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Review

Beyond Morphology: Molecular Testing and Integrative Diagnostic Framework for Primary Intracranial DICER1-Mutant Sarcoma in the Era of Precision Pathology

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Abstract

Primary intracranial sarcoma, DICER1-mutant (PIS-DICER1), is a rare malignant mesenchymal tumor of the central nervous system (CNS) with nonspecific clinical, radiological, and histological features. Tumors most often show spindle-cell or pleomorphic morphology and may contain eosinophilic cytoplasmic globules or focal rhabdomyoblastic or cartilaginous differentiation. Immunohistochemistry is variable and supportive rather than defining. Tumor sequencing is central to molecular characterization because it can identify RNase IIIb hotspot variants and additional DICER1 alterations; however, a DICER1 variant alone does not establish primary intracranial origin or germline status. DNA methylation profiling may support classification in selected unresolved cases, although the available reference cohorts remain limited. This narrative review critically synthesizes the clinicopathological, molecular, and clinical evidence and proposes an evidence-informed workflow integrating morphology, immunophenotype, sequencing, methylation profiling, and clinical correlation. Particular emphasis is placed on distinguishing PIS-DICER1 from metastatic pleuropulmonary blastoma and other DICER1-associated CNS neoplasms, interpreting incomplete or discordant molecular results, and separating tumor -associated alterations from inherited predisposition. The proposed framework has not undergone prospective validation, and treatment and prognostic conclusions remain limited by small, heterogeneous, and potentially overlapping published cohorts.

Keywords: intracranial sarcoma; DICER1-mutant; molecular pathology; DNA methylation profiling; integrated diagnosis

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1. Introduction

The fifth edition of the WHO Classification of Tumors of the Central Nervous System recognizes primary intracranial sarcoma, DICER1-mutant, as a distinct mesenchymal, non-meningothelial tumor type [1–3]. This classification reflects the increasing role of molecular findings in CNS tumor taxonomy [4]. Nevertheless, recognition of the entity has not eliminated the practical diagnostic difficulty: its clinical and radiological features are nonspecific, and its spindle-cell or pleomorphic morphology overlaps with glial, meningeal, and other mesenchymal neoplasms [5].

The central diagnostic challenge is not simply to detect a DICER1 variant, but to determine whether the combined morphology, molecular profile, and clinical context support a primary intracranial sarcoma rather than a metastasis or another DICER1-associated

neoplasm [6–8]. Spindle-cell or pleomorphic growth may mimic gliosarcoma, anaplastic meningioma, malignant peripheral nerve sheath tumor (MPNST), or other sarcomas. Immunohistochemical findings are variable, so no single marker or isolated DICER1 alteration is sufficient. The distinction between somatic and constitutional status also affects genetic counseling and surveillance. These questions require different evidence. Morphology and immunophenotype narrow the differential diagnosis, tumor molecular testing supports entity classification, and testing of non-neoplastic tissue establishes constitutional status.

Although the WHO classification establishes the diagnostic entity, it does not provide a detailed decision pathway for several recurring real-world scenarios: a high-grade sarcoma with incomplete or atypical immunophenotype; detection of a single RNase IIIb hotspot without a demonstrable second event; a methylation result with low calibrated confidence or discordance with sequencing; a DICER1-mutant intracranial lesion in a patient with no known DICER1-associated tumor; or a tumor-only sequencing result that cannot resolve germline status. Published cohort studies have characterized the clinicopathological and molecular spectrum, but practical guidance for integrating these distinct evidence streams remains dispersed across case reports, molecular series, and syndrome-specific recommendations.

The practical contribution of this review is an evidence-informed workflow that assigns different roles to each test. NGS assesses the DICER1 variant spectrum, allelic context, and selected co-alterations; methylation profiling assesses whether the tumor-wide epigenetic pattern is concordant with the proposed entity; and clinical evaluation addresses primary site versus metastasis. None of these modalities alone establishes all three diagnostic questions. The workflow is intended to clarify when additional testing is useful and how uncertainty should be reported; it is not a substitute for WHO criteria, expert neuropathology review, or multidisciplinary correlation, and it has not been prospectively validated.

2. Literature Review Approach

This article is a narrative review rather than a systematic review or meta-analysis. PubMed and Web of Science were searched from database inception to September 2026. Search concepts were combined using the following terms and variants: (“primary intracranial sarcoma” OR “primary CNS sarcoma” OR “DICER1-mutant sarcoma”) AND DICER1; DICER1 AND (“RNase IIIb” OR microRNA OR miRNA OR “5p strand” OR “two-hit”); DICER1 AND (“DNA methylation” OR methylation profiling OR classifier); DICER1 AND (pineoblastoma OR “pituitary blastoma” OR “pleuropulmonary blastoma” OR metastasis); and DICER1 AND (treatment OR outcome OR recurrence OR prognosis OR germline OR surveillance). Reference lists of relevant original studies, case reports, reviews, and guidelines were also screened.

Eligible sources included the WHO CNS classification and related classification papers; original clinicopathological or molecular studies; DNA methylation studies; case reports and retrospective case series of PIS-DICER1; studies of other DICER1-associated CNS tumors relevant to the differential diagnosis or molecular mechanism; systematic reviews; and DICER1 predisposition/surveillance guidelines. Studies of extracranial DICER1-associated tumors were retained when they informed the two-hit mechanism or the differential diagnosis. Reports were not included as evidence for PIS-DICER1 outcomes when they described metastatic or extracranial tumors. Experimental studies were considered only when directly relevant to DICER1-mediated miRNA processing or a proposed mechanism.

Because individual cases may be reported in an initial molecular series, a later clinical follow-up, and a subsequent systematic review, study-level reports were compared by author group, institution, accrual period, and case description where available. Potentially overlapping cohorts were flagged, and patient counts from reviews and primary studies

were not added together. For each cohort, the reported denominator was retained for the relevant analysis (for example, all patients, sequenced tumors, methylation-profiled tumors, or patients with available follow-up). Patient-level deduplication was not possible when source publications did not provide sufficient identifiers. Findings were therefore synthesized qualitatively; no pooled estimates or formal risk-of-bias assessment were performed. Diagnostic performance and outcome estimates should be interpreted in light of small samples, selection and publication bias, variable molecular work-up, and limited external validation.

3. DICER1: Core Functions in microRNA Biogenesis and Tumor Predisposition

3.1. An Essential RNase III Enzyme

DICER1 is located at 14q32.13 and encodes an RNase III endoribonuclease involved in the maturation of precursor microRNAs into mature microRNAs [9]. The Dicer protein contains an N-terminal helicase/ATPase domain, a DUF283 (domain of unknown function 283), a PAZ domain, two RNase III domains (IIIa and IIIb) that form the catalytic core, and double-stranded RNA-binding domains [10]; these domains cooperate in substrate recognition, positioning, and cleavage during miRNA maturation [11]. Pathogenic DICER1 alterations can therefore disturb miRNA processing and are found both in sporadic tumors and in the inherited DICER1 tumor-predisposition syndrome [12,13]. In diagnostic practice, the variant should not be interpreted in isolation: variant type (e.g., truncating, missense, splice-site, or copy-number), allelic context (germline versus somatic status, second-hit status, and possible mosaicism), and clinical history (tumor spectrum, age at onset, and family history) need to be considered together.

3.2. DICER1 Gene Mutation: Disruption of miRNA Biogenesis and Oncogenic Pathways

DICER1-associated tumorigenesis is molecularly heterogeneous. In many DICER1-associated neoplasms, tumor formation follows a two-hit pattern in which a loss-of-function DICER1 alteration, often a germline frameshift, nonsense, or splice-site variant in predisposition syndrome, is combined with a second alteration clustered in the RNase IIIb domain [14]. Recurrent RNase IIIb hotspot substitutions affect residues involved in metal-dependent cleavage of precursor miRNAs, including E1705K, D1709N, G1809R, D1810H, and E1813K [15,16]. This pattern is not equivalent to complete loss of all DICER1 activity: the effects of a variant depend on its position and functional consequence, and many tumors retain partial miRNA-processing capacity [16–18].

RNase IIIb hotspot mutations selectively impair 5p-arm cleavage from pre-miRNA hairpins while relatively preserving 3p-arm processing. The mature miRNA repertoire may therefore shift toward 3p-derived products, with reductions or changes in selected 5p-derived miRNAs rather than a uniform decrease in all mature miRNAs [12]. Because miRNAs repress target transcripts through sequence-specific interactions, altered 5p miRNAs can release target mRNAs from post-transcriptional repression and change gene-expression programs. The affected targets and pathways depend on cellular lineage and tumor context; findings from one tumor type should not be generalized to all DICER1-associated neoplasms.

Studies of DICER1-mutated pituitary blastoma illustrate this selective-processing effect. RNase IIIb hotspot variants were associated with an altered 5p/3p miRNA balance, dysregulation of hundreds of miRNAs and mRNA targets, marked PRAME upregulation, and changes involving retinoic-acid receptor, WNT, NOTCH, and PI3K signaling [19]. These findings come from pituitary blastoma and have not been validated as downstream targets in PIS-DICER1. Independent small-RNA sequencing and transcriptomic studies are needed

to define sarcoma-specific target networks and their biological or prognostic significance. Systematic small-RNA sequencing and transcriptomic studies in independent PIS-DICER1 cohorts are still needed to define sarcoma-specific target networks and their biological or prognostic significance.

Reported PIS-DICER1 tumors frequently harbor biallelic DICER1 alterations, usually an RNase IIIb hotspot missense variant together with another inactivating alteration or loss of the other allele [20–23]. Co-occurring TP53 and ATRX alterations and RAS/MAPK-pathway changes, including KRAS, NRAS, and NF1, have been reported in several cohorts [22–27]. FGFR4 alterations and EGFR amplification were found in small subsets of an early molecular cohort [22]. One case carried a PDGFRA mutation together with TP53 and KEAP1 alterations and SMARCB1 loss [28]; this isolated finding does not establish a recurrent molecular signature. The frequencies of these co-alterations vary across cohorts and assays, and none is required for diagnosis or validated for predicting treatment response.

Somatic and germline status should be distinguished explicitly. Tumor-only sequencing may identify a DICER1 alteration but cannot reliably establish constitutional status. When a pathogenic or likely pathogenic germline variant is suspected, testing of an appropriate non-neoplastic specimen and referral for genetic counseling should be considered in accordance with local consent and laboratory procedures. Variant allele fraction alone is insufficient to classify a tumor finding as germline, particularly when tumor purity, copy-number state, mosaicism, or hematopoietic contamination may affect the result.

4. Diagnostic Characteristics of Primary Intracranial DICER1-Mutant Sarcoma

4.1. Clinical Presentation and Neuroimaging Features

Primary intracranial sarcoma, DICER1-mutant, has been reported across a broad age range, although many published cases involve children or young adults [29,30]. The supratentorial cerebral hemispheres are a common site, but other CNS locations have been described. Symptoms, including headache and focal neurological deficits, are nonspecific [31,32].

MRI findings overlap with those of other CNS neoplasms. Hemorrhage, heterogeneous enhancement, cystic change, and variable relationships to the dura or leptomeninges may raise suspicion for an aggressive neoplasm, but none is specific [33–35] (Figure 1). A recent systematic review of the heterogeneous imaging literature reported frequent supratentorial location, intratumoral hemorrhage, and heterogeneous enhancement [36]; a separate case report also described a hemorrhagic presentation [37]. MRI helps define the lesion and its relationship to surrounding structures and may identify a possible extracranial primary origin, but it cannot establish the diagnosis. Radiology reports and multidisciplinary discussions should specify whether the lesion is intra-axial, extra-axial, or trans-compartmental and whether systemic imaging or prior tumor history raises concern for an extracranial primary origin. A history of a DICER1-associated tumor or evidence of a pulmonary or other extracranial lesion should raise concern for metastasis.

4.2. Histopathological Features

Grossly, the tumor has been described as gray-tan and soft to moderately firm. Histologically, it shows a broad spectrum of patterns, most often a spindle-cell or pleomorphic sarcoma arranged in sheets, fascicles, interwoven bundles, or haphazard arrays [32,38]. Storiform, whorled, or herringbone-like areas may be present, sometimes alternating with hypocellular or myxoid regions [21]. Tumor cells may have oval, short-spindled, or elongated nuclei with variable atypia; bizarre or multinucleated cells and brisk mitotic activity have been reported [39]. Eosinophilic cytoplasm and eosinophilic cytoplasmic globules,

which may be PAS-positive, are useful clues but are not invariably present [26,40]. Focal rhabdomyoblast-like cells, gland-like or cord-like structures, and chondroid or myxoid differentiation may occur [22,41,42]. Hemorrhage, necrosis, and vascular proliferation contribute to the morphological variability.

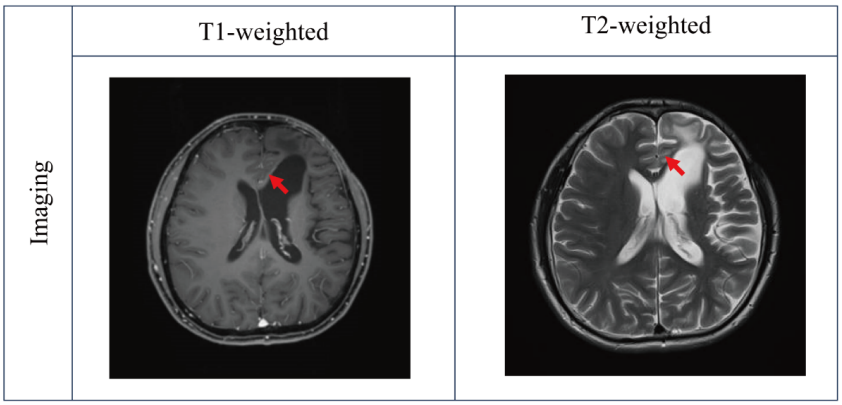


Figure 1. MRI characteristics of primary intracranial DICER1-mutant sarcoma. The arrow indicates the tumor. T1-weighted hypointensity and T2-weighted hyperintensity have been reported but are nonspecific.

Eosinophilic cytoplasmic globules are a useful clue when present, but they are neither obligatory nor pathognomonic [26]. Their absence does not exclude PIS-DICER1. Focal myogenic differentiation also does not, by itself, establish rhabdomyosarcoma. Pathology reports should document the dominant architecture, cytological features, mitotic activity, necrosis, vascular pattern, and any divergent differentiation [43].

4.3. Immunohistochemical Profile

The immunophenotype is variable and should not be treated as a diagnostic signature. In the 22-case molecular series reported by Koelsche et al., vimentin was generally expressed; among 17 evaluable tumors, smooth muscle actin (SMA) was positive in 17/17, desmin in 14/17, and myogenin in 5/17, usually with focal or weak nuclear staining [22]. Other reports have documented cases with absent or only focal myogenic-marker expression [21,23,44]. Tumor cells are commonly negative for glial markers such as GFAP and Olig2, but this finding is supportive rather than conclusive. Loss of INI1, diffuse p53 overexpression, ATRX loss, high Ki-67 labeling, H3K27me3 loss, and TLE1 expression have each been described in subsets; none is specific, and frequencies vary across small series [20,24,25,43,45,46].

The immunohistochemical panel should be selected to test the leading differential diagnoses rather than to accumulate positive and negative stains. A practical first-line panel may include glial markers (GFAP and Olig2), epithelial markers (broad-spectrum cytokeratins and EMA where appropriate), myogenic markers (desmin, myogenin, and MyoD1), neural or melanocytic markers (S100 and SOX10), and selected meningeal or fibroblastic markers (including STAT6 when solitary fibrous tumor is considered). INI1 and BRG1 are important when a rhabdoid tumor is considered; H3K27me3 may contribute to MPNST assessment but is not specific and can be lost in other neoplasms [6,46]. The panel should be adapted to morphology, local assay validation, and tissue availability. Focal lineage-marker expression may reflect partial differentiation and does not necessarily establish a conventional tumor category. Conversely, absence of GFAP or Olig2 supports but does not independently prove a non-glial lineage. Discordant findings should prompt review of internal controls, fixation, staining distribution, and possible intratumoral heterogeneity.

4.4. Detection of DICER1 Mutations via NGS

NGS can identify DICER1 single-nucleotide variants and small insertions/deletions and, depending on assay design, copy-number changes, loss of heterozygosity, and selected structural alterations [22,23,47]. In a morphologically compatible tumor, an RNase IIIb hotspot, together with a second inactivating event or loss of the other allele, provides stronger molecular support than a single hotspot alone [23,45,47]. The assay should adequately cover relevant coding exons and splice junctions and should be capable, where possible, of assessing copy-number changes and allelic imbalance, including larger deletions where assay design permits [48]. Co-alterations such as TP53, ATRX, KRAS, NRAS, NF1, FGFR4, EGFR, and, rarely, PDGFRA may provide biological context; they are not required for diagnosis and should not be interpreted as entity-defining or treatment-predictive finding [22,24,25,28].

Targeted DNA panels differ in their ability to detect large deletions, copy-number changes, structural variants, low-allele-fraction variants, and variants in technically challenging regions. RNA-based assays may help assess selected fusion-defined differential diagnoses, but they do not replace adequate DICER1 sequence and copy-number assessment. If a likely pathogenic DICER1 alteration is not detected despite strong morphological suspicion, tumor cellularity, necrosis, DNA quality, coverage metrics, variant-calling thresholds, and the assay's ability to detect copy-number loss or loss of heterozygosity should be reviewed [29,49]. Macro-dissection, repeat extraction, an orthogonal assay, or broader sequencing may be appropriate.

Variant interpretation should distinguish pathogenic or likely pathogenic alterations from variants of uncertain significance (VUS). A rare DICER1 variant, particularly one classified as uncertain or detected at a low variant allele fraction, is insufficient to establish causality. A second event may remain undetected if the assay cannot detect the relevant alteration class. Copy-number and allelic-imbalance analyses, together with review of sequencing metrics, may help identify a second event. If the findings remain incomplete, the report should specify the limitation and whether further testing is likely to change the classification.

Tumor sequencing and germline testing answer different questions. Variant allele fraction in a tumor-only assay is influenced by tumor purity, copy-number state, clonality, and normal-cell admixture; a value near 50% is compatible with, but does not prove, a germline event. If constitutional status would alter counseling or surveillance, an appropriate non-neoplastic specimen should be tested by a qualified laboratory. The selected specimen and assay should account for possible mosaicism and, where relevant, hematopoietic contamination. Germline variant classification should follow established DICER1-specific guidance rather than being inferred from tumor sequencing alone [50,51].

Primary intracranial sarcoma and metastatic pleuropulmonary blastoma (PPB) may share DICER1 RNase IIIb hotspot mutations; the hotspot itself therefore cannot establish the site of origin [52–54]. Reported differences in co-alterations or copy-number profiles come from limited datasets and are not validated stand-alone classifiers [55]. Assessment should include age, prior tumor history, systemic imaging, review of previous pathology, constitutional testing when indicated, and the complete molecular profile. A negative history does not rule out an occult or previously unrecognized extracranial primary. If the origin remains uncertain, the report should state this rather than assign a primary intracranial site from the brain specimen alone.

4.5. Methylation Profile

DNA methylation profiling can provide additional diagnostic evidence when morphology, immunohistochemistry, and sequencing do not resolve the classification [56]. The original molecular series identified a distinctive methylation signature among primary

intracranial spindle-cell sarcomas with DICER1 alterations, and a large pediatric cohort subsequently found that all 28 methylation-profiled tumors clustered with PIS-DICER1 [22,23]. Additional case reports, real-world implementation studies, and a more recent five-case series have demonstrated the potential value of methylation profiling when combined with sequencing [25,57–61]. Together, these studies identify a recurrent epigenetic pattern but do not establish classifier performance across routine laboratories or clinical settings.

Subsequent integrative analysis of DICER1-associated mesenchymal neoplasms has further characterized this epigenetic profile. PIS-DICER1 was identified as a distinct methylation class, separate from low-grade mesenchymal tumors and other sarcomas with DICER1 alterations. Among the DICER1-associated mesenchymal classes examined, PIS-DICER1 showed the lowest global DNA methylation levels. Differentially methylated probes and regions were predominantly hypomethylated and distributed across the genome; a similar, although less pronounced, pattern was also observed in CpG islands, gene bodies, and promoter regions. The greatest overlap in differentially methylated regions was observed between PIS-DICER1 and other sarcomas with DICER1 alterations, indicating an epigenetic relationship between these sarcomatous groups while retaining distinguishable methylation classes. Genes overlapping these regions were enriched for gene-ontology terms related to RNA/miRNA-mediated gene silencing. Methylation-array-derived copy-number profiles were complex and heterogeneous rather than defining a uniform recurrent pattern. These findings support global hypomethylation as a component of the PIS-DICER1 methylation phenotype; however, its mechanistic significance and diagnostic specificity require further evaluation in larger independent cohorts.

Pre-analytic factors are important. Small biopsies, extensive necrosis, prior treatment, decalcification, and low tumor-cell content can compromise methylation analysis. The most representative tumor-rich area should be selected, and limitations affecting interpretation should be documented. Copy-number profiles derived from methylation arrays can provide clues but may not substitute for a dedicated assay when a specific amplification or deletion must be established. If methylation classification conflicts with sequencing, review sample identity, tissue selection, tumor purity, classifier version, and alternative DICER1-associated entities. Repeat testing on another block or consultation with a specialist molecular neuropathology laboratory may be appropriate.

Methylation results should be interpreted with the calibrated score, classifier version and reference-class composition, tumor purity, DNA quality, and histological **differences**. A low-confidence or unclassified result may reflect an underrepresented class, low tumor purity, degraded DNA, or an atypical neoplasm; it should prompt technical review and reconsideration of the differential diagnosis, not automatic exclusion or reclassification. Methylation profiling is an adjunct to integrated diagnosis. On its own, it cannot establish primary site or germline predisposition and should be interpreted alongside morphology, DICER1 testing, and clinical assessment for meta-static disease.

4.6. Other Differential Diagnosis

The main differential diagnoses are summarized in Table 1. MPNST may show spindle-cell morphology, focal S100/SOX10 expression, and H3K27me3 loss; these findings are not decisive without an appropriate nerve-associated context. AT/RT may contain rhabdoid cells, making SMARCB1/INI1 and, when appropriate, SMAR-CA4/BRG1 assessment important. Nuclear STAT6 expression and a NAB2::STAT6 fusion support solitary fibrous tumor, whereas pattern-less architecture alone is insufficient. Gliosarcoma requires assessment for an infiltrative glial component and appropriate glial and molecular work-up. Pineoblastoma and pituitary blastoma are important DICER1-associated CNS mimics; anatomical site, age, morphology, and molecular context help distinguish them from PIS-DICER1 [32,62,63].

Table 1. Differential diagnosis of primary intracranial sarcoma, DICER1-mutant: discriminatory features and interpretive pitfalls.

Differential Diagnosis	Clinical/Anatomic Clues	Discriminatory Morphology or Ancillary Findings	Molecular Findings and Key Pitfall
Metastatic pleuropulmonary blastoma (PPB)	Child or young patient; prior or concurrent pulmonary/other DICER1-associated tumor; systemic lesions	Compare intracranial tumor with prior extracranial pathology; clinical imaging and staging are essential	PPB and PIS-DICER1 may share RNase IIIb hotspots. A shared hotspot cannot establish primary site; clinical and pathological correlation is required
Pineoblastoma	Pineal-region mass, usually in the first two decades; obstructive hydrocephalus may be present	Primitive small-cell/pineal parenchymal tumor phenotype; use appropriate pineal tumor markers and methylation-based subtype assessment	DICER1 alterations occur in a subset; DICER1-related pineoblastoma may show biallelic loss-of-function configurations distinct from the common RNase IIIbplus-second-hit pattern in PIS-DICER1. DICER1 positivity is not sarcoma-specific
Pituitary blastoma	Infant or very young child; sellar/suprasellar mass; Cushing syndrome, ophthalmoplegia, or diabetes insipidus	Rathke-type epithelial rosettes/glands admixed with primitive cells and secretory elements; ACTH and other neuroendocrine hormones may be expressed in subsets	Strongly associated with germline DICER1 predisposition and a second tumor-associated DICER1 event; location and characteristic epithelial/endocrine morphology distinguish it from PIS-DICER1
MPNST/malignant triton tumor	Fascicular spindle-cell growth; possible nerve association; malignant triton tumor may show rhabdomyoblastic differentiation	S100/SOX10 may be focal; H3K27me3 may be lost; evaluate nerve relationship and clinical setting	H3K27me3 loss and focal neural-marker expression are not specific; neither alone establishes MPNST
Atypical teratoid/rhabdoid tumor (AT/RT)	Often pediatric; poorly differentiated or rhabdoid morphology	Loss of INI1/SMARCB1 or, in a subset, BRG1/SMARCA4 supports the relevant molecular subtype	Some PIS-DICER1 cases can show INI1 loss; interpret in a complete differential and molecular context
Gliosarcoma/high-grade glioma	Infiltrative growth; possible glial component, necrosis, or microvascular proliferation	GFAP and Olig2 may support glial differentiation; evaluate for a conventional gliomatous component	Negative glial markers alone do not prove sarcoma; limited biopsies may undersample a glial component
Anaplastic meningioma	Dural association or residual meningothelial morphology may be present	EMA and SSTR2A may support meningioma, but expression may be reduced in high-grade tumors	No single immunostain establishes the diagnosis; integrate location, morphology, and molecular findings
Solitary fibrous tumor (SFT)	Often dural-based; patternless spindle-cell growth and collagenous stroma	Nuclear STAT6 expression supports NAB2::STAT6 fusion-associated SFT	Correlate STAT6 with molecular findings; patternless architecture alone is insufficient
Rhabdomyosarcoma	Rhabdomyoblasts or convincing skeletal-muscle differentiation pattern	Desmin, myogenin, and MyoD1 support myogenic differentiation when diffuse and coherent with morphology	Focal myogenic-marker expression may occur in PIS-DICER1 and is not sufficient for conventional rhabdomyosarcoma

Figure 2 summarizes the diagnostic workflow. It is evidence-informed and has not been prospectively validated. Review the clinical history and imaging for a possible extracranial primary or another DICER1-associated CNS tumor. Use morphology to select the immunohistochemical panel. For an otherwise unexplained high-grade spindle-cell or pleomorphic sarcoma, sequence the tumor for DICER1 hotspots and a possible second event, checking assay coverage and copy-number/allelic limitations. Consider methylation profiling when morphology and sequencing remain inconclusive or discordant, and report the classifier score and technical quality. If a germline alteration is suspected, test non-neoplastic tissue and refer for genetic counseling. When the tumor entity or primary site remains unresolved, state this in the report.

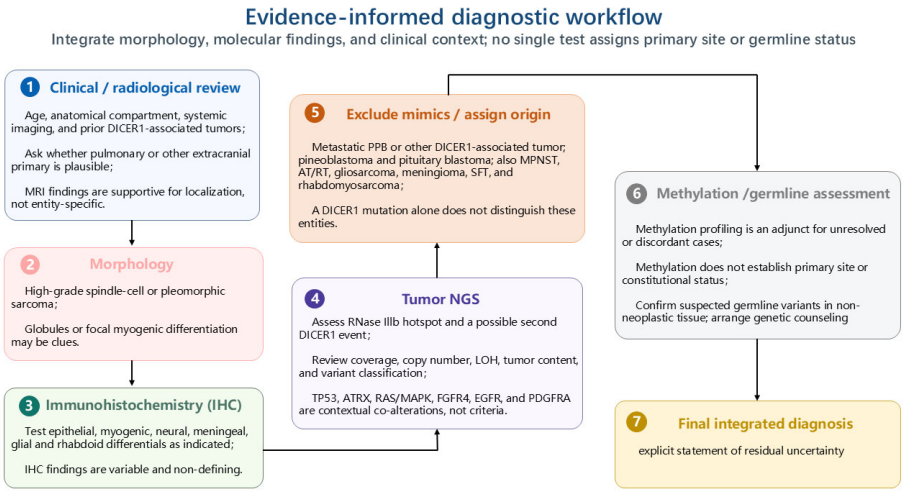


Figure 2. Integrated diagnostic workflow for primary intracranial DICER1-mutant sarcoma.

4.7. Integrated Reporting and Communication of Uncertainty

The pathology report should give the preferred diagnosis using current WHO terminology and summarize the findings that support it: morphology, immunophenotype, DICER1 alteration(s), assay, and methylation result and confidence, if available. It should also identify unresolved issues concerning primary site or germline status and indicate whether further testing could address them. A single alteration should not determine the classification when other findings are discordant; use a descriptive diagnosis when the integrated evidence is insufficient.

Communication among neuropathology, molecular pathology, radiology, neurosurgery, neuro-oncology, and clinical genetics is essential. A DICER1-associated molecular result may prompt review of a prior extracranial specimen or additional imaging; a pulmonary lesion on imaging may, in turn, support metastatic disease. The classification may need to change as clinical, radiological, or molecular information becomes available, and the final report should document the basis for that change.

5. Treatment and Prognosis

There is no prospectively validated, disease-specific treatment protocol for PIS-DICER1. The available clinical evidence comes from molecular cohorts, retrospective case series, case reports, and systematic reviews that differ in eligibility criteria and may include overlapping patients. A large pediatric Peruvian cohort included 70 patients with histologically diagnosed primary CNS sarcoma; among the molecularly characterized subsets, 28/28 tumors were classified as PIS-DICER1 by methylation profiling and 26/27 sequenced tumors harbored DICER1 alterations. Among 46 patients with nonmetastatic disease treated with combination therapy, the reported 2-year progression-free survival (PFS) and overall survival (OS) rates were 58% and 71%, respectively, after a median follow-up of 2.1 years [23]. These outcome estimates apply to the specified nonmetastatic treatment subgroup, not to all 70 patients.

A separate PIS-focused systematic review published in 2025 included eight studies and 10 biopsy-proven patients. Gross-total resection (GTR) was reported in 5/10 patients, 7/10 received adjuvant chemotherapy plus radiotherapy, and 5/10 had stable disease at last reported follow-up. Follow-up duration was available from only five studies and ranged from 6 weeks to 4 years (estimated mean, 17.5 months) [64]. This mean applies only to the studies that reported follow-up, not to all 10 patients.

A broader 2022 systematic review aggregated 118 DICER1-mutant malignant CNS neoplasms, including 52 PIS-DICER1 tumors together with pineoblastoma, pituitary blastoma, and embryonal tumor with multilayered rosettes. In the pooled analysis, gross-total resection and radiotherapy were associated with longer OS. Because the analysis combined biologically distinct entities and relied on retrospective reports, this association cannot be interpreted as a PIS-specific treatment effect [32]. The review reported a median OS of approximately 21 months for the PIS subgroup, but heterogeneous case ascertainment, follow-up, and treatment limit the use of this figure as an individualized prognostic estimate.

One case report also described preclinical investigation, but these data do not establish a disease-specific clinical regimen [65]. Outcomes have varied across other cohorts. In an eight-patient young-adult series (median age 20 years), all patients ultimately developed progression despite surgery and adjuvant therapy; median time to progression was 14.5 months and median OS was 30.8 months [31]. In a seven-patient series of patients aged 10–32 years, all were alive at the May 2024 follow-up cutoff, although follow-up duration and completeness varied [21]. A 2026 five-case series reported two patients alive without evidence of disease at 26.7 and 39.3 months and one disease-related death at 20.1 months among cases with available outcome data [61]. The cohorts differ in age, selection, treatment, molecular work-up, and follow-up, so their outcomes are not directly comparable.

Maximal safe resection is generally considered when feasible because it provides diagnostic tissue and reduces tumor burden; it should not be pursued at the expense of unacceptable neurological morbidity. Postoperative radiotherapy and systemic chemotherapy have frequently been used, especially for high-grade tumors, residual disease, or recurrence, but regimens are heterogeneous and commonly adapted from other pediatric or adult sarcomas and malignant CNS tumors. Reported approaches include ifosfamide/carboplatin/etoposide-based regimens, doxorubicin/ifosfamide, and other multi-agent protocols [23,31,64,66,67]. Individual reports of tumor control after surgery plus radiotherapy alone or stereotactic radiotherapy with chemotherapy are clinically informative but cannot establish superiority of a modality or regimen [66,67].

Follow-up should include serial contrast-enhanced brain MRI, with the schedule tailored to the clinical course and treatment received. Repeat resection may be considered for accessible local recurrence when it can reduce tumor burden, relieve mass effect, or clarify the diagnosis. Salvage radiotherapy, re-irradiation, and additional systemic therapy require individualized assessment because evidence is sparse and cumulative toxicity may be substantial. A reported child with a germline DICER1 pathogenic variant developed local recurrence approximately 2.5 years after initial multimodal therapy [45].

No DICER1 variant class, second-hit configuration, co-mutation pattern, or methylation profile has been validated to guide treatment selection or estimate an individual patient's prognosis. RAS/MAPK-pathway alterations may be biologically relevant, but they do not establish sensitivity to a targeted agent in the absence of disease-specific clinical data. Treatment should be selected by a multidisciplinary team, taking into account the small sample sizes, heterogeneous regimens, variable follow-up, and publication bias in the available reports.

Current management centers on maximal safe resection, with radiotherapy and systemic chemotherapy considered individually and close radiological surveillance. The available evidence does not establish a standard regimen or reliable treatment-effect estimates. International registries should use standardized definitions for extent of resection, radiotherapy dose and field, systemic regimens, molecular findings, recurrence, toxicity, and longitudinal outcomes. Table 2 summarizes selected published clinical cohorts and systematic reviews of PIS-DICER1.

Table 2. Summary of selected published clinical cohorts and systematic reviews of PIS-DICER1.

Study/Design/Population	Clinicopathological and Molecular Findings	Treatment and Reported Outcomes	Interpretive Limitations
Koelsche et al., 2018; molecular cohort, $n = 22$ [22]	18 patients were children. A distinctive methylation signature was identified; DICER1 hotspot variants in 21/22, TP53 alterations in 12/22, and MAPK-pathway alterations in 17/22 (including KRAS, NF1, FGFR4, NRAS, and EGFR amplification).	The study primarily established clinicopathological and molecular features; it was not designed as a comparative treatment study.	Early discovery cohort; molecular and methylation reference data underpin later studies and should not be counted as independent cases when reports overlap.
Diaz Coronado et al., 2022; pediatric CNS sarcoma cohort, $n = 70$ [23]	Median age 6 years (range 2–17.5); 66/70 tumors were supratentorial. Molecular subsets: methylation classified 28/28 as PIS-DICER1; DICER1 variants in 26/27 sequenced tumors; TP53 in 22/27; RAS-pathway alterations in 19/27.	Among 46 nonmetastatic patients treated with combination therapy, 2-year PFS was 58% (95% CI 44–76%) and 2-year OS was 71% (95% CI 57–87%); median follow-up 2.1 years.	The full cohort was 70 histologically diagnosed CNS sarcomas; only subsets had methylation or sequencing. Survival estimates apply to the defined nonmetastatic treatment subgroup.
Cardona et al., 2023; young-adult series, $n = 8$ [31]	Median age 20 years (range 17–29); seven supratentorial and one cerebellar tumor. Histology included fusiform, undifferentiated, and chondrosarcomatous patterns; two germline DICER1 variants; TP53 and MAPK-pathway co-alterations were common.	Seven patients received surgery, radiotherapy, and ICE chemotherapy; one received VAC. Best objective response rate was 75%; all patients eventually progressed; median time to progression was 14.5 months and median OS was 30.8 months.	Small selected young-adult cohort; treatment was not randomized, and the findings should not be generalized to children or all PIS-DICER1 patients.
Ou et al., 2024; clinicopathological series, $n = 7$ [21]	Age 10–32 years (median 23); six males. Six tumors had eosinophilic globules; three showed rhabdomyoblastic differentiation; 3/7 had focal desmin, 3/7 ATRX loss, and 4/7 a mutant-pattern p53 stain. All seven had somatic DICER1 variants; five carried p.E1813D.	All seven patients were alive at the May 2024 cutoff; longer-term outcome estimates were not established.	Single-center retrospective series; follow-up duration and treatment details were not uniform.
Vuong et al., 2022; systematic review of DICER1-mutant malignant CNS neoplasms, $n = 118$ [32]	Included ETMR ($n = 9$), pineoblastoma ($n = 30$), PIS ($n = 52$), and pituitary blastoma ($n = 27$); median age in the PIS subgroup was 6.5 years.	GTR and radiotherapy were associated with longer OS in the pooled analysis; the reported median OS for the PIS subgroup was approximately 21 months.	Pooled analysis combines distinct tumor entities and heterogeneous retrospective data. The GTR/RT association is not a PIS-specific causal effect.
Qadri et al., 2025; PIS-focused systematic review, 8 studies/10 patients [64]	Ten biopsy-proven cases; DICER1 alterations reported in all. Patient-level reporting varied across source studies.	GTR in 5/10; adjuvant chemotherapy plus radiotherapy in 7/10; stable disease in 5/10. Follow-up reported by five studies ranged from 6 weeks to 4 years (estimated mean 17.5 months).	The mean follow-up is based on the subset of studies reporting follow-up, not complete follow-up for all 10 patients. The review may include cases reported elsewhere.
Gestrich et al., 2026; five additional cases [61]	Age 6–40 years; includes an infratentorial case, an adult case, and one germline DICER1 carrier. All had RNase IIIb hotspots; 2 had concurrent DICER1 loss; 3 had KRAS alterations, and one of these also had TP53 alteration.	Among cases with outcome information, two patients had no evidence of disease at 26.7 and 39.3 months; one died of disease at 20.1 months.	Only five cases; outcomes available for a subset and follow-up remains limited.
Selected case reports: Wang et al. (2023), Huang et al. (2024), Kappa et al. and Fujita et al. (2026), and Wu et al. (2026) [28,66–70]	Individual reports describe varied presentations and molecular profiles; a recent case identified DICER1, TP53, PDGFRA, and KEAP1 alterations with SMARCB1 loss.	Isolated reports include tumor control after resection plus radiotherapy or stereotactic radiotherapy with doxorubicin/ifosfamide; the PDGFRA-positive case progressed at 10 months.	Single-patient observations are hypothesis-generating and cannot establish efficacy, prognostic significance, or a recurrent PDGFRA-associated subtype.

Abbreviations: PIS-DICER1, primary intracranial sarcoma, DICER1-mutant; GTR, gross-total resection; OS, overall survival; PFS, progression-free survival; ICE, ifosfamide/carboplatin/etoposide; VAC, vincristine/actinomycin/cyclophosphamide. Counts from primary cohorts and reviews are not additive; possible overlap among published cases is acknowledged where patient-level deduplication was not possible.

6. Identification of At-Risk Individuals and Recommended Surveillance Strategies

A diagnosis of PIS-DICER1 should prompt consideration of whether the tumor alteration is somatic or germline [49,50]. Young age, a personal or family history of DICER1-associated tumors, multiple related neoplasms, or a molecular pattern suggestive of constitutional predisposition should prompt referral for genetic counseling. Tumor-only sequencing cannot reliably establish germline status; confirmatory testing requires an appropriate non-neoplastic specimen and consent in accordance with local practice. DICER1 tumor-predisposition syndrome is inherited in an autosomal dominant manner, but clinical expression is pleiotropic, and penetrance is incomplete and variable [71]. Reported risks are age- and organ-dependent: cumulative risk for any DICER1-associated neoplasm has been estimated at approximately 5.3% by age 10 years and 9.4% by age 20 years, compared with 0.16% by age 10 years in the general population [72]. PPB most often presents in early childhood; ovarian sex cord–stromal tumors occur predominantly before age 40 years; and multinodular goiter is common in carriers. These estimates describe DICER1 predisposition syndrome and should not be applied directly to an individual patient with PIS-DICER1.

After a pathogenic or likely pathogenic germline variant is confirmed, counseling should address implications for the patient and at-risk relatives, including the 50% chance of transmission to each biological child. Cascade testing and surveillance should follow current DICER1-specific guidance and be individualized by a clinical genetics or DICER1-experienced team. Published recommendations include age-specific clinical review and surveillance of the lungs, kidneys, thyroid, and reproductive tract [73–75]. Variants of uncertain significance should not by themselves direct predictive testing or surveillance [50]. For a patient with PIS-DICER1, these recommendations apply when a constitutional pathogenic or likely pathogenic variant is confirmed.

CNS surveillance is less prescriptive. Current guidance emphasizes symptom review and prompt brain MRI when neurological or endocrine symptoms raise concern; shared decision-making about screening brain MRI in asymptomatic individuals may be considered in selected age groups or clinical contexts [73,74]. No PIS-DICER1-specific imaging schedule has been validated for all asymptomatic carriers. Surveillance for ciliary body medulloepithelioma should follow syndrome-specific guidance and individual risk assessment [75].

7. Discussion and Future Perspectives

Across published cohorts, the recurring histological pattern is a spindle-cell or pleomorphic sarcoma, sometimes with eosinophilic globules or focal myogenic differentiation; none of these features is obligatory or pathognomonic. Many tumors harbor DICER1 RNase IIIb hotspot alterations with a second inactivating event. TP53 and RAS/MAPK alterations recur in several series, whereas ATRX, FGFR4, EGFR, PDGFRA, and other co-alterations are less consistent or supported by smaller numbers. Current data do not show that any hotspot residue, allelic configuration, co-mutation pattern, or methylation profile predicts recurrence, survival, or treatment response.

NGS and methylation profiling provide different types of diagnostic information. NGS identifies sequence-level alterations, possible biallelic events, copy-number changes, and selected co-mutations; constitutional testing of an appropriate non-neoplastic specimen is needed to establish germline status. Methylation profiling assesses the tumor-wide epigenetic pattern and can support classification when histology and sequencing are ambiguous. Its use remains constrained by the small PIS-DICER1 reference cohorts and limited independent validation.

Primary intracranial origin cannot be assigned from the brain specimen alone. Metastatic PPB can share DICER1 hotspots and overlapping sarcomatous morphology, and a history of DICER1 syndrome may be absent or unrecognized. Pineoblastoma and pituitary blastoma also harbor DICER1 alterations but are distinguished by anatomical site, age, morphology, endocrine phenotype, and molecular context. Assignment of PIS-DICER1 therefore requires review of clinical history, systemic imaging, and relevant prior pathology, in addition to tumor findings.

The proposed workflow is a practical interpretation of the WHO-recognized entity and published diagnostic studies, not a validated decision rule. Surveillance should follow established DICER1 tumor-predisposition guidance when a constitutional pathogenic or likely pathogenic variant is confirmed. At present, no molecular alteration or methylation profile has shown a sufficiently reproducible association with tumor behavior or treatment response to support routine risk stratification.

Liquid biopsy remains investigational in CNS tumors, and its role in PIS-DICER1 has not been established. No PIS-DICER1-specific study has demonstrated validated diagnostic or surveillance utility. General studies of circulating tumor DNA in CNS tumors provide a rationale for further work, but analytical sensitivity, optimal specimen type (plasma versus cerebrospinal fluid), tumor-derived signal, concordance with tissue testing, and clinical utility must be established before liquid biopsy can be used in routine practice [76,77].

8. Limitations

The evidence base for PIS-DICER1 is limited by the small number of published patients and the predominance of case reports, small retrospective series, and secondary reviews. These study designs restrict generalizability and prevent reliable estimates of diagnostic sensitivity, treatment efficacy, recurrence risk, and survival. Publication and selection biases are likely because unusual morphology, distinctive molecular profiles, and favorable or adverse outcomes may be preferentially reported. Cohort overlap is also possible: individual patients may appear in an initial molecular series, a later clinical follow-up, and subsequent systematic reviews. This review compares study characteristics and avoids adding review-level and primary-cohort counts, but patient-level deduplication is not possible when source publications lack identifying details.

Molecular characterization is incomplete in some published cases. Paired tumor-normal sequencing, germline testing, copy-number and allelic analysis, and independent methylation profiling are not uniformly available, and assays differ in coverage and sensitivity. Methylation reference cohorts remain small, and the proposed diagnostic workflow has not undergone large prospective external validation. Follow-up is variable and often short, so associations between DICER1 variants, second-hit patterns, co-mutations, methylation profiles, treatment response, recurrence, and survival remain unproven. Prospective multicenter studies using standardized diagnostic, molecular, treatment, and outcome data are needed to validate the workflow and improve clinical recommendations.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbrev.	Definition
CNS	central nervous system
NGS	next-generation sequencing
RNase	ribonuclease
miRNA	microRNA
PAS	periodic acid–Schiff
SMA	smooth muscle actin
PIS-DICER1	primary intracranial sarcoma, DICER1-mutant
PPB	pleuropulmonary blastoma
MPNST	malignant peripheral nerve sheath tumor
AT/RT	atypical teratoid/rhabdoid tumor
SFT	solitary fibrous tumor
GTR	gross-total resection
OS	overall survival
PFS	progression-free survival
ICE	ifosfamide/carboplatin/etoposide
VAC	vincristine/actinomycin/cyclophosphamide
VUS	variant of uncertain significance

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