

Mantle cell lymphoma: recommendations for next-generation sequencing

Linfoma de células del manto: recomendaciones para 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 the scientific evidence. **Conclusions:** This guide aims to assist professionals in the use of targeted NGS panels in mantle cell lymphoma.

Keywords: Mantle cell lymphoma. Next generation sequencing. 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, next-generation sequencing) 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 el manejo de los pacientes con neoplasias hematológicas. Las clasificaciones recientes de la Organización Mundial

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de la Salud (OMS), la International Consensus 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:** Establecer un consenso sobre la metodología y los genes y regiones que se deben evaluar para el linfoma de células del manto. **Material y método:** El Grupo de Biología Molecular en Hematología (GBMH), en colaboración con un panel de expertos, elaboró esta guía consensuada de los genes y regiones que deben analizarse mediante secuenciación masiva en linfoma de células del manto. **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 linfoma de células del manto.

Palabras clave: Linfoma de células del manto. Secuenciación masiva. Guías de consenso.

Introduction

Mantle cell lymphoma (MCL) is a neoplasm characterized by the expansion of mature B cells, predominantly affecting males with a median age of 60-68 years at diagnosis. Tumor cells are mainly located in lymph nodes, spleen, and bone marrow, and frequently also infiltrate peripheral blood, as well as other extranodal sites, the most common being the GI tract. The central nervous system may also be involved, although this is more common at relapse than at diagnosis. MCL is a rare neoplasm, accounting for approximately 3-10% of non-Hodgkin lymphomas.¹

MCL has traditionally been considered a highly aggressive and incurable disease, generally requiring intensive treatment from diagnosis. However, in recent years, more indolent variants (non-nodal leukemic MCL [nnMCL] and in situ mantle cell neoplasia) have been identified and recognized by the World Health Organization.¹ Some of these less aggressive clinical forms may be managed with a non-interventional approach, not requiring or delaying the initiation of treatment.

From a molecular perspective, the chromosomal translocation t(11;14)(q13;q32), which causes overexpression of the oncogene *CCND1*, is characteristic of MCL and is found in more than 95% of cases. As an alternative mechanism to *CCND1* gene translocation, MCL cases may present rearrangements of the *CCND2* or *CCND3* genes (cyclin D1-negative MCL variant).² The *CCND1* translocation (considered a weak oncogene) is regarded as the primary oncogenic event, and most tumors acquire numerous additional secondary genetic alterations (gains, losses, rearrangements, mutations), which confer greater tumor aggressiveness. MCL generally presents complex karyotypes with numerous numerical and structural alterations.

Currently, 2 molecular subtypes of MCL are recognized:

- Conventional MCL (cMCL), the most frequent (70-90% of cases), typically does not present somatic hypermutation of the *IGH* gene variable region, is positive for the transcription factor SOX11 (generally assessed by immunohistochemistry), shows high genomic instability, and usually presents with generalized lymphadenopathy and aggressive clinical behavior.
- nnMCL, less frequent (10-30% of cases), is characterized by mutations in the *IGH* gene (via somatic hypermutation), reflecting passage through the germinal center, is negative for the SOX11 marker, and generally presents t(11;14) as the sole genomic alteration in most cases. Patients mainly show leukemic involvement, without lymph node involvement or with minimal lymphadenopathy, may have splenic involvement, and initially present an indolent clinical course that can remain stable for long periods.

In patients with nnMCL, the presence of *TP53* gene mutations (or 17p deletion) or high genomic instability has been associated with a very poor prognosis.^{3,4} Although these alterations may occur independently, their coexistence tends to indicate greater biological aggressiveness and a more adverse clinical course. In particular, the blastoid/pleomorphic variant of MCL, present in both molecular subtypes (cMCL and nnMCL), is characterized by a high proliferation rate of tumor cells, a higher frequency of high-risk mutations (such as *TP53* or *CDKN2A* alterations) and marked genomic complexity; all these factors contribute to a very unfavorable prognosis in patients with this variant.

Initial study recommendations for MCL include karyotype analysis from peripheral blood or bone marrow, and fluorescence in situ hybridization (FISH) using fusion probes (*CCND1:IGH*) or break-apart probes (*CCND1*), and in cases with paraffin-embedded tissue, FISH analysis of *CCND1*. The utility of next-generation sequencing (NGS) studies in MCL to identify prognostic

biomarkers and resistance to standard or novel therapies is still under investigation; however, *TP53* analysis by NGS is justified based on current evidence and has been included in recent reviews of genomic studies to support clinical decision-making.⁵

Relevant methodological aspects in mantle cell lymphoma

- Timing of the study: at diagnosis and upon failure of different lines of treatment (relapse or primary or secondary refractoriness to treatment).
- Studies to be performed: NGS studies may be carried out at the time of diagnosis along with karyotype and FISH studies, using the same blood, bone marrow, or affected tissue samples. DNA may be extracted from both fixed tumor tissue and infiltrated peripheral blood and bone marrow samples. In blood and bone marrow, separation of CD19⁺ cells is recommended to increase tumor purity and optimize the interpretation of molecular studies, especially in samples with low infiltration.

Although there is no universally accepted threshold, it is suggested that when tumor infiltration is $\geq 20\text{--}30\%$ (by morphology or cytometry), NGS analysis can be performed without the need for CD19⁺ cell separation. Below this threshold, enrichment of tumor B cells through CD19⁺ selection may significantly improve the sensitivity of mutational analysis. CD19⁺ cell separation may be performed using magnetic selection methods or flow cytometry with cell sorting.

Studies using NGS panels in mantle cell lymphoma

After reviewing the literature, the MCL group has agreed on a list of genes (Table 1) and chromosomal regions (Table 2). Table 1 includes mutations in coding regions, splicing regions, and 3' and 5' UTR regions in genes with previously described functional alterations in MCL. The final list includes:

- *ATM*, *KMT2D*, *TP53*, *BIRC3*, and *CCND1*, with a high mutation frequency in the disease ($> 15\%$).
- *CDKN2A* and *CDKN2B*, commonly affected by deletions.
- *MYC*, *BCL2*, *BMI1*, and *MIR17HG*, with amplifications reported in high-risk subgroups.

In addition, it is recommended to include genes whose alterations have been associated with resistance to targeted therapies, particularly BTK inhibitors (such as ibrutinib and acalabrutinib): *BTK*, *PLCG2*, *TLR2*,

TRAF2, and *TRAF3*. Genes with less frequent mutations but with biological and clinical relevance are also considered important: *CARD11*, *HNRNP1*, *NOTCH1*, *NOTCH2*, *NSD2/MMSET*, *RB1*, *SMARCA4*, and *SP140*.

For some tumor suppressor genes selected for mutation analysis, chromosomal losses should also be evaluated (*ATM*, *BIRC3*, *KMT2D*, *RB1*, *SMARCA4*, *SP140*, *TP53*, *TRAF2*, and *TRAF3*). For certain genes, the prognostic impact of loss is better documented than for others (for example, *TP53*, *RB1*, and *CDKN2A/CDKN2B*), but prior validation studies are required to establish deletion thresholds using NGS panels. In the case of *CDKN2A/CDKN2B*, differentiation between homozygous and heterozygous deletions is necessary. With appropriate probe design,⁶ detection of translocations involving immunoglobulin genes (*IGH*, *IGK*, or *IGL*) with *CCND1* could be included in the NGS panel to detect all variants of the primary MCL translocation, alternative translocations involving *CCND2* and *CCND3*, and translocations with *MYC*, which are rare and generally acquired during disease progression.

For the study of mutations in MCL, considering the high heterogeneity, the absence of hotspot regions, and the possibility of identifying potentially subclonal mutations, the use of NGS panels is considered the most appropriate methodology.

Detection of copy number variations using NGS panels is based on the relative quantification of sequencing reads from the test sample compared with a baseline generated from healthy controls without alterations. Although this application is not yet fully standardized and does not replace conventional techniques such as FISH or karyotyping, it may be useful as a complementary tool, particularly for detecting focal copy number variations not detected by conventional cytogenetics. For its implementation, the use of specific bioinformatic algorithms and hybrid capture panels is recommended, as panels based solely on amplicons have limitations for reliable copy number variation analysis. At present, its routine diagnostic use is not recommended until sufficient clinical validation is available, although its potential as an emerging tool is recognized.

Clinical utility of NGS panel studies in mantle cell lymphoma

In general, detection of *CCND1* translocation (or *CCND2* and *CCND3*), *ATM* mutation, and the *NSD2/MMSET* hotspot mutation has diagnostic value in MCL, whereas most of the selected genes and regions have prognostic value—*BIRC3*, *BMI1* (*10p13*), *BTK*,

Table 1. Most relevant genes related to mantle cell lymphoma included in the next-generation sequencing (NGS) panel

Genes	Clinical value	Level of evidence
<i>TP53</i>	Prognosis	Mandatory
<i>ATM</i>	Diagnosis	Recommended
<i>BTK</i>	Prognosis, treatment	Recommended
<i>CCND1</i>	Prognosis	Recommended
<i>CDKN2A</i>	Prognosis	Recommended
<i>KMT2D</i>	Prognosis	Recommended
<i>NOTCH1</i>	Prognosis	Recommended
<i>NOTCH2</i>	Prognosis	Recommended
<i>NSD2</i>	Diagnosis	Recommended
<i>RB1</i>	Prognosis	Recommended
<i>BIRC3</i>	Prognosis, treatment	Optional
<i>CARD11</i>	Prognosis	Optional
<i>HNRNPH 1</i>	Prognosis	Optional
<i>IKBKB</i>	Prognosis	Optional
<i>PLCG2</i>	Prognosis, treatment	Optional
<i>SMARCA4</i>	Prognosis, treatment	Optional
<i>SP140</i>	Prognosis	Optional
<i>TLR2</i>	Prognosis	Optional
<i>TRAF2</i>	Prognosis	Optional
<i>TRAF3</i>	Prognosis	Optional

CARD11, *CCND1*, *CDKN2A/CDKN2B* (9p21), *HNRNPH1*, *KMT2D*, *MIR17HG* (13q31), *MYC*, *NOTCH1*, *NOTCH2*, *PLCG2*, *RB1*, *SMARCA4*, *SP140*, *TLR2*, *TP53*, *TRAF2*, and *TRAF3* — and some have predictive value for response to therapies with BTK or BCL2 inhibitors (*BTK*, *PLCG2*, *BIRC3*, *SMARCA4*, and *BCL2*).⁷⁻¹⁶ Currently, determining whether the *BTK* gene harbors mutations after therapy with BTK inhibitors is useful for selecting new non-covalent BTK inhibitors; therefore, its assessment before initiating a new treatment is recommended. In contrast, unlike chronic lymphocytic leukemia, few MCL cases harbor *PLCG2* mutations, and their analysis by NGS panels and practical application are less clearly established.

Of note, alteration of the *TP53* gene is included in both the prognostic and predictive categories. However, some studies indicate that only mutation is relevant,

Table 2. Most relevant structural alterations related to mantle cell lymphoma that may be included in a next-generation sequencing (NGS) panel

Structural alterations	Clinical value	Level of evidence
Rearrangements <i>CCND1::IG</i> <i>CCND2::IG</i> <i>CCND3::IG</i> <i>MYC::IG</i>	Diagnosis Diagnosis Diagnosis Diagnosis, prognosis	Mandatory Mandatory if <i>CCND1</i> negative Mandatory if <i>CCND1</i> negative Recommended
Copy number variations 17p13 (<i>TP53</i>) deletion 8q24.21 (<i>MYC</i>) gain, amplification 9p21.3 (<i>CDKN2A/CDKN2B</i>) deletion 8p deletion 10p12.2 (<i>BM11</i>) gain, amplification 13q14 (<i>RB1</i>) deletion 13q31 (<i>MIR17HG</i>) gain, amplification 18q21.33 (<i>BCL2</i>) gain, amplification	Prognosis, treatment Prognosis Prognosis Prognosis Prognosis Prognosis Prognosis	Mandatory Recommended Optional Optional Optional Optional Optional

**IG* indicates rearrangement with any of the immunoglobulin genes (*IGH*, *IGK*, or *IGL*).

whereas others consider both mutation and deletion, as well as monoallelic or biallelic alterations. In general, there is currently considerable consensus that mutation of one allele of the *TP53* gene is sufficient to define the worst prognosis in patients.

Table 1 indicates the level of recommendation for each of the genes.

Alterations in 17p/*TP53*

Based on the available evidence, analysis of mutations across the entire gene and deletion of the *TP53* gene in MCL is mandatory for all newly diagnosed patients and those with relapse or progression. In MCL, a classification into indolent, standard risk, high risk, and ultra-high risk has been proposed.¹⁵ Variables for ultra-high risk include pleomorphic histology, high proliferation (Ki67 > 30%), central nervous system involvement, and *TP53* gene mutation, together with other high-risk alterations (the truncated and more active form of *CCND1*, *KMT2D*, *NOTCH1*, *CDKN2A*, *NOTCH2*, and *SMARCA4*). The high-risk category includes *TP53* mutation (when presenting high allelic frequencies, > 10%), 17p deletion detected by FISH (which also

implies high allelic frequencies), complex karyotype, and high proliferation, among other clinical variables.

Since the variant allele frequency (VAF) of *TP53* mutations has prognostic value, it is important to note that enrichment of CD19⁺ B cells may artificially increase VAF. Therefore, it is recommended that, whenever possible, NGS panels be performed on whole peripheral blood or bone marrow, or on mononuclear cells without CD19⁺ separation to more accurately reflect the true tumor burden.

TP53 alterations in MCL are associated with all aggressive features: blastoid histology, high proliferation, complex karyotype, and high-risk MCL International Prognostic Index (MIPI), and consequently predict poor prognosis. In newly diagnosed MCL, the frequency of *TP53* alteration is relatively low (10-15%) and increases considerably at relapse, being very common in progressive nnMCL (> 50%).

In addition to the well-documented association of *TP53* alteration with worse prognosis, *TP53* is also associated with resistance to first-line therapies and inferior responses after treatment with ibrutinib. Furthermore, intensive treatments followed by transplantation appear to be less effective in cases with *TP53* mutation. Cases of nnMCL, initially presenting with indolent clinical features and no need for treatment, may already harbor *TP53* mutation and deletion (with high allelic burden) at diagnosis, or may acquire these alterations during disease progression. In such cases, monitoring *TP53* gene status using NGS panels is particularly important, as the acquisition of new alterations in this gene or an increase in the allelic frequency of existing ones may indicate disease progression and the need for treatment, especially when occurring alongside a complex karyotype.^{7,15}

Deletions of *CDKN2A/CDKN2B*

Based on the available evidence, the study of homozygous or heterozygous deletions of the *CDKN2A/CDKN2B* genes in MCL is highly recommended for all newly diagnosed patients and those with relapse or progression. In MCL, *CDKN2A* deletions have been widely demonstrated to confer poor prognosis and are associated with blastoid forms. In addition, concomitant alteration of *CDKN2A* and *TP53* has an additive effect, resulting in much shorter survival than with individual alterations, even in patients treated with intensive immunochemotherapy regimens and autologous transplantation in younger. Therefore, patients with concomitant *CDKN2A* and *TP53* alterations should be

considered candidates for clinical trials, alternative therapeutic strategies, or even CAR-T (Chimeric Antigen Receptor T-cell) therapy as a first option.¹⁶

Other genetic alterations are not currently evaluated in routine clinical practice, although their inclusion in NGS studies may be of potential interest.

Conclusions

NGS panel studies in MCL are necessary to identify patients with poorer prognosis and reduced response to treatments, including intensive therapies, thereby enabling the possibility of offering CAR-T therapy at earlier stages. The genes with the strongest evidence are *TP53* (mutation and deletion) and *CDKN2A* (homozygous and heterozygous deletion), but alterations in other much less frequent genes may also be relevant, such as mutations in *NOTCH1* and *NOTCH2*, associated with aggressive blastoid variants, and amplification or translocation of *MYC*, associated with more aggressive histologies, disease progression, and central nervous system involvement.

cmMCL may present alterations in all the abovementioned genes from diagnosis or acquire them during disease evolution or progression, whereas nnMCL mainly presents *TP53* gene alterations. In addition to alterations in these genes, other parameters associated with poor prognosis in MCL include: 1) high tumor cell proliferation, measured by immunohistochemistry (Ki67 > 30%) or overexpression of proliferation signature genes (microarrays, digital quantification using NanoString®); and 2) high genomic complexity, detected by conventional cytogenetics, DNA microarrays, genome/exome sequencing, optical genome mapping, or adaptation of NGS panels. Current evidence suggests that rare mutations in other genes not yet validated may play a relevant role in diagnosis, stratification, or treatment of the disease. Therefore, an NGS panel encompassing the largest possible number of these variables in a single test would be useful for the clinical management of patients with MCL, regardless of molecular subtype, and would also enable a precision personalized medicine strategy tailored to the molecular characteristics of each patient, both at diagnosis and at relapse or in refractory settings, which are highly characteristic of MCL patients.

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Conflicts of interest

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Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. SAGER guidelines were not applied.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the drafting of this manuscript.

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