Review Article

Narrative review: precision medicine applications in neuroblastoma—current status and future prospects

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Background and Objective: Neuroblastoma (NB) is a common malignant tumor in children, and its treatment remains challenging. Precision medicine, as an individualized treatment strategy, aims to improve efficacy and reduce toxicity by combining unique patient- and tumor-related factors, bringing new hope for NB treatment. In this article, we review the evidence related to precision medicine in NB, with a focus on potential clinically actionable targets and a series of targeted drugs associated with NB.

Methods: We conducted an extensive search in PubMed, EMBASE, and Web of Science using key terms and database-specific strategies, filtered for time and language, to ensure a comprehensive collection of literature related to precision medicine in NB. The main search terms consisted of "neuroblastoma", "precision medicine", "pediatrics", and "targeting". The articles included in this study encompass those published from 1985 to the present, without restrictions on the type of articles.

Key Content and Findings: ALK inhibitors and MYCN inhibitors have been developed to interfere with tumor cell growth and dissemination, thereby improving treatment outcomes. Additionally, systematic testing to identify relevant driver mutations is crucial and can be used for diagnosis and prognostic assessment through the detection of many associated molecular markers. Furthermore, liquid biopsy, a non-invasive tumor detection method, can complement tissue biopsy and play a role in NB by analyzing circulating tumor DNA and circulating tumor cells to provide genetic information and molecular characteristics of the tumor. Recently, trials conducted by many pediatric oncology groups have shown the urgent need for new approaches to cure relapsed and refractory patients.

Conclusions: The purpose of this review is to summarize the latest advances in clinical treatment of NB, to better understand and focus on the development of promising treatment approaches, and to expedite the transition to the precision medicine clinical relevance in NB patients.

Keywords: Neuroblastoma (NB); precision medicine; targeted therapy; molecular biomarker

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Introduction

Neuroblastoma (NB), which arises from undeveloped neural crest cells in the sympathetic nervous system, is the most common solid tumor found in children. It is responsible for approximately 15% of all pediatric cancer-related deaths (1). Based on clinical and biological prognostic factors such as the standard International NB Risk Group staging, age, histological category, tumor differentiation grade, *MYCN* status, presence of 11q aberrations, and tumor cell ploidy, the Children's Oncology Group (COG) has established a risk classification system for NB. This system categorizes NB into very low-, low-, intermediate-,

and high-risk groups (2). For the majority of patients with low-risk NB, surgery alone constitutes a curative treatment, with the use of chemotherapy being limited to specific circumstances (3). In the case of the intermediate-risk group, the duration and dosage of chemotherapy treatment have been significantly reduced compared to the regimens used in early clinical trials (4). The survival rates for patients with low- and intermediate-risk NB are nearly 100%, whereas those with high-risk NB have survival rates below 50% (5-7). Treatment for high-risk patients includes five to six stages of induction chemotherapy, surgery, high-dose therapy with autologous hematopoietic stem cell transplantation, consolidation therapy with radiotherapy, and subsequent therapy to manage minimal residual disease (7). The majority of patients with high-risk NB do not respond to initial treatments or experience relapse within 2 years of treatment initiation. Survival rates are notably low for patients with recurrent or refractory NB (8-10). Most cancer therapies are based on a "one-size-fits-all" strategy that works for a subset of patients. The concept of precision medicine relies on molecular profiling of genetics, focusing on individual differences, adapting treatment and follow-up according to the individual patient, and tailoring diagnosis and treatment (11). The application of precision medicine to solid tumors was initiated through the use of imatinib in gastrointestinal mesenchymal tumors (12). The core of precision medicine lies in the application of genomics technology, which integrates treatment strategies that take into account individual genetic, environmental, and lifestyle differences (13). The precision medicine approach relies on the selection of appropriate biomarkers to predict the efficacy of targeted therapies in specific patient populations (14). Despite the remarkable advances in genomic precision medicine in adult cancers, we still face many challenges in pediatric oncology. The genetic characteristics of pediatric tumors are significantly different from those of adult tumors, and in-depth studies are needed to address the specificities of pediatric tumors. In this paper, we will discuss several aspects of targeted therapy, molecular biomarkers, liquid biopsy, and immunotherapy for NB. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-557/rc).

Methods

We conducted extensive searches in PubMed, EMBASE, and Web of Science using key terms and database-specific strategies, and filtered for time and language to ensure a comprehensive collection of literature related to precision medicine for NB (*Figure 1*). The main keywords included neuroblastoma, precision medicine, pediatrics and targeting, and articles were searched from 1985 to the present, with no restrictions on article type. The synthesis evaluated pre-treatment-related studies of NB as well as studies regarding long-term prognosis. If additional data were required for the review and these were considered to be time-insensitive the search was extended to an earlier time. The methodology of the studies used in this narrative review is detailed in *Table 1*.

Targeted therapy

Traditional therapies such as chemotherapy and radiotherapy are effective against NB but often come with a range of side effects. In contrast, targeted therapy offers a more refined treatment approach, utilizing specific drugs or substances to identify and further attack cancer cells, while minimizing harm to normal human cells. This is particularly important in the treatment of pediatric tumors, as the subsequent growth and development of children are also a crucial aspect of treatment. Additionally, targeted therapy is quite effective for high-risk cases that are resistant to traditional treatments. With more and more targets being identified, a variety of new therapies have been developed.

MYCN inhibitors

The *MYCN* oncogene encodes transcription factors that regulate multiple cellular processes. *MYCN* amplification is observed in 20–30% of NB cases, and this amplification is strongly correlated with disease stage and aggressiveness (15,16). Multiple studies conducted on pediatric NB patients have consistently shown that those with *MYCN*-amplified tumors experience significantly lower event-free survival (EFS) and overall survival (OS) (17,18). In an analysis of 6,000 patient samples, it was found that patients with wild-type *MYCN* had a better prognosis compared to those with homozygous or heterozygous *MYCN* amplification (16). While there is a clear clinical significance in NB, the development of small molecules directly targeting MYCN is challenging due to the lack of stable and specific binding pockets. The most effective approach for inhibiting MYCN or controlling its regulation seems to be through indirect targeted therapies.

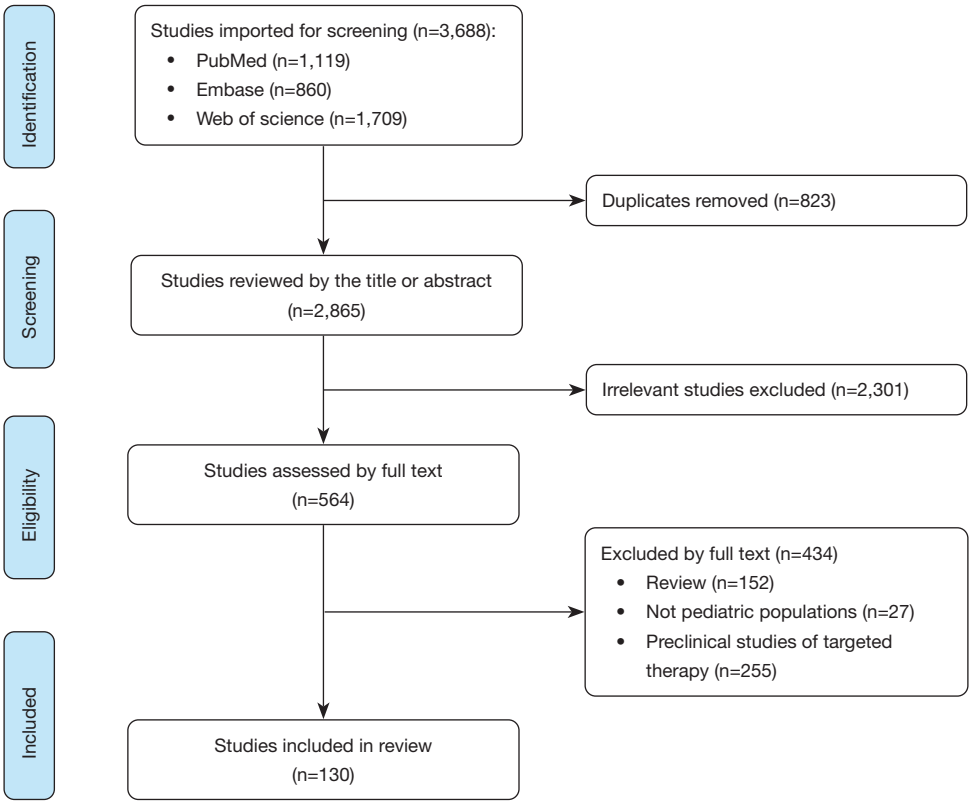

Figure 1 Flow diagram of study selection process.

Table 1 The search strategy summary

Items	Specification
Date of search	1 June 2023 to 31 July 2023
Databases and other sources searched	PubMed, EMBASE, and Web of Science
Search terms used	"Neuroblastoma", "precision medicine", "Targeted therapy", "molecular biomarker"
Timeframe	1985-present
Inclusion and exclusion criteria	Inclusion: human studies, randomized control trials, cohort studies, case control studies, reviews, care guidelines; exclusion: non-English language
Selection process	Identification of articles by the first author; consensus was obtained after discussion

Aurora kinase inhibitors

AURKA is a therapeutic target in a variety of malignant tumors, including NB, and elevated levels of its expression correlate with lower OS and EFS in NB patients. The expression of AURKA is strongly correlated with the state of MYCN amplification, which plays a key role in NB cell growth (19,20). Current studies focus on indirectly interfering with MYCN activity, using drugs or interaction partners of AURKA to promote the stability of MYCN protein (21,22). A phase I clinical trial and pharmacokinetic study in pediatrics evaluated the safety, tolerability, and pharmacokinetic properties of alisertib in pediatric patients, and determined its recommended dosage and preliminary efficacy in pediatric cancer therapy (23). Although alisertib showed compelling pharmacokinetic-pharmacodynamic relationships in preclinical models and adults and was active in pediatric xenograft models, objective remission rates in

children and adolescents treated with alisertib alone were less than 5% in a phase 2 trial of pediatric patients with refractory or recurrent solid tumors or acute leukemia. Therefore, we should explore novel combinatorial strategies that include targeting other oncogenic signaling pathways in order to exploit this pathway while minimizing toxicity (24,25). A clinical study demonstrated that combining the Aurora kinase inhibitor alisertib with irinotecan and temozolomide exceeded the expected anti-tumor activity compared to using irinotecan and temozolomide alone. This combination therapy showed a good response rate and progression-free survival (26,27). Key research indicates that the overexpression of AURKB in NB cells is closely linked to poor prognosis and acquired resistance to carboplatin, a commonly used chemotherapy drug for treating NB. Therefore, inhibiting the AURKB-ERK axis may offer a potential therapeutic strategy to overcome carboplatin resistance in NB patients (28).

Cyclin-dependent kinase (CDK) inhibitor

In eukaryotes, cell CDK plays a key role as a serine/threonine-specific protein kinase responsible for regulation at different stages of the cell cycle, and plays a crucial role in a number of key processes such as cell proliferation, transcription, differentiation, metabolism, and apoptosis. CDKs are divided into two classes: those that regulate the cell cycle, including CDK 1, 2, 4, and 6; and those involved in phosphorylating transcriptional regulators, including CDK 7–9, 12, and 13 (29-31).

The FDA has approved four such drugs, including palbociclib, ribociclib, abemaciclib, and trilaciclib. As the prototypical drug among them, palbociclib has been approved for the treatment of a specific type of advanced breast cancer, namely, estrogen receptor-positive (ER^+) and human epidermal growth factor receptor 2-negative ($HER2^-$) cases (32,33).

The first subsequent clinical trial exploring CDK4/6 inhibitors in pediatric tumors evaluated the maximum tolerated dose of the CDK4/6 inhibitor ribociclib in the treatment of diseases such as NB in children and the recommended dose for phase II trials (34).

Anaplastic lymphoma kinase (ALK) inhibitors

ALK is an oncogene, with mutations including copy number variations, amplifications, and point mutations. *ALK* activating mutations account for approximately 6–10% of NB cases, and an additional 3–4% carry high-risk *ALK* mutations (35). The most common *ALK* mutations in sporadic NB cases are found at the R1275, F1174, and F1245 sites, which are located in the critical regulatory region of the receptor tyrosine kinases structural domain and possess both *in vitro* and *in vivo* transforming abilities (36). The incidence of *ALK* gene mutations increases in recurrent NB, occurring in approximately 20% of cases (37,38). In a high-risk NB cohort, the presence of abnormal *ALK* copy number status is highly associated with clinical phenotypes, such as metastasis at diagnosis and disease-related mortality (39).

Crizotinib is the most extensively studied ALK inhibitor in the treatment of NB. In pediatric clinical trials, it has demonstrated good tolerability, especially in patients with relapsed or refractory cancer, when administered at about double the adult recommended dose (approximately 280 mg/m^2) (40). Additionally, crizotinib has shown success in treating children with anaplastic large cell lymphoma and inflammatory myofibroblastic tumors (41). The ADVL0912 study investigated the application of crizotinib in patients with ALK-abnormal relapsed or refractory NB. This study found that crizotinib's effectiveness was limited in these cases, primarily due to its inability to achieve high enough concentrations to counteract ATP affinity competition (42). Furthermore, a phase II trial (NCT00939770) by the COG evaluated crizotinib's effectiveness in pediatric patients with relapsed or refractory ALK-driven NB. This trial noted that only a minority of patients showed an objective response, which was mainly attributed to the intrinsic resistance of certain ALK hotspot mutations to crizotinib (40). The relative resistance of children with NB carrying F1174 and F1245 residue mutations may be due to enhanced adenosine triphosphate (ATP)-binding affinity, which can be compensated by higher doses of *ALK* inhibitors or alternatives (43). The focus has shifted to enhancing crizotinib's effectiveness through combination therapies. When crizotinib was combined with chemotherapy agents typically used in high-risk NB, a synergistic effect was observed. This synergy is partly why crizotinib has been incorporated into the treatment protocol for high-risk NB patients with *ALK* mutations in the COG phase 3 ANBL1531 trial.

Meanwhile, second- and third-generation ALK inhibitors have been tested in phase I/II. The next-generation *ALK* inhibitors, including ceritinib, ensartinib, entrectinib, lorlatinib, and alectinib, have shown efficacy against crizotinib-resistant mutations. Ceritinib can

overcome crizotinib resistance in non-small cell lung cancer (NSCLC) carrying *ALK* rearrangements (44,45). An open-label, multicenter phase I clinical study detailed the dose escalation and expansion of ceritinib in pediatric patients with ALK-positive, focusing on the drug's safety, tolerability, maximum tolerated dose, and anti-tumor activity (46). A subsequent case reported the successful and sustained remission of refractory metastatic NB in an infant carrying a genetic variant of the *ALKAL2* gene who was in good condition after more than 4 years of continuous and ongoing treatment with entrectinib (47). A phase 1/2 study of entrectinib in pediatric patients with advanced or metastatic solid central nervous system tumors without great treatment options (NCT02650401) is also ongoing another inhibitor, lorlatinib, has been extensively studied to demonstrate its use as an alternative to crizotinib in newly diagnosed high-risk NB patients with ALK genetic alterations (48,49). The results of phase I clinical trials have shown that lorlatinib, either as a stand-alone treatment or in combination with chemotherapy, has demonstrated the potential to be a safe and effective treatment for ALK-driven refractory or recurrent high-risk NB (50). Moreover, Lorlatinib has shown promise in the treatment of adult-onset NB, with 69% of patients presenting durable primary responses and nearly all patients receiving this treatment having objective efficacy responses (51).

Tropomyosin receptor kinase (TrK) inhibitors

Elevated TrkB expression is associated with high-risk NB and low survival rates, whereas increased TrkA expression is associated with low-risk NB and tumors prone to spontaneous regression (52). TrkB has been reported to increase angiogenesis and metastasis. Therefore, Trk is a target for NB therapy (53). Lestaurtinib, entrectinib, larotrectinib are multi-target Trk kinase inhibitors. Initial clinical trials in paediatric patients with refractory, high-risk NB, demonstrated that Lestaurtinib was well tolerated by patients, and effective doses were identified. At higher doses, these drugs not only demonstrated a favourable safety profile, but also showed initial efficacy. This provides an important basis for further research and treatment of NB (54). In phase 1 clinical trials in adults, entrectinib is currently being used as a monotherapy for patients with molecular alterations in neurotrophic tropomyosin kinase receptors (*NTRK)*, *ALK*, and *ROS1* genes (ALKA-372-001, STARTRK-1). Furthermore, when entrectinib is used in combination, it significantly enhances the efficacy of chemotherapy without additional toxicity (55). In numerous clinical trials, larotrectinib has shown quick and sustained effects, substantial disease management success, and a positive safety record in individuals with TRK fusion-positive central nervous system tumors, irrespective of the patient's age or the kind of tumor (56-60).

Angiogenesis inhibitors

Angiogenesis inhibitors play a crucial role in the sustained growth and metastasis of NB, with a high vascular index being associated with poor disease prognosis. These include vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), fibroblast growth factor-2 (FGF-2), transforming growth factor-alpha (TGF-α), platelet-derived growth factor A (PDGF-A), erythropoietin, and angiopoietin (61). High levels of expression of angiogenic factors are strongly associated with high risk and high stage NB, making them sensitive targets for anti-angiogenic therapy (62,63). Antiangiogenic agents include single-pathway inhibitors and multi-pathway inhibitors. Bevacizumab, a single-pathway anti-angiogenic antibody, specifically targets VEGF and inhibits its binding to receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) (64). Following the completion of the COG Phase 1 clinical trial evaluating the safety of bevacizumab in paediatric patients with drug-resistant solid tumours, the efficacy of incorporating bevacizumab into the chemotherapy combination of irinotecan and temozolomide was further investigated. However, this new chemotherapy combination did not significantly improve remission rates, so the current findings do not support the inclusion of bevacizumab in the standard chemotherapy regimen for patients with high-risk NB (64,65). Cabozantinib is a small molecule inhibitor targeting a number of tyrosine kinases including MET, VEGFR2, RET and AXL. Initial Phase 1 studies have shown it to be safe and tolerable in the treatment of recurrent or refractory solid tumours in children. Subsequent single institution case studies have also confirmed the therapeutic potential of cabozantinib. However, additional follow-up studies are still needed to fully evaluate its long-term use (66,67).

Mammalian target of rapamycin (mTOR) inhibitors

mTOR, a protein kinase known to be dysregulated in cancer and metabolic disorders, has been demonstrated through numerous preclinical studies to play a significant role in the occurrence and development of NB (68,69).

Therefore, targeting key protein activities in the mTOR signaling pathway can be a potential therapeutic approach for NB. mTOR inhibitors, mTOR kinase inhibitors, and mTOR regulatory factor inhibitors have been studied for their safety and efficacy in patients with cancer, including NB. Combining mTOR inhibitors with other anticancer drugs may sensitize tumor cells to these treatments. These combinations have the potential to produce additional activity or may delay or prevent the development of resistance to these drugs (69,70). In the treatment of pediatric solid tumors, mTOR inhibitors such as ridaforolimus, sirolimus, temsirolimus, everolimus, and vistusertib have been proven to have good tolerability. Clinical trials have demonstrated their effectiveness, whether used alone or in combination with other drugs. This indicates significant potential for further research in this field (71-75).

Immunotherapy

Immunotherapy has a powerful effect on immunity and immunosuppression and has a greater role in the treatment of high-risk NB and other aggressive solid tumors.

Anti-GD2 antibodies

The bis-sialic acid ganglioside GD2, a glycosphingolipid containing sialic acid, has significant clinical and pathological implications. GD2 is involved in cell–cell adhesion and signal transduction on the cell surface, playing a crucial role in proliferation, angiogenesis, immune evasion, and invasion in both physiological and pathological processes. It is predominantly expressed on the cell surface and is mainly found in the central nervous system and rarely in peripheral nerves and skin melanocytes (76). When GD2 binds to the antibody, immune cells such as macrophages and granulocytes can recognize the tumor cells and initiate an active attack (77). The anti-GD2 monoclonal antibody dinutuximab has been approved as a first-line treatment for high-risk pediatric NB (78-80).

Based on preclinical data and studies of anti-HER2 monoclonal antibodies in combination with chemotherapy for the treatment of breast cancer, a follow-up study found that the addition of Dinutuximab beta to the chemoimmunotherapy combination resulted in significantly better EFS and OS than chemotherapy alone (81-84). However, the further addition of subcutaneously administered IL-2 to dinutuximab beta treatment did not achieve the expected results (85). There is substantial evidence that GM-CSF with anti-GD2 antibodies has demonstrated safety and efficacy in both the consolidation/maintenance phase and the relapsed/refractory disease setting in NB patients (86,87).

Chimeric antigen receptor (CAR) T cells

In the field of treatment of advanced malignancies, despite significant advances, patient survival remains suboptimal. The potential of emerging cellular immunotherapies, such as CAR-T cells, is immense. CAR-T therapy uses recombinant antigen receptors to re-target T-lymphocytes and other immune cells with the aim of improving specificity and functionality against tumours (88). Its main advantage is the ability to rapidly generate T cells that target tumours, bypassing the limitations of natural immunity and thus improving the kinetics of the immune response. Although CAR-T cell therapy is currently used primarily for haematological malignancies, it is being progressively researched in other cancer types such as NB (89).

The latest clinical trials have shown that administering the right amount of GD2 CAR-T cell therapy to patients significantly shrinks tumours. In the group of patients receiving the recommended dose, a 3-year OS rate of 60% and an EFS rate of 36% were observed (90,91). This suggests that GD2 CAR-T cell therapy has great potential for future applications. Nonetheless, this therapeutic approach still faces challenges, including insufficient T-cell persistence, target antigen selection challenges, and the inhibitory effects of the tumour microenvironment. Therefore, more in-depth exploration and improvement in these areas are needed.

Molecular biomarker

Biomarkers can enable specific early detection and prognostic assessment of tumors, allowing for the categorization of NB into different groups to enhance treatment and prognosis. Therefore, the discovery of novel biomarkers is crucial for the advancement of NB detection, prediction, and the development of new targeted therapeutic strategies.

Paired-like homeobox 2B (PHOX2B)

PHOX2B protein is encoded by the *PHOX2B* gene, which is located on chromosome 4p13. As a major

regulator of neuronal, ganglion cell, and neural crest-derived cell development, it plays an important role in the differentiation and maturation of the nervous system. A study suggest that mutations in the *PHOX2B* gene, found in familial and syndromic peripheral NB, may play a role in the development of NB, thereby clarifying the gene's relevance to this condition (92). Warren *et al.* showed that *PHOX2B* has a high (approximately 93–100%) sensitivity in NB tumors and is strongly expressed in undifferentiated and poorly differentiated NBs (93). In addition, a study on *PHOX2B* expression and its mimics in NB revealed exciting results. This study found that *PHOX2B* expression was both sensitive and specific for the diagnosis of NB in tissue specimens as well as in smaller specimens such as cytology specimens (94).

Programmed cell death ligand-1 (PD-L1)

Multivariable Cox regression analysis has indicated that the combination of PD-L1 and HLA class I tumor cell density can serve as a prognostic biomarker for predicting OS in NB patients. The expression of PD-L1 in NB cells can effectively assess the patients' risk of survival and guide the selection of immunotherapy for NB (95,96).

Proviral integration site for Moloney murine leukemia virus (PIM) kinase

PIM serine/threonine kinase is significantly associated with poor OS in patients with solid tumors such as NB and many hematologic malignancies (97). Consequently, the expression of PIM has been identified as a promising prognostic indicator and novel therapeutic target in the treatment of NB (98).

Aryl hydrocarbon receptor (AHR)

The AHR, a ligand-activated transcription factor, influences migration genes through pathways affecting tumor migration (99,100). Studies based on a small group of patient samples have shown a negative correlation between AHR expression and *MYCN* as well as histological grading in NB tumors. Survival analysis has also demonstrated that positive AHR expression is associated with better prognosis (101,102). It has also been demonstrated *in vitro* that *AhR* can mediate the directional migration of human NB cells induced by low concentrations of a potent agonist of *AhR*. However, further research is needed to understand its *in vivo* effects (103).

Ubiquitin C-terminal hydrolase L1 (UCHL1)

UCH is a class of thiol proteases involved in the hydrolysis of polymerized ubiquitin (104). Based on tissue microarray and validation datasets, *UCHL1* has been reported as a biomarker for detecting minimal residual disease in the bone marrow and peripheral blood of NB patients, with its expression positively correlated with differentiation markers. Therefore, *UCHL1* can serve as a prognostic marker for better clinical outcomes in NB (105,106).

Tropomodulin (TMOD)

TMOD is a conserved protein family that cover the ends of actin filaments, stabilizing them and inhibiting their disassembly and turnover (107). Both *TMOD1* and *TMOD2* are highly expressed in NB, and the strong association between high expression of these 2 genes and favorable prognosis in NB makes them independent prognostic markers (108).

The PTPN11 gene

Through exome, genome and transcriptome sequencing, it was found that *PTPN11* has a high frequency of mutations in the RAS/ERK pathway (35,109). These mutations can activate the Ras-Erk signaling pathway, leading to the development of Noonan syndrome (NS), an autosomal dominant disorder. Of note, NS patients are more likely to develop NB (110). The tyrosine phosphatase SHP2 encoded by *PTPN11* acts as an activator of the RAS pathway. It has been pointed out that the combined inhibition of SHP2, MEK, or ERK within the RAS-MAPK pathway can effectively treat drug-resistant recurrent NBs (111,112). Multiple cases have already shown that NS patients develop multiple NBs due to *PTPN11* mutations (113,114).

Liquid biopsy

A diagnostic concept known as "liquid biopsy" has emerged, primarily involving the detection of tumor fragments that have shed into the circulatory system through the analysis of body fluids such as blood and urine. These fragments can be identified and isolated from the blood using high-throughput methods, allowing for subsequent analysis at the single-cell level (115,116). Compared to traditional

diagnostic techniques, liquid biopsy is an attractive non-invasive method for tracking disease progression in real time (117,118).

Circulating tumor DNA (ctDNA)

Analysis of genomic ctDNA reveals the clonal evolutionary dynamics within somatic alterations, which increase upon recurrence and can be targeted for therapy (119). Pediatric tumors carry relatively fewer mutations at diagnosis compared to many adult malignancies, but they often exhibit enriched potential targetable mutations upon relapse. Tissue biopsies do not allow for continuous monitoring, whereas continuous sampling of ctDNA provides us with the ability to assess potential tumor heterogeneity and its evolution, as well as detect genetic changes conferring resistance during treatment (49). Less ctDNA is released into the bloodstream at NB recurrence than at diagnosis. Alterations in ctDNA are prevalent in children with high-risk NB and are valuable for follow-up during treatment (120-122).

Circulating tumor cells (CTCs)

Cell-free DNA (cfDNA) interpretation reveals that aggressive tumors, often associated with areas of necrosis, result in higher DNA release. Its levels are related to staging and tumor burden, increasing up to 50 times higher than normal levels. Rapid reduction in cfDNA concentration in the blood of high-risk NB patients is indicative of a better response to cancer treatment (123). Detection of 17q gain in cfDNA increases with increasing stages of NB. Moreover, the detection of unique markers in cfDNA aligns with tumor load, reducing during initial treatment, vanishing with full remission, and re-emerging at the time of relapse (124,125).

Circulating RNA

Tyrosine hydroxylase messenger RNA (mRNA) demonstrates high sensitivity and specificity in identifying hidden NB cells in both bone marrow and peripheral blood. It can detect NB cells in the bone marrow even in the absence of cytologic evidence of the tumor, with stage 4 children being significantly more likely to be diagnosed than those in stages 1–3 (126,127).

Lactate dehydrogenase (LDH)

LDH is often released following tissue injury and is therefore considered a marker of tissue damage and disease. High levels of LDH have been found to be associated with poor prognosis in a review of outcome studies of melanoma, prostate cancer, and renal cell carcinoma, among others (128). Recent studies have investigated both LDH and serum ferritin as prognostic markers of NB, and they can also be used as factors in NB risk stratification (129,130).

Conclusions

Over the years, there has been a continuous search for more comprehensive and effective methods for diagnosing and treating NB. Precision medicine has demonstrated significant potential in the field of NB, offering diagnostic and therapeutic value. The discovery of biological markers has provided clinicians with a convenient tool for the diagnosis and treatment of NB. However, only a few mutations have been shown to have therapeutic value in NB, and research on NB remains relatively limited. In this context, the development of precision medicine for NB becomes particularly important as it can enhance the accuracy of diagnosis and treatment for patients.

Currently, there is still inconsistency in research findings regarding the treatment of NB, and combination therapies aimed at known treatment targets are continuously being improved. It is necessary to continue conducting research and strive to enhance treatment efficacy while reducing toxicity. The continuous progress of precision medicine has laid a solid foundation for innovation and validation in NB and has paved the way for its future development.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-557/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-557/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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