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# ***N-myc*** **oncogene amplification in neuroblastoma: prognostic implications and the development of targeted therapies.**

*N-myc oncogene amplification in neuroblastoma: prognostic implications and the development of targeted therapies*

Amplification of N-myc oncogene in neuroblastoma: prognostic implications and development of targeted therapies

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**Summary**

Neuroblastoma is the most common extracranial solid neoplasm in childhood, characterized by high clinical heterogeneity. This study aimed to investigate the correlation between *MYCN oncogene amplification,* disease staging, and prognosis, as well as to review emerging therapies. An integrative literature review was conducted in the PubMed, SciELO, and Google Scholar databases, selecting 10 articles published between 2018 and 2026. The results indicate that *MYCN* overexpression is the main predictor of poor prognosis and resistance, directing the patient to a high-risk protocol. Strategies such as targeted therapies (via PI3K/Akt/mTOR) and immunotherapies (anti-GD2 and CAR-T) emerge as ways to overcome this aggressiveness.

It is concluded that precision oncology is indispensable to the management of the disease, highlighting the strategic role of the biomedical scientist in molecular diagnosis and translational research.
**Descriptors:** Neuroblastoma. N-Myc Proto-Oncogene Protein. Prognosis. Molecular Targeted Therapy. Immunotherapy.

## 1 INTRODUCTION

Neuroblastoma (NB) is the most prevalent extracranial solid neoplasm in the pediatric population.
being the most common malignant tumor diagnosed in infants and children under five years of age.
(Cochran et al., 2020). Characterized by remarkable biological heterogeneity, the NB presents a
Variable clinical spectrum, ranging from spontaneous regression in low-risk cases to
Aggressive metastatic progression that is refractory to treatment, in high-risk cases. This variation
Biological risk assessment requires robust stratification systems, such as the International Risk Group of
Neuroblastoma (INRGSS), which uses clinical and molecular factors to determine prognosis and
the intensity of the therapeutic protocol (Van Nimwegen et al., 2022).
The basis of this aggressiveness lies in specific genetic alterations, with the amplification of
oncogene *MYCN* is the most determinant biological marker of unfavorable prognosis (Zafar et al.,
2021). Located on chromosome 2p24.3, *MYCN* acts as a potent transcription factor that,
When overexpressed, it drives pathways of unrestricted cell proliferation, angiogenesis, and resistance.
to chemotherapy. Present in about 20% of cases, this genetic amplification allows the
tumor cells avoid programmed cell death (apoptosis) mechanisms and activate signaling pathways.
crucial for tumor survival, such as the PI3K/Akt/mTOR pathway (Sharma et al., 2021).

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In this context, early identification of *MYCN* gene status plays a key role.
in clinical management and in the allocation of patients to intensive treatment protocols. Unlike
Unlike other tumors, *MYCN* amplification is such a robust predictor of poor prognosis that
classifies the patient immediately into the high-risk category, regardless of the stage.
anatomical or age-related (Van Nimwegen et al., 2022). Accurate detection of this change through
Molecular biology techniques are essential, since MYCN-amplified patients exhibit
significantly lower rates of overall survival and event-free survival (Park et al.,
2018).

In addition to conventional stratification, the development of new therapeutic approaches has
The goal was to overcome the resistance induced by this genetic alteration. Among the emerging strategies,
Of particular note is immunotherapy with anti-GD2 monoclonal antibodies, which has become the standard.
maintenance therapy in high-risk cases, and CAR-T cell-based therapies, which represent
The frontier of cancer research by targeting specific neuroblastoma antigens (Cafferkey)
et al., 2024). The combined use of multimodal treatments and molecularly targeted therapies has been...
shown to be the key to improving survival and reducing morbidity and mortality associated with the subtypes.
more aggressive forms of the disease (Medscape, 2025).

Given this scenario, the present study aims to investigate the correlation between the
*MYCN* gene amplification , the staging and prognosis of neuroblastoma in children, as well
how to conduct a review of emerging therapeutic approaches that seek to neutralize the effects
Biological agents of this oncogene and overcome tumor aggressiveness.

## 2 METHODOLOGY

This study consisted of an integrative literature review. The bibliographic survey
It was carried out between August 2025 and June 2026, through a structured search in the databases of
SciELO, PubMed, and Google Scholar data, without language restrictions, considering articles.
published in the last five years. The following descriptors were used, obtained from the
Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH): "Neuroblastoma",
*"MYCN* Amplification", *"N-Myc* Proto-Oncogene Protein", "Prognosis", "Targeted Therapy" and
"Immunotherapy", combined using the connectors "AND" and "OR". For the article search, it was
The following strategy was adopted, structured in the following databases: "Neuroblastoma" AND *"MYCN*
Amplification" OR *"N-Myc* Proto-Oncogene Protein" AND "Prognosis" AND "Targeted Therapy"
OR "Immunotherapy".

Studies related to neuroblastoma in pediatric patients were considered for inclusion;


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studies that addressed the correlation between *MYCN* gene amplification and clinical prognosis; and studies that described emerging therapies, such as anti-GD2 antibodies and CAR-T cells, focused on high-risk treatment.

Studies conducted solely on animal models were not considered; studies that addressed other types of solid tumors unrelated to the neural crest; duplicate studies in the databases of data; and works that did not present the complete text available for analysis.

## 3 RESULTS

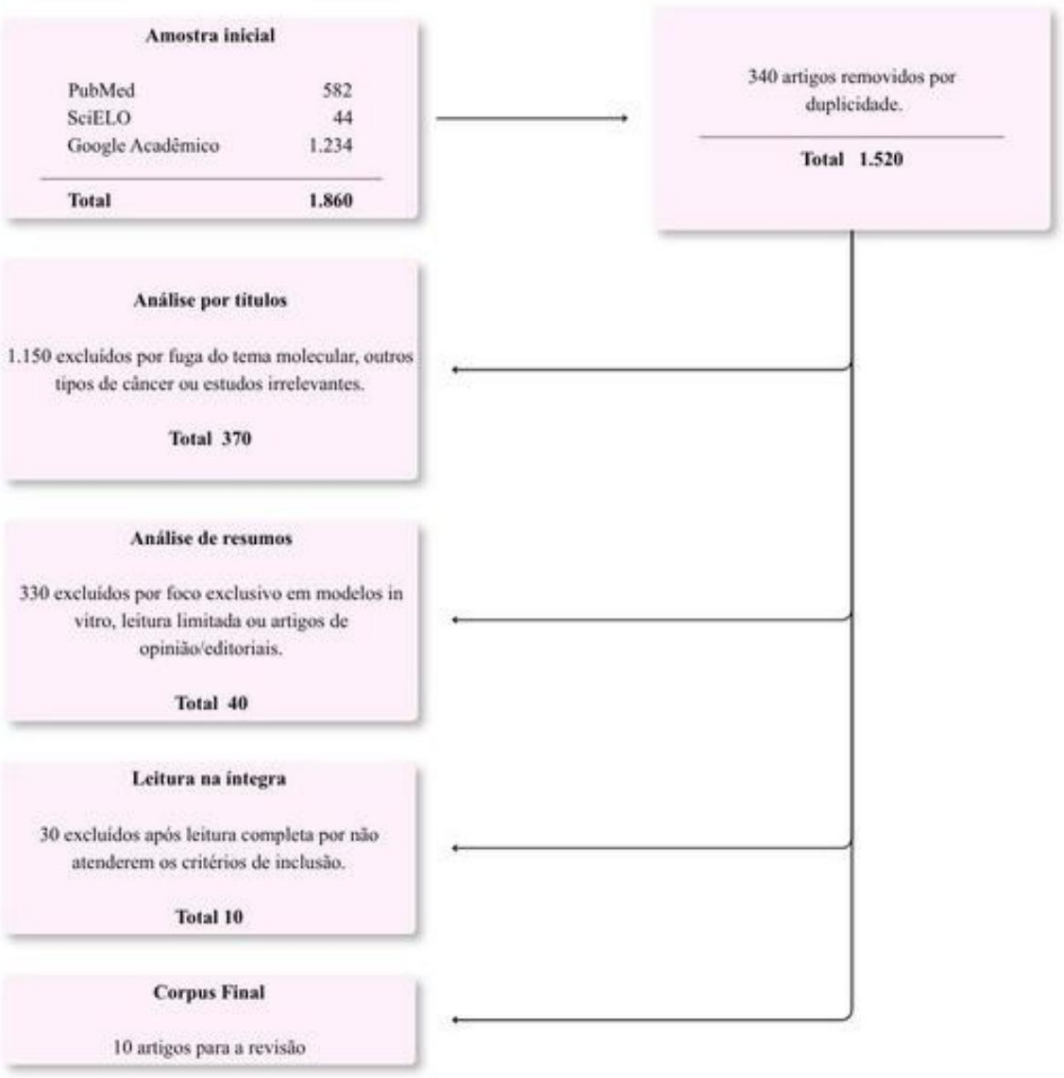
Based on a structured search conducted in the PubMed Central (PMC), SciELO, and Google databases. Academically, 1,860 studies were identified. Of these, 340 articles were excluded because they were... duplicates across platforms, leaving 1,520 studies for analysis. After a careful reading of Of the titles, 1,150 articles were excluded because they did not have a direct relationship with molecular biology. from *MYCN* or because they deal with pediatric neoplasms in general. In the abstract reading stage, 330 studies were excluded for not meeting the inclusion criteria — such as lack of focus. in new therapeutic strategies or unavailability of the full text—totaling 40 articles. for full reading. After a complete and systematic analysis of the content, 10 were selected. articles that best answered the research question, correlating *MYCN* amplification with risk stratification and current therapeutic management, comprising the final corpus of this analysis. (Figure 1).


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Figure 1. Flowchart for article selection, 2026.




Source: Author's own work, 2026.

The systematic analysis of the 10 selected studies allowed for a critical overview of the role...
The central role of molecular biology in the clinical management of neuroblastoma. The data show that...
The aggressiveness of the disease is not a random factor, but rather the direct result of axis dysregulation.
specific molecular parameters, in which MYCN amplification acts as the main catalyst for
resistance.

Unlike traditional oncological approaches, which are primarily based on staging.
Anatomically, the corpus of this work reveals a transition towards precision oncology. The articles
They discuss three fundamental pillars: molecular characterization as a determinant of risk, the
interdependence between signaling routes (especially the PI3K/Akt/mTOR route) and strategies

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border crossings, which seek to circumvent the historical difficulty of reaching MYCN directly through of innovative immunotherapies. A synthesis of this evidence, detailing the goals of each study and its... The respective findings are presented in Table 1.

Table 1. Characteristics of the selected scientific articles, according to title, authors, year of publication, focus of the investigation and results, 2026.

| Title | Authors | Year | Focus of the investigation | Results |
|---|---|---|---|---|
| The role of the *MYCN* oncogene and its therapeutic implications in neuroblastoma | Sharma et al. | 2021 | Analyze the molecular biology of *MYCN* overexpression and strategies for *MYCN* to neutralize its oncogenic function. | It disrupts cell survival genes; indirect inhibitors emerge as the main pathway to neutralize it. the tumor. |
| Neuroblastoma: from molecular pathogenesis to therapy | Cochran et al. | 2020 | Review the molecular pathogenesis and evolution of neuroblastoma treatment protocols. | Risk stratification based on *MYCN* status is the central pillar for defining intensive multimodal protocols. and |
| Targeting *MYCN* and neuroblastoma | Kappel et al. | 2023 | Investigating signaling pathways regulated by *MYCN* potential pharmacological targets. | MYCN *acts* in the control of metabolic pathways; the blocking of cooperating proteins (BET inhibitors) is effective in reducing tumor size. |
| CAR T-cell therapy for neuroblastoma: current status and future directions | Cafferkey et al. | 2024 | Describe the development and challenges of CAR-T cells in the treatment of high-risk neuroblastomas. | Targeted cellular immunotherapy It presents itself as a promising alternative for the control of persistent refractory diseases. and |
| Prognostic | Van | 2022 | Assess the impact of amplification | Patients with |

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| relevance of *MYCN* amplification in neuroblastoma | Nimwegen et al. | | *MYCN* 's work on overall survival and amplification of event-free survival. | Genetic mutations exhibit drastically reduced survival rates. smaller, which consolidates the *MYCN* as a predictor of poor prognosis. |
| Molecular mechanisms of MYCN-driven neuroblastoma in oncogenesis | Zafar et al. 2021 | Analyze the | cellular mechanisms by which *MYCN* overexpression promotes oncogenesis. | The *MYCN* protein It accelerates protein synthesis and and blocks the apoptosis, ensuring a proliferative advantage over and tumor aggressiveness. |
| Anti-GD2 Immunotherapy for Neuroblastoma: Current State and Future Directions | Park et al. 2018 | Assessing | the clinical benefit of maintenance anti-GD2 immunotherapy on long-term survival with anti-GD2 monoclonal antibodies in high-risk patients. | GD2 increased significantly. event-free survival in high-risk groups. |
| Targeting the PI3K/Akt/mTOR pathway in neuroblastoma | Sharma et al. | 2023 To | elucidate the role of the PI3K/Akt/mTOR pathway in MYCN-mediated aggression. | THE via PI3K/Akt/mTOR is fundamental for the tumor survival under Stress, making it a critical target for co-therapies. |
| New insights into the biology and treatment of high-risk neuroblastoma | Medscape (Org) | 2025 Re | view updates to the integration of treatment protocols and new molecular diagnostic tools. | allows one intervention Early and intervention tailored for high-progression phenotypes. |

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| The Landscape of Kappel et al. 2022 Mapping new drugs in | | | targeted clinical trials in neuroblastoma<br>to resistant neuroblastomas. | The future of clinical management lies in targeted in therapies that destabilize the *MYCN* protein and strengthen the host's the immune response. |

## 4. DISCUSSION

A combined analysis of the literature reveals that neuroblastoma is no longer understood solely by...
its clinical anatomy and began to be interpreted through its molecular signature. The central role
The point of convergence among the consulted authors regarding the *MYCN* oncogene is that it is described by Zafar.
et al. (2021) as a protein synthesis accelerator that blocks apoptosis, conferring to the cells
tumors possess an unparalleled proliferative advantage. This biological aggressiveness translates directly into
in epidemiological and clinical data; while Cochran et al. (2020) reinforce that NB is the tumor
The most common extracranial solid in children is the presence of MYCN amplification, which determines...
the clinical outcome.

The prognostic relevance of this genetic alteration is emphasized by Van Nimwegen et al. (2022), who
Studies show that patients with *MYCN amplification* have higher overall survival rates.
drastically lower. This view is corroborated by Cochran et al. (2020), who position the status
MYCN as the central pillar for high-risk stratification, justifying the immediate adoption *of*
more intensive and multimodal therapeutic protocols, regardless of the patient's age or
of the tumor staging.

However, the historical challenge lies in the difficulty of directly targeting the MYCN protein, due to
due to its "non-drugable" molecular structure. In light of this, Sharma et al. (2021) discuss the need
of indirect strategies to neutralize its function. One of the most promising avenues for this
The intervention is via the PI3K/Akt/mTOR pathway. According to Sharma et al. (2023), this signaling pathway is
fundamental for the tumor to survive under stress conditions, making it a critical target for
Co-therapies that aim to sensitize MYCN-amplified cells to conventional treatment.
Complementing this view, Kappel et al. (2023) highlight that blocking cooperating proteins,
Like BET inhibitors, it offers an effective alternative to reduce tumor burden by
to destabilize the metabolic control exerted by the oncogene.

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The transition to precision oncology is also evident in the advancement of immunotherapies. Park et al. (2018) demonstrate that the introduction of anti-GD2 monoclonal antibodies significantly increased event-free survival in high-risk groups, establishing a new gold standard for the phase for treatment maintenance. Going further, Cafferkey et al. (2024) point to CAR-T cells as the current frontier, offering hope for cases of refractory or persistent disease, in which therapies Conventional treatments fail to eradicate the aggressive tumor clone.

Finally, the scenario outlined by Medscape (2025) and Kappel et al. (2022) suggests that the future of Clinical management of neuroblastoma depends on the integration of early molecular biopsies and... developing drugs that not only attack the tumor, but also strengthen the immune response. The host's immune response. In short, current literature is unanimous: overcoming mediated aggression The *MYCN* approach requires a methodology that combines a deep understanding of cell biology with... Targeted therapies that destabilize the tumor's survival networks.

## FINAL CONSIDERATIONS

This study fulfilled its objective by correlating the amplification of the MYCN oncogene with the unfavorable clinical outcome in neuroblastoma, demonstrating that this biological marker is the central pillar for the immediate stratification of patients into the high-risk category. The review of Literature has shown that, although the molecular structure of *MYCN* makes direct blocking unfeasible, the development of targeted therapies directed at cooperating pathways (such as PI3K/Akt/mTOR and the BET proteins) and the advancement of immunotherapeutic frontiers (through anti-GD2 antibodies and cells) T-CAR) represent established strategies for overcoming tumor aggressiveness and resistance.

Thus, the theoretical hypotheses that the multimodal approach based on genetic signature The improvements in event-free survival were confirmed by the scientific evidence analyzed.

The relevance of this research for biomedical professionals lies in the need to provide a foundation for... His expertise lies in precision oncology and highly complex molecular diagnostics. Being the Neuroblastoma is a rapidly progressive neoplasm, and the technical responsibility for its diagnosis falls to a biomedical professional. through the accurate conduct and interpretation of molecular assays that detect MYCN status . The accuracy of your laboratory report is the critical factor that determines the allocation of the pediatric patient. in intensive therapeutic protocols. Furthermore, this study reinforces the role of the biomedical professional in Translational research, since the elucidation of new signaling routes and monitoring by The methods of molecular biopsies depend directly on the development of benchtop scientific research. conducted by this professional.

As a suggestion for future research, clinical studies evaluating the following are recommended.

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long-term efficacy and toxicity profiles of co-therapies combining pathway inhibitors

Cellular treatment with CAR-T cells in patients with disease recurrence is also recommended.

To investigate the impact of incorporating early molecular screening methodologies into routine practice.

public laboratory, aiming to optimize the interval between initial diagnosis and the start of treatment.

targeted.

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