INPLASY

Molecular Markers and Clinical Outcomes in Pediatric Atypical Spitz Tumors and Spitzoid Tumors of Uncertain Malignant Potential (STUMP): A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202640088

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2026 and was last updated on 24 April 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review is to evaluate the association between molecular alterations and clinical outcomes in pediatric patients diagnosed with atypical Spitz tumors (ASTs) and spitzoid tumors of uncertain malignant potential (STUMPs). Specifically, this review aims to identify and synthesize evidence regarding the prognostic significance of genetic markers within these lesions, including but not limited to TERT promoter mutations, kinase fusions, HRAS mutations, and BAP1 alterations, and their relationship with clinical outcomes, tumor recurrence, sentinel lymph node positivity, regional or distant metastasis, disease-specific survival, and varying follow-up outcomes. Findings from this review will inform risk stratification and clinical decision-making in the management of pediatric spitzoid neoplasms.

Rationale Pediatric Spitz tumors comprise a biologically distinct and heterogeneous group of melanocytic neoplasms that include Spitz nevi, atypical Spitz tumors (ASTs), spitzoid tumors of uncertain malignant potential, and Spitz melanomas. Distinguishing among these diagnoses remains an ongoing challenge due to overlapping clinical and histopathologic features. As a result, there is substantial variability in diagnosis, prognosis, and outcomes, often leading to uncertainty regarding the appropriate extent of surgical intervention and follow-up. Advances in molecular diagnostics have identified a wide range of genetic alterations associated with pediatric Spitz tumors, including point mutations (e.g., HRAS), kinase fusions involving serine/threonine kinases (e.g., BRAF, MAP3K8), receptor tyrosine kinases (e.g., ALK, NTRK1/3, ROS1, RET, MET), and tumor suppressor gene alterations (e.g., CDKN2A, BAP1, PTEN, TERT promoter mutations). Existing systematic reviews in this area have largely focused on histopathologic features, sentinel lymph node biopsy outcomes, or pediatric melanoma broadly, rather than specifically evaluating how distinct molecular alterations in Spitz tumors correlate with varying patient outcomes and presentation characteristics.

Consequently, there is currently minimal consolidated information to guide clinicians in using molecular findings to inform risk stratification or management decisions in pediatric patients. This gap is particularly relevant given emerging data suggesting that certain molecular alterations may be associated with benign behavior (e.g., HRAS mutations), while others may correlate with more aggressive clinical courses (e.g., TERT promoter mutations or CDKN2A loss).
The purpose of this systematic review is to systematically identify, synthesize, and analyze the published pediatric literature evaluating molecular markers in Spitz tumors and their associated clinical, pathologic, and management-related outcomes. Specifically, this review will examine associations between molecular alterations and their impact on biological behavior, including local recurrence, regional or distant metastasis, disease progression, reclassification as melanoma, treatment approach (e.g., excision alone versus sentinel lymph node biopsy), and follow-up course. By integrating molecular data with reported outcomes, this review aims to clarify the prognostic and clinical relevance of specific genetic alterations in pediatric Spitz tumors and to inform more evidence-based diagnostic and management strategies.

Condition being studied Pediatric spitzoid melanocytic neoplasms, including Spitz nevi, atypical Spitz tumors (ASTs), spitzoid tumors of uncertain malignant potential (STUMPs), and Spitz melanomas. These lesions represent a heterogeneous spectrum of melanocytic tumors that occur predominantly in children and adolescents, characterized by overlapping clinical and histopathologic features and a range of molecular alterations with variable prognostic significance.

METHODS

Search strategy Databases:
MEDLINE (Ovid)
EMBASE (Elsevier)
Web of Science Core Collection, Science Citation Index Expanded
Web of Science Preprints Index
CENTRAL, Cochrane Database of Systematic Reviews
Scopus
ProQuest Dissertations

Search Strategy:
An initial strategy was developed and executed in Embase (Elsevier). After reviewing the preliminary results with the team, the agreed-upon strategy contains terms describing the atypical spitz tumor only. Due to the rarity of AST, additional terms for markers or outcomes would limit the retrieval. The Embase search strategy utilizes the “syn” field because it retrieves literature through both controlled vocabulary and entry keywords. The entry keywords will be incorporated into strategies for the other databases: MEDLINE (Ovid), Science Citation Index Expanded (Web of Science), Preprints Index (Web of Science), CENTRAL (Cochrane), Scopus and Dissertations and Theses (ProQuest). No filters will be used.
The Embase search strategy, provided below, retrieved 536 articles on April 21, 2026:
'atypical spitz nevus'/syn OR (atypical NEXT/2 spitz*):ti,ab OR (spitz* NEAR/3 uncertain):ti,ab OR (spitz* NEAR/2 melanocytoma*):ti,ab.

Participant or population Pediatric patients (≤18 years of age) with a histopathologic diagnosis of atypical Spitz tumor (AST), spitzoid tumor of uncertain malignant potential (STUMP), or Spitz melanocytoma.

Intervention Studies reporting molecular or genetic profiling of Spitz neoplasms, including somatic genetic alterations, gene fusions, copy number variations, point mutations, and immunohistochemical surrogate markers relevant to tumor classification, diagnostic stratification, and risk assessment across the Spitz tumor spectrum.

Comparator No comparator group; This is a descriptive systematic review of molecular and genetic profiling of Spitz neoplasms and their associations with biological behavior and clinical outcomes.

Study designs to be included Due to the rarity of atypical Spitz tumors/neoplasms, a broad range of study designs will be included. Eligible designs include prospective and retrospective cohort studies, case series (≥3 patients), case reports with extractable patient data, cross-sectional studies with outcome data, registry studies, and dissertations. Conference abstracts and posters will be included where indexed within selected databases and where molecular and/or outcome data are extractable.

Eligibility criteria Inclusion:
Pediatric patients (≤18 years of age) with a histopathologic diagnosis of atypical Spitz tumor (AST), spitzoid tumor of uncertain malignant potential (STUMP), or Spitz melanocytoma. Mixed adult/pediatric studies will be included only if pediatric-specific data is extractable.

Exclusion:
Adult-only cohorts (>18 years of age). Studies reporting no molecular data or reporting molecular data without associated follow-up or clinical outcome variables.

Information sources Electronic databases, including MEDLINE (Ovid), EMBASE (Elsevier), Web of Science Core Collection (Science Citation Index Expanded), Web of Science Preprints Index, CENTRAL (Cochrane Database of Systematic Reviews), Scopus, and ProQuest Dissertations and Theses, will be searched from inception to the present.

Conference abstracts and poster presentations will be included where indexed within the selected databases or retrieved through database search results. Grey literature will be captured through ProQuest Dissertations and Theses.

Reference lists of included studies and relevant review articles will be manually screened for additional eligible studies.

No date restrictions will be applied. Non-English language studies will be included if sufficient data can be extracted or translated.

Contact with study authors will be undertaken where clarification or additional data are required.

Main outcome(s) The primary outcome is the biological behavior of pediatric atypical Spitz tumors (ASTs), spitzoid tumors of uncertain malignant potential (STUMPs), and spitzoid melanocytomas as characterized by their associated molecular alterations. Biological behavior encompasses local recurrence (present/absent, time in months, number of events), regional metastasis (present/absent, detection method, time in months, number of nodes involved), distant metastasis (present/absent, sites involved, time in months), and benign behavior (defined as no recurrence, no metastasis, and no disease-related death at last follow-up). Secondary outcomes include disease-free survival (time from diagnosis or excision to first recurrence, metastasis, or last event-free follow-up), overall survival (time from diagnosis to death from any cause or last follow-up), disease-specific survival (time from diagnosis to death attributed to AST or Spitz melanoma), disease status at most recent documented follow-up, and mortality attributed to AST or Spitz melanoma. All outcomes will be assessed in relation to molecular alterations, including point mutations (e.g., HRAS, BRAF V600E), kinase fusions involving serine/threonine kinases (e.g., BRAF, MAP3K8) and receptor tyrosine kinases (e.g., ALK, NTRK1/3, ROS1, RET, MET), tumor suppressor gene alterations (e.g., CDKN2A loss, BAP1 loss, PTEN loss), and TERT promoter mutations. Effect measures will include odds ratios, hazard ratios, risk ratios, or descriptive proportions as reported in individual studies. Where quantitative pooling is not feasible due to heterogeneity, outcomes will be synthesized narratively. Timing of outcome assessment will be based on follow-up durations as reported in each included study, with no minimum follow-up period required for inclusion.

Additional outcome(s) Tertiary outcomes include sentinel lymph node biopsy (SLNB) findings and management-related clinical outcomes. SLNB status (positive, negative, or not performed), nodal deposit characteristics, and clinical course following positive SLNB will be extracted. Surgical outcomes will be stratified by approach (excision alone versus excision with SLNB), margin width (wide local excision versus conservative excision), completion lymphadenectomy (performed or not, with associated outcome), adjuvant therapy (type and response), and re-excision (need for additional surgical intervention and outcome). Follow-up duration in months will be recorded for all included patients. Quaternary outcomes include diagnostic reclassification. Explicit reclassification is defined as a documented change in diagnosis after molecular testing, including initial histopathological diagnosis, final post-molecular diagnosis, reclassified category, and proportion reclassified overall and per molecular marker. Implicit reclassification addresses studies published before the 2018 WHO Classification of Skin Tumors (4th edition), which redefined Spitz neoplasms by their molecular drivers rather than morphology alone. Before 2018, melanocytic neoplasms with spitzoid morphology were classified as Spitz tumors regardless of underlying genomic drivers. Under current WHO criteria, only tumors harboring Spitz-associated drivers (e.g., kinase fusions, HRAS mutations) are classified as true Spitz neoplasms; tumors with conventional melanoma drivers (e.g., BRAF V600E/K, NRAS Q61, NF1) are now reclassified as melanoma with spitzoid morphology. This review will identify such cases in older studies and assess their outcomes separately, regardless of whether formal reclassification occurred. Clinical outcomes will be stratified by marker profile: Spitz lineage drivers only versus Spitz lineage drivers plus high-risk markers versus conventional melanoma drivers. The following will be excluded from outcome analysis: cosmetic outcomes without disease or molecular marker correlation, dermoscopic or

imaging findings without clinical outcome correlation, and clinical outcomes reported without corresponding molecular marker data.

Data management Records retrieved from all database searches will be imported into Covidence systematic review software for deduplication, screening, and data extraction. Duplicates will be removed automatically, with manual review of suspected duplicates as needed. Title and abstract screening followed by full-text review will be performed independently by two reviewers, with a third reviewer consulted to resolve disagreements. Interrater agreement will be assessed using Cohen's kappa at both screening stages. Reasons for exclusion at the full-text stage will be documented. Data extraction will be performed independently by at least two reviewers using a standardized form piloted on 3–5 included studies prior to formal extraction, with discrepancies resolved by discussion or a third reviewer. Extracted data will be exported to Microsoft Excel for cleaning, coding, and analysis. A PRISMA flow diagram will document the study selection process. All records and data will be stored within Covidence and institutional cloud storage to ensure integrity and reproducibility.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers. Assessment tools will be selected based on study design: case reports and case series will be evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, and cohort studies will be assessed using the Newcastle–Ottawa Scale (NOS). If randomized controlled trials are identified, the Cochrane Risk of Bias tool (RoB 2) will be used. Discrepancies between reviewers will be resolved by consensus or consultation with a third reviewer. Overall risk of bias for each included study will be categorized as low, moderate, or high based on tool-specific criteria. Results will be summarized in a table and considered when interpreting the strength of the synthesized evidence.

Strategy of data synthesis Due to anticipated clinical and methodological heterogeneity across studies (including variability in diagnostic terminology, molecular testing platforms, and follow-up duration), and the expected predominance of observational studies, case reports, and small case series, a quantitative meta-analysis is not initially anticipated. However, where sufficient homogeneity in study design, outcomes, and molecular categorization exists, quantitative synthesis may be considered. In the absence of suitable data for pooling, findings will primarily be synthesized using a structured narrative approach, supported by summary presentation of study-, patient-, and tumor-level data. Studies will be grouped according to molecular alteration categories, including TERT promoter alterations, kinase fusions (e.g., ALK, ROS1, NTRK1/3, RET, BRAF, MAP3K8), HRAS alterations, BAP1 alterations, and copy number variations or aneuploidy. Cases with multiple concurrent molecular alterations will be classified as “multiple alterations” and described separately. Where data is sufficiently consistent, descriptive statistics will be used to summarize findings. Continuous variables (e.g., age at diagnosis, tumor thickness, mitotic rate) will be reported using mean and standard deviation or median and interquartile range, depending on data distribution and reporting. Categorical variables (e.g., sex, anatomic site, ulceration, sentinel lymph node status, surgical management, recurrence, metastasis, and survival outcomes) will be summarized using frequencies and percentages. Primary outcomes—including disease recurrence, regional or distant metastasis, disease-specific mortality, and diagnostic reclassification (benign behavior versus malignant transformation or reclassification as melanoma) will be summarized overall and stratified by molecular alteration category. Secondary outcomes, including treatment approach (e.g., excision alone versus sentinel lymph node biopsy, margin status, and adjuvant therapy) and follow-up duration, will also be described within each molecular subgroup. Where possible, descriptive comparisons between molecular categories and clinical outcomes will be explored. No formal statistical hypothesis testing is currently anticipated due to the expected heterogeneity and limited sample sizes. Findings will be presented in narrative form, supported by structured summary presentations to facilitate comparison across molecular subgroups and outcomes.

Subgroup analysis If sufficient data are available, the following pre-specified subgroup analyses will be conducted to explore potential sources of heterogeneity and to identify clinically meaningful differences in outcomes:

By molecular alteration category: Spitz-lineage drivers only (e.g., kinase fusions, HRAS mutations) versus Spitz-lineage drivers with co-occurring high-risk markers (e.g., TERT promoter mutations, homozygous CDKN2A loss) versus conventional melanoma drivers (e.g., BRAF V600E/K, NRAS Q61).By specific kinase fusion type: ALK, NTRK1/3, ROS1, RET, BRAF fusions, and MAP3K8 analyzed separately, where case numbers permit.

By WHO classification era: Studies with patient diagnoses occurring pre-2018 (prior to WHO reclassification, excluding BRAF/NRAS-mutated tumors from the Spitz category) versus post-2018, to assess the impact of evolving diagnostic criteria on reported outcomes.

By age group: Young children (≤10 years) versus adolescents (11–18 years), given potential differences in tumor biology and clinical behavior across pediatric age groups.

By SLNB status: SLNB-positive versus SLNB-negative versus SLNB not performed, to evaluate whether sentinel lymph node involvement correlates with disease progression in the context of specific molecular profiles.

By management approach: Excision alone versus excision plus SLNB, to explore whether the surgical approach influences outcomes when stratified by molecular marker category.

Subgroup analyses will be interpreted with careful consideration, given the anticipated small sample sizes, and will be considered hypothesis-generating rather than confirmatory. Results will be presented descriptively with counts and proportions where formal statistical comparison is not feasible.

Sensitivity analysis A formal sensitivity analysis is not planned at this stage. Due to the rarity of atypical Spitz tumors and the anticipated predominance of case reports, small case series, and retrospective cohort studies, findings will be synthesized using a structured narrative approach rather than quantitative meta-analysis. In the absence of pooled effect estimates, traditional sensitivity analyses are not applicable. However, the influence of study quality on overall findings will be considered when interpreting the synthesized evidence, informed by risk of bias assessments using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for case reports and case series and the Newcastle–Ottawa Scale (NOS) for cohort studies. Studies categorized as high risk of bias will be noted, and their contribution to the overall narrative synthesis will be discussed. If sufficient homogeneity in study design, molecular categorization, and outcome reporting is identified during data extraction to permit quantitative pooling for any outcome, sensitivity analyses will be defined and conducted at that stage.

Language restriction No language restrictions will be applied; non-English studies will be included if translation or extractable data are available, otherwise they will be excluded with a documented rationale for exclusion.

Country(ies) involved United States.

Keywords Atypical Spitz; pediatric; molecular markers; TERT; kinase fusions; HRAS; BAP1; clinical outcomes; risk stratification; diagnostic reclassification; systematic review.

Dissemination plans Findings will be disseminated through publication in a peer-reviewed journal and presentation at relevant national or international dermatology, dermatopathology, or pediatric oncology conferences. Results may also be shared through institutional research forums and academic collaborations.

Contributions of each author

Author 1 - Emily Miller - Conceived the study concept and research question. Designed the protocol, eligibility criteria, and outcome framework. Will serve as an independent reviewer for screening, data extraction, and quality assessment. Will lead data synthesis, manuscript drafting, and overall project coordination.
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Author 2 - Julia Herbst - Completed the systematic review registration. Co-authored the protocol, eligibility criteria, and data extraction framework. Will serve as the second independent reviewer for screening, data extraction, and risk of bias assessment. Will contribute to data synthesis and manuscript writing and revision.
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Author 3 - Elizabeth Huggins - Developed, refined, and executed the systematic search strategy across all databases. Managed citation retrieval and deduplication. Will provide ongoing search methodology consultation and review the manuscript for accuracy of search-related reporting.
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Author 4 - Dr. Zisansha S. Zahirsha - Supervising physician overseeing the project. Provided clinical expertise guiding study design, eligibility criteria, and outcome selection. Will review and approve the final manuscript.
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