionally, biallelic alteration of *TP53* (double-hit myeloma), which occurs in 25-40% of patients with del(17p13), constitutes an additional risk factor associated with an extremely poor prognosis¹⁶. Based on the evidence, the study of splicing variants and the coding region of *TP53* is considered mandatory for all newly diagnosed or relapsed/progressing patients.

On the other hand, the study of 17p structural alterations by NGS is proposed as complementary to FISH.

– *KRAS*: alterations in this gene are especially frequent in newly diagnosed MM patients (20-25%) and their incidence increases in successive disease relapses (30-50%)^{1,5,9,10,12,17}. Several publications associate the presence of *KRAS* variants with disease progression from indolent to symptomatic forms^{13,18}. Based on the evidence, the study of the *KRAS* coding region by NGS techniques is recommended.

– *NRAS*: alterations in this gene are especially frequent in newly diagnosed MM patients (18-25%) and their incidence increases in successive disease relapses^{1,5,9-12,17}. Between 80 and 90% are located in hotspots of exons 2 and 3 (amino acids p.G12, p.G13, and p.Q61)^{1,9,11}.

NRAS mutations have been associated with disease progression and transition to active myeloma^{18,19}. Based on the evidence, the study of exons 2 and 3 by NGS techniques is recommended.

NGS panel studies in MM are necessary to identify patients with a poorer prognosis based primarily on the presence of pathogenic or likely pathogenic variants in *TP53*, but also in other genes (Supplementary Table 1).

In the current context, the use of NGS panels for studying MM patients is necessary at diagnosis and upon relapse or refractoriness of the disease. Moreover, in the future, NGS could be a fundamental technique in monitoring minimal residual disease. Its clinical utility lies primarily in the detection of pathogenic variants in *TP53*, which allows identification of a group of patients with a poor prognosis, especially in the previously mentioned double-hit cases.

However, current evidence suggests that other variants or the degree of overall genetic instability may have diagnostic, prognostic, or predictive utility. Therefore, encompassing their analysis in a single study may be useful for clinical patient management from a personalized precision medicine perspective. However, today, the NGS technique in myeloma still has limitations, such as a lack of standardization, the need for specialized equipment, high cost, and the absence of international guidelines defining its clinical use.

Table 2. Rearrangements of the recommended/mandatory study

Region	Diagnosis	Prognosis	Treatment	Drug resistance
11q13 - <i>CCND1</i>			X	
<i>CCND2</i>		X		
6p21 - <i>CCND3</i>		X		
16q23 - <i>MAF</i>	X	X		
20q12 - <i>MAFB</i>		X		
8q24 - <i>MYC</i>		X		
4p16 - <i>NSD2/FGFR3</i>	X	X		

Table 3. Recommended/mandatory copy number variation study

Region	Diagnosis	Prognosis	Treatment	Drug resistance
<i>TP53</i> /del17p	X	X		X
del1p	X			
gain/amp 1q	X	X		
gain/amp 8q24		X		

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Conflicts of interest

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Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient

data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary material

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