Pediatric Pure Erythroid Leukemia: Diagnostic Challenges, Immunophenotypic Features, Molecular Pathogenesis, and Practical Diagnostic Approach

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Abstract

Pure erythroid leukemia (PEL), termed acute erythroid leukemia in the 2022 World Health Organization classification, is an uncommon and aggressive acute myeloid neoplasm in which immature erythroid precursors predominate within the marrow and show marked maturation arrest. Pediatric recognition remains challenging because adult PEL is usually defined by biallelic TP53 alteration and complex karyotype, whereas reported childhood disease encompasses NUP98-, NFIA-, CIC-, and other fusion-defined presentations. This structured narrative review summarizes classification, morphology, immunophenotype, molecular pathogenesis, genotype-phenotype heterogeneity, differential diagnosis, treatment, prognosis, measurable residual disease (MRD), and a practical diagnostic workflow. Evidence was weighted according to source type, with priority given to WHO and International Consensus Classification documents, multicenter pediatric cohorts, comparative molecular studies, and molecularly characterized case series. A pediatric PEL-specific treatment standard has not yet been established. Most reported children receive protocol-based therapy for acute myeloid leukemia, while hematopoietic stem-cell transplantation is considered according to adverse genetics, treatment response, MRD, relapse status, and extramedullary involvement. The largest pediatric cooperative-group dataset reported 5-year overall and event-free survival of approximately 20% for the PEL subset, although genotype-specific outcome estimates remain sparse. MRD assessment should combine baseline immunophenotypic documentation with molecular tracking when a stable fusion or mutation is available, and cerebrospinal fluid monitoring should be considered when central nervous system disease is documented. Integrated diagnosis and management require coordinated morphology, flow cytometry, immunohistochemistry, cytogenetics, DNA sequencing, and early RNA-based fusion testing. This approach should explicitly account for the limited evidence base underlying current recommendations.

Keywords

pediatric acute myeloid leukemia; pure erythroid leukemia; molecular pathogenesis; immunophenotyping; erythroblastic sarcoma

Introduction

Pure erythroid leukemia (PEL) is an exceptionally uncommon acute leukemia and remains a difficult diagnosis in pediatric hematopathology. In conventional acute myeloid leukemia (AML), the abnormal population is usually recognizable as myeloblasts; in PEL, the malignant compartment is composed mainly of immature erythroid precursors with abrupt maturation arrest. This lineage pattern creates several diagnostic pitfalls. Peripheral blood may contain few obvious blasts, aspirates may be dilute or necrotic, and blastoid erythroid cells can resemble lymphoblasts, minimally differentiated AML, megakaryoblasts, plasma cell neoplasms, or non-hematopoietic small round-cell tumors. Morphology is therefore an entry point, not the final diagnostic basis. Current classification systems provide a necessary framework,[1,2] while earlier WHO revisions and hematopathology reviews remain useful for understanding how thresholds and lineage assignment evolved.[3-5] A defensible diagnosis requires concordant marrow architecture, cytology, flow cytometry, immunohistochemistry, cytogenetics, and molecular testing.[6-8] In children, ribonucleic acid (RNA)-based fusion testing deserves early consideration when the morphology and phenotype suggest erythroid-lineage leukemia.[9]

The classification of erythroid-predominant leukemias has narrowed considerably over time. The older French-American-British AML-M6 category grouped together biologically different disorders, including cases that would now be classified as myelodysplastic neoplasms, AML with myelodysplasia-related genetics, therapy-related AML, or other genomically defined

AML subtypes. In contemporary practice, true PEL is not simply erythroid hyperplasia with dysplasia; it is a leukemic proliferation dominated by immature erythroid precursors. The 2022 World Health Organization (WHO) classification retains acute erythroid leukemia as a morphologic entity, whereas the 2022 International Consensus Classification (ICC) places many TP53-mutated adult cases within AML with mutated TP53.[1,2] This difference matters clinically because terminology affects risk communication, trial eligibility, and interpretation of older AML-M6 studies.

The pediatric literature requires separate interpretation. Adult PEL is strongly linked to advanced age, antecedent or therapy-related myeloid disease, complex or monosomal karyotype, chromosome 5 and 7 abnormalities, and very poor survival.[10-12] Biallelic TP53 inactivation and adverse cytogenetics are central to this adult model.[13,14] Pediatric reports, however, point to broader heterogeneity, including NUP98 rearrangements,[9] NFIA::CBFA2T3 and NFIA::RUNX1T1 fusions,[15,16] other erythroid leukemia-associated rearrangements,[17-19] CNS or soft-tissue erythroblastic sarcoma presentations,[20,21] marrow-based adolescent acute erythroid leukemia,[22] NFIA::CBFA2T3-associated erythroblastic sarcoma or PEL,[23] CIC-rearranged disease,[24] multi-institutional erythroblastic sarcoma series,[25] and more recent NFIA::CBFA2T3 reports with disseminated or cerebrospinal-fluid-based disease.[26,27] Experimental work on NFIA-ETO2 supports a direct maturation-arrest mechanism, particularly in cooperation with mutant TP53.[28] Limited existing evidence suggests that some children present with central nervous system or soft-tissue disease before marrow disease is obvious. These observations argue against treating pediatric PEL as a simple age-shifted counterpart of adult TP53-mutated AML. They also expose major evidence gaps in treatment, prognosis, MRD standardization, and genotype-specific risk assessment. This review therefore integrates diagnostic reasoning with treatment principles, prognostic stratification, MRD monitoring, and practical reporting considerations.

Methods

This narrative review used a structured search and evidence-weighting process informed by the SANRA framework for narrative reviews.[29] PubMed records, was searched from 1 January 2000 through 13 June 2026, with older landmark papers retained when required to explain classification or erythroid biology. The review was restricted to English-language full-text publications. Four Boolean search blocks were used: (1) ("pure erythroid leukemia" OR "acute erythroid leukemia" OR erythroleukemia OR "erythroblastic sarcoma") AND (classification OR morphology OR immunophenotype OR diagnosis OR WHO OR ICC); (2) the same disease block AND (child* OR pediatric* OR infant* OR adolescent*) AND (NUP98 OR NFIA OR CBFA2T3 OR RUNX1T1 OR TP53 OR EPOR OR JAK2 OR CIC OR GATA1); (3) the same disease block AND (treatment OR chemotherapy OR transplantation OR HSCT OR outcome OR survival OR prognosis OR relapse); and (4) the same disease block AND ("measurable residual disease" OR "minimal residual disease" OR MRD OR flow cytometry OR "molecular monitoring" OR cerebrospinal fluid OR CSF). The term "minimal residual disease" was included only as a legacy search synonym; throughout the manuscript, MRD refers to measurable residual disease. Backward and forward citation screening of key articles and targeted journal-site searches were used to identify additional classification documents, mechanistic studies, and recent molecularly defined pediatric reports.

Title and abstract screening was performed by YY and followed by full-text assessment. RP verified the final included set and reviewed uncertain eligibility decisions; disagreements were resolved through discussion. Because the initial database hit counts were not prospectively archived, the numerical flow was reconstructed during revision from the final deduplicated source library. The reconstructed library contained 61 unique English-language full-text publications. All 61 publications were reassessed against the final eligibility criteria and retained in the narrative synthesis; no additional publication was excluded during this reconstructed audit. Publications were included when they addressed official classification, diagnostic criteria, erythroid morphology or immunophenotype, pediatric or fusion-defined PEL or erythroblastic sarcoma, molecular pathogenesis, Down syndrome-associated mimics, treatment, transplantation, prognosis, or MRD. For interpretation, evidence was grouped into the same five priority categories shown in Figure 1: Highest, WHO or ICC classification documents and consensus guidance; High, multicenter or cooperative-group cohorts; Moderate, comparative clinicopathologic or molecular studies; Limited, small series and molecularly characterized case reports, including representative single-case reports; and Exploratory, preclinical models, drug-sensitivity studies, or hypothesis-generating targeted-therapy data. Single-case reports are therefore included within the Limited category, whereas the Exploratory category is reserved for preclinical or hypothesis-generating evidence and is not combined with case-report evidence. Adult studies were included only when pediatric evidence was unavailable or when they clarified classification, TP53 biology, treatment resistance, MRD methodology, or investigational targets. Abstract-only reports, duplicate descriptions without additional information, non-English articles, studies limited to reactive erythroid hyperplasia, and reports without sufficient lineage or molecular detail were excluded during the original literature selection and were not represented in the reconstructed final library.

Evidence statements were calibrated to source strength. WHO or ICC diagnostic statements are identified as classification-based conclusions. Results from multicenter or cooperative-group cohorts are presented as the strongest clinical evidence. Comparative clinicopathologic or molecular studies are treated as moderate evidence. Small series and molecularly characterized case reports, including representative single cases, are treated as limited evidence and are not used as validated prognostic rules. Preclinical models, drug-sensitivity studies, and hypothesis-generating targeted-therapy data are labeled exploratory and do not constitute treatment recommendations. Because this is a narrative review rather than a systematic review or meta-analysis, no pooled effect estimate or formal risk-of-bias score was calculated. Figure 1 summarizes the reconstructed source-library accounting and this five-category evidence hierarchy. The figure is not presented as a PRISMA-compliant systematic-review flow.

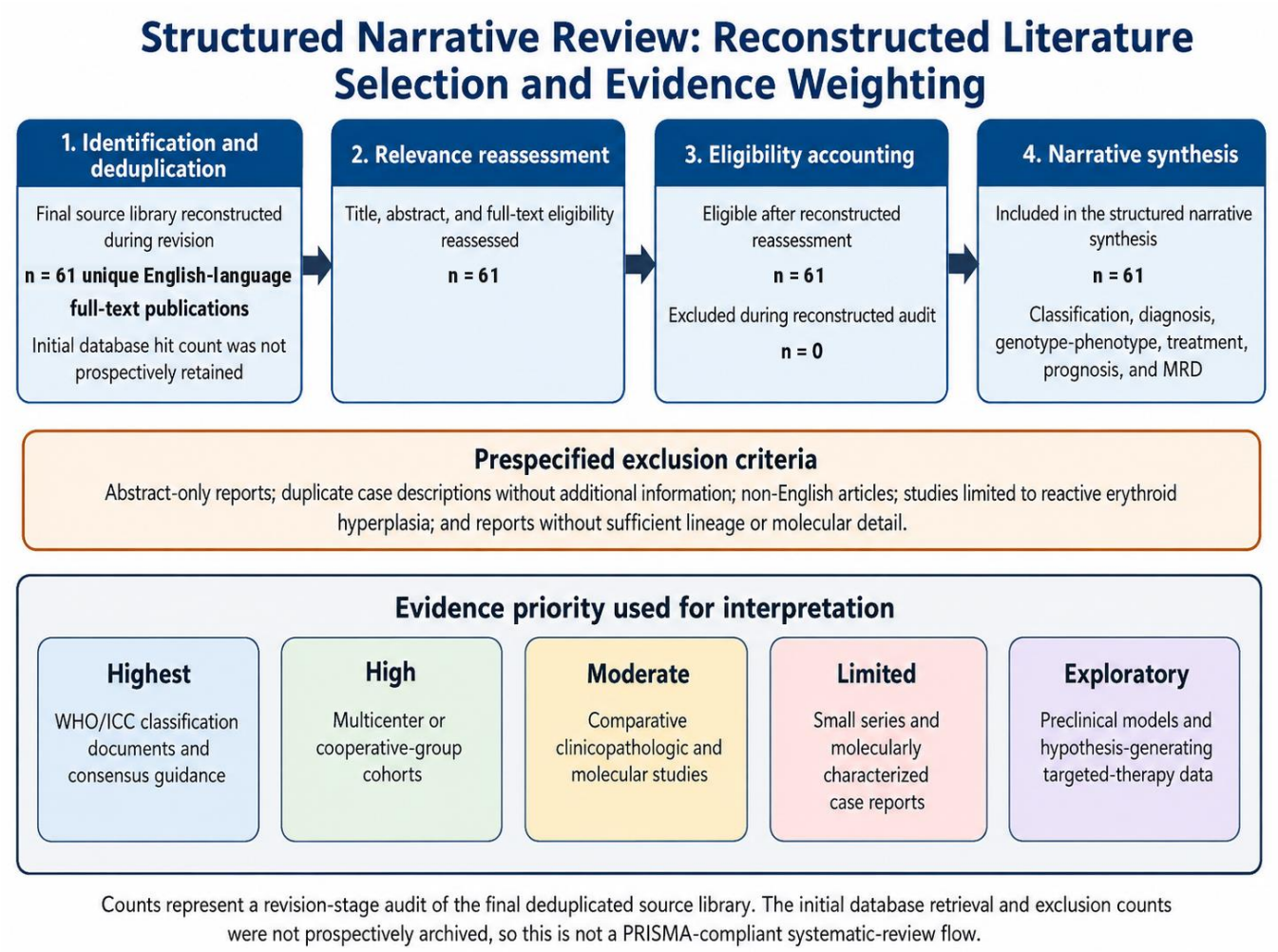

Figure 1: Reconstructed literature selection accounting and evidence weighting for this structured narrative review. Counts represent a revision-stage audit of the final deduplicated source library because initial database hit and exclusion counts were not prospectively archived. The evidence-priority categories correspond directly to the Methods section: Highest, High, Moderate, Limited, and Exploratory. Single-case reports are included within Limited, whereas preclinical and hypothesis-generating evidence is categorized separately as Exploratory.

Definition and Classification

PEL is best understood as acute leukemia dominated by immature erythroid precursors, usually with severe maturation arrest at the proerythroblast or pronormoblast stage. The 2022 WHO framework preserves pure erythroid leukemia within acute myeloid leukemia defined by differentiation.[1] Historical WHO revisions and hematopathology reviews describe commonly used thresholds of at least 80% erythroid precursors and at least 30% proerythroblasts, although wording has varied across classifications and reports.[3-5] These thresholds provide a classification basis, but sampling error can limit exact counting. Aspirate dilution, dry tap, fibrosis, necrosis, marked dyserythropoiesis, or extramedullary presentation can make the differential count unreliable. In such cases, biopsy architecture, erythroid immunohistochemistry, and genomic evidence of clonality carry greater diagnostic weight.[6-8]

The central diagnostic problem is not whether erythroid cells are numerous, but whether they are neoplastic and developmentally arrested. Erythroid hyperplasia can be reactive, nutritional, regenerative, drug-related, or secondary to hemolysis. It can also accompany myelodysplastic neoplasms and AML with myelodysplasia-related features. PEL differs because the abnormal population is not a normally maturing erythroid series; it is a monomorphic or near-monomorphic population of immature erythroid blasts that displaces normal hematopoiesis. A useful diagnostic report should therefore document marrow cellularity, erythroid percentage, proerythroblast proportion, presence or absence of a separate myeloblast population, dysplasia in non-erythroid lineages, fibrosis, p53 staining pattern when performed, flow cytometry findings, and the results of karyotype, fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), and fusion testing.[6-8]

For children, reporting is best framed by combining morphologic and genomic language rather than forcing every case into an adult-derived category. WHO terminology preserves the erythroid phenotype, while ICC terminology highlights TP53-mutated AML biology when TP53 criteria are fulfilled. A child with a NUP98 or NFIA-related fusion, however, should not be described as though the adult TP53-mutated paradigm fully explains the disease. Practical wording may include acute erythroid leukemia/pure erythroid leukemia, with specific genetic lesion when erythroid-lineage leukemia is supported, AML with mutated TP53 showing pure erythroid phenotype when TP53-mutated AML criteria are met, or erythroblastic sarcoma, with specific fusion and marrow involvement status specified when the first manifestation is a mass lesion. Such integrated wording communicates lineage, genetics, and risk without overstating certainty.[6-8] Key classification issues relevant to pediatric PEL are summarized in Table 1.

Table 1: Classification issues relevant to pediatric pure erythroid leukemia.

Framework	Key point	Practical implication
WHO 2022	Recognizes acute erythroid leukemia as an erythroid-lineage AML dominated by immature erythroid precursors.	Useful for preserving the morphologic and lineage-based diagnosis.
ICC 2022	Classifies most TP53-mutated cases as AML with mutated TP53.	Highlights adverse biology and the need to document TP53 allelic status.
Pediatric practice	Requires morphology plus genomic testing, not adult extrapolation alone.	Report erythroid percentages, marker profile, karyotype, TP53 status, and fusion results.

Pediatric Epidemiology and Clinical Presentation

PEL is rare at any age and is particularly uncommon in children. The true pediatric incidence remains uncertain because older reports used overlapping labels, including AML-M6, erythroleukemia, pure erythroid leukemia, erythroblastic sarcoma, acute undifferentiated leukemia, and AML not otherwise specified. Reclassification under current WHO and ICC systems further limits comparison across cohorts. Adult AML studies indicate that PEL represents only a small fraction of cases.[10] Pediatric evidence is much thinner and comes mainly from cooperative group data,[9] NFIA-associated case reports,[15,16] recent erythroblastic sarcoma reports,[20,21] and cytogenetic or mechanistic descriptions of rarer erythroid fusion events.[17-19,28] This limited evidence base has practical consequences: clinicians may not consider PEL early, and no pediatric PEL-specific therapeutic standard has been established.

Clinical presentation usually reflects bone marrow failure rather than a distinctive leukemia syndrome. Children may present with pallor, fatigue, fever, recurrent infection, bruising, mucosal bleeding, petechiae, bone pain, or poor general condition. Hepatomegaly and splenomegaly can occur but are non-specific. Laboratory findings typically include anemia and thrombocytopenia, with variable leukocyte counts. Circulating blasts may be absent, low, or morphologically ambiguous. Lactate dehydrogenase and uric acid may rise when tumor burden is high. Because erythroid blasts may not be recognized as leukemic blasts on automated or manual peripheral blood review, persistent or unexplained cytopenias with abnormal nucleated red cell forms should prompt marrow assessment. Extramedullary disease deserves particular attention in children. Erythroblastic sarcoma may involve the central nervous system, skull, spine, soft tissue, lymph nodes, or other sites and can be mistaken for lymphoma, myeloid sarcoma, Ewing sarcoma, rhabdomyosarcoma, poorly differentiated carcinoma, or inflammatory lesions. Immunohistochemistry is often decisive because the tumor may be CD45-negative or weak and may lack conventional myeloid markers. A panel including CD71, E-cadherin, CD36, glycophorin A, hemoglobin, GLUT1, CD117, CD34, myeloperoxidase, CD41, CD61, cytokeratin, desmin, and lymphoid markers helps prevent misclassification. CNS or infant erythroblastic sarcoma presentations have been associated with NFIA-related fusions,[15,16] and recent pediatric reports continue to broaden this spectrum.[20,21] Sufficient tissue should be reserved for cytogenetic and RNA-based testing because rare or cryptic fusions may provide the decisive diagnostic clue.[17-19,28]

Age and constitutional context should be recorded carefully. In neonates and infants, transient abnormal myelopoiesis (TAM) and myeloid leukemia of Down syndrome (ML-DS) must remain in the differential diagnosis, including in phenotypically subtle or mosaic trisomy 21. These disorders may show megakaryocytic-erythroid features and GATA1 mutations and can be confused with erythroid leukemia when lineage work-up is incomplete.[30,31] Their progression patterns and clinical spectrum differ from classic PEL.[32-34] Broader Down syndrome leukemia risk and the molecular evolution from TAM to ML-DS have been characterized separately,[35,36] and additional genomic studies have clarified cooperating lesions during progression.[37-39] In suspected pediatric PEL, clinical history, physical examination, karyotype, assessment for constitutional or mosaic trisomy 21 when indicated, and GATA1 mutation testing are therefore not peripheral details; they are part of the diagnostic framework. Table 2 summarizes the pediatric reports most relevant to acute erythroid leukemia/pure erythroid leukemia and erythroblastic sarcoma. These cases should not be interpreted as a mature epidemiologic dataset. They are better interpreted as a signal that childhood erythroid-lineage leukemia and sarcoma may represent a heterogeneous, fusion-enriched spectrum that overlaps with, but is not identical to, adult TP53-mutated PEL.[9,15,16] Early CNS and soft-tissue reports highlight NFIA-associated presentations.[20,21] Later reports broaden the marrow-based, CIC-rearranged, and multi-institutional spectrum,[22-25] while recent NFIA::CBFA2T3 reports strengthen the molecular subgroup and support cerebrospinal-fluid-based molecular diagnosis.[26,27] The pediatric reports most relevant to AEL/PEL and erythroblastic sarcoma are summarized in Table 2.

Table 2: Reported pediatric acute erythroid leukemia/pure erythroid leukemia and erythroblastic sarcoma cases or series.

Study/year	Evidence type / age	Site or presentation	Erythroid phenotype	Genetics	Treatment / outcome	Main interpretive value
Chisholm et al., 2020 [9]	COG pediatric AEL series; 24 cases, including 5 PEL cases	Marrow-based AEL/PEL within pediatric AML trials	Central pathology review with morphologic, immunophenotypic, cytogenetic, molecular, and clinical data	NUP98 fusions in 7/22 molecularly evaluable AEL cases; 3/5 PEL cases had NUP98 fusions; 4/5 PEL cases had complex karyotype	PEL subset had adverse outcome; 5-year OS and EFS each approximately 20%	Largest pediatric cooperative-group dataset; establishes NUP98 enrichment and poor outcome in pediatric PEL
Liu et al., 2020 [15]	Case report; 2-year-old girl	Primary CNS PEL/sarcoma; brain involvement without classic marrow-based presentation	Immature erythroid-lineage neoplasm requiring integrated tissue and molecular work-up	t(1;16)(p31;q24) with NFIA::CBFA2T3; reported cooperating EPOR/JAK2/ARID1A alterations	AML-type therapy with transplant; alive at reported follow-up	Shows that pediatric PEL/ES may present as isolated CNS disease and that RNA-based fusion testing can be diagnostic
King et al., 2021 [16]	Case report; infant	Extramedullary erythroblastic sarcoma, reported with abdominal involvement	Erythroid sarcoma phenotype in infancy	Novel t(1;8)(p31.3;q21.3) NFIA::RUNX1T1; additional KIT/ARID1A alterations reported in later summaries	Managed using pediatric AML framework	Supports NFIA::RUNX1T1 as an NFIA-fusion analogue within pediatric erythroblastic sarcoma
Tauziede-Espariat et al., 2024 [20]	Case report; 3-year-old boy	Isolated CNS erythroblastic sarcoma with seizures and leptomeningeal dissemination	CD45-negative tumor; CD43/CD117 supportive; erythroid markers and fusion result central to diagnosis	NFIA::RUNX1T1 fusion	MyeChild 01-based AML therapy; died within months of presentation	Shows CNS diagnostic mimicry and raises concern for poor outcome in de novo CNS presentations
Anelo et al., 2024 [21]	Case report; 22-month-old girl	Left parotid-region mass with CNS involvement	Highly proliferative erythroid sarcoma; initial histology difficult because of crush/fixation artifact	NFIA::CBFA2T3 detected by clinical RNA sequencing	Chemotherapy reported; alive in summarized follow-up sources	Demonstrates that RNA sequencing may be decisive when morphology and immunohistochemistry are inconclusive
Gupta et al., 2025 [22]	Case report; 15-year-old girl	De novo marrow-based AEL with fever, abnormal vaginal bleeding, leukocytosis, severe anemia	PB 87% erythroid cells; marrow 90% erythroid precursors with 60% proerythroblasts; CD71, CD235a, CD36 positive; myeloid markers negative	46,XX,add(4)(p16); ARID1A and ATM variants; no TP53 mutation	7+3 AML induction; alive at 3-month post-induction follow-up	Adds a marrow-based adolescent AEL case without TP53 mutation and without the adult-type complex-karyotype paradigm

Study/year	Evidence type / age	Site or presentation	Erythroid phenotype	Genetics	Treatment / outcome	Main interpretive value
Cardoni et al., 2025 [23]	Two pediatric ES/PEL cases plus literature review	Pediatric erythroid leukemia/sarcoma with frequent extramedullary presentation	Erythroid-lineage leukemia/sarcoma spectrum	NFIA::CBFA2T3 in both cases; one case also had TP53 mutation	Case-specific management summarized in review	Strengthens the recurrent NFIA::CBFA2T3/NFIA::RUNX1T1 fusion-defined pediatric subgroup
Chang-Graham et al., 2025 [24]	Pediatric AEL/erythroblastic sarcoma report	Neonatal/infant presentation; abdominal disease described in later literature summaries	Erythroid-lineage leukemia/sarcoma phenotype	CIC rearrangement, including SREBF1::CIC in summarized sources	Cytarabine-based treatment; poor early outcome in summarized case	Expands pediatric erythroid leukemia/sarcoma genetics beyond NUP98 and NFIA fusions
Fitzpatrick et al., 2025 [25]	Multi-institutional ES series; 56 total ES cases, including pediatric cohort and literature cases	Children showed frequent soft tissue and CNS involvement	CD71 and GLUT1 highly sensitive; E-cadherin and CD117 often supportive; CD45 often absent/weak	Pediatric ES enriched for gene fusions, especially NFIA; adult ES enriched for TP53-mutated disease	Overall prognosis poor; median survival short in combined evaluable cohort	Provides the most substantial comparative dataset to date, while still leaving pediatric prognosis and treatment unresolved
Brunetti et al., 2026 [26]	Case report; 2.5-year-old boy	Extensive extramedullary disease involving mediastinum, gastrointestinal tract, pleura/peritoneum, kidneys, and lymph nodes; minimal marrow involvement	Pleural effusion phenotype CD45-, strong CD117/CD71/CD36/CD235a, MPO-; marrow showed only a small matching population	NFIA::CBFA2T3 with novel breakpoint/insertion; no TP53 pathogenic variant reported	AML-like therapy followed by allogeneic HSCT; complete remission 28 months after transplant	Shows disseminated ES with minimal marrow disease and reinforces NFIA::CBFA2T3 as a molecularly defined pediatric entity
Zhao et al., 2026 [27]	Case report and literature review; 1-year-old boy	Diffuse CNS parenchymal infiltration without a discrete mass; diagnosis made from CSF rather than tissue biopsy	CSF flow cytometry showed immature erythroid cells; RNA sequencing established diagnosis	NFIA::CBFA2T3; TP53 mutation and chromosome 17 loss negative; JAK2/EPOR/ARID1A alterations reported	AML-type induction plus azacitidine, venetoclax, intrathecal therapy, and consolidation; complete remission at 27 months	Adds a CSF-based diagnostic strategy for critically ill pediatric CNS disease and supports molecular MRD monitoring

Morphology and Immunophenotyping

Morphologic assessment starts by asking whether the marrow or tissue is dominated by immature erythroid cells. Proerythroblasts are usually large, with round to irregular nuclei, fine chromatin, prominent nucleoli, deeply basophilic cytoplasm, and frequent cytoplasmic vacuolization. Multinuclearity, nuclear budding, megaloblastoid change, cytoplasmic blebbing, and dyserythropoiesis may be present. The marrow is often hypercellular and may show extensive replacement by immature erythroid elements with suppression of granulopoiesis and megakaryopoiesis. Auer rods are typically absent, and myeloperoxidase staining is negative in the neoplastic erythroid population. These features are suggestive, but none is sufficiently specific to establish lineage in isolation. Representative bone marrow morphology is shown in Figure 2. Flow cytometry and immunohistochemistry should be used together. Erythroid precursors are fragile, may be underrepresented after red-cell lysis, and often show weak or absent CD45. CD71 is highly sensitive and usually strong, but it is not fully specific because transferrin-receptor expression also reflects proliferation.[40,41] E-cadherin is useful for highlighting immature erythroid precursors in marrow biopsy and tissue sections. CD36 supports erythroid differentiation but also appears in monocytes and megakaryocytic cells. Glycophorin A and hemoglobin are more specific markers of erythroid maturation, yet they may be weak or absent in very immature proerythroblastic disease.[40] GLUT1 is a useful adjunctive erythroid marker in tissue sections.[42] Given the overlap between erythroid and megakaryoblastic leukemias, interpretation should remain panel-based rather than dependent on a single marker.[43]

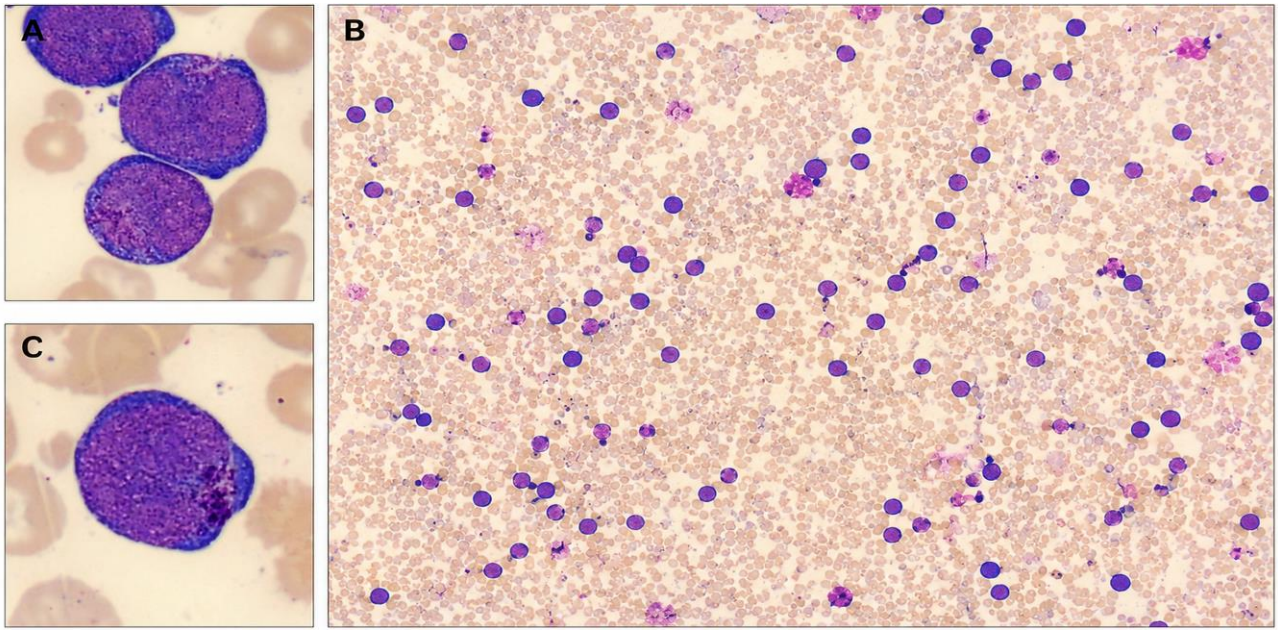

Figure 2: Representative bone marrow aspirate morphology in pediatric pure erythroid leukemia.

(A, C) High-power digital crops show large immature erythroid cells/proerythroblasts with round to slightly irregular nuclei, fine chromatin, prominent nucleoli, deeply basophilic cytoplasm, and cytoplasmic vacuolization.

(B) Lower-power overview shows numerous dispersed erythroblasts and marked erythroid predominance. The panels comprise anonymized, previously unpublished, patient-derived bone marrow aspirate smear images obtained during routine clinical care and supplied by the authors; they were cropped only for panel assembly. The smears were processed and stained using the Sysmex SP-50 Slidemaker Stainer. Panel B was examined using a 10× objective, and the digital image was acquired using the CellaVision DC-1 system. Panels A and C were examined using an oil-immersion objective and imaged using the same CellaVision DC-1 system. The exact objective magnification for Panels A and C, the specific staining reagent/protocol, and the pixel-to-micrometer calibration could not be independently verified from the available original records. Therefore, no scale bar is provided. Morphologic findings should be interpreted together with the immunophenotypic and molecular findings. Written informed consent for publication of these anonymized images was obtained from the patient's parent/legal guardian; further ethical details are provided in the Ethical Approval and Consent for Publication sections.

CD34 and CD117 require cautious interpretation in suspected pure erythroid leukemia. CD117 may be expressed in a subset of PEL cases, whereas CD34 may be negative, dim, or limited to only a minor population; therefore, absence of CD34 does not exclude acute leukemia, and CD117 positivity alone should not be interpreted as definitive evidence of myeloid lineage.[5,8,10,43] Myeloperoxidase is usually negative in neoplastic erythroid blasts, while megakaryocytic markers, including CD41, CD61, and CD42b, are useful for excluding acute megakaryoblastic leukemia, although aberrant or partial expression must be interpreted within the full morphologic and immunophenotypic context.[8,43] Lymphoid markers should also be included to exclude B- or T-lymphoblastic leukemia, particularly when the abnormal cells are blastoid and CD45-dim. In tissue-based or extramedullary presentations, epithelial, neural, muscle, germ-cell, and other tumor markers may be required to exclude non-hematopoietic small round-cell tumors.[43] The diagnosis is strongest when morphology, immunophenotype, and genetic findings are concordant. A marrow replaced by proerythroblasts with strong CD71 and E-cadherin expression, supportive CD36 or GLUT1 staining, absent myeloperoxidase, absence of lineage-defining lymphoid markers, and a clonal cytogenetic or fusion abnormality strongly supports PEL.[10,40-43] By contrast, isolated CD71 positivity is insufficient because CD71 also reflects erythroid proliferation and may be seen in non-neoplastic erythroid expansion.[40,41] Likewise, glycophorin A negativity does not exclude PEL when the cells are highly immature and other erythroid markers are convincing.[40] In children, p53 immunohistochemistry should be regarded as supportive rather than obligatory. An abnormal overexpression or null pattern supports TP53-altered disease, whereas a wild-type pattern should prompt careful evaluation for alternative pediatric drivers,

including fusion-defined disease, rather than dismissal of the erythroid diagnosis.[13] The main immunophenotypic markers used in suspected pediatric PEL are summarized in Table 3.

Table 3: Immunophenotypic markers used in suspected pediatric pure erythroid leukemia.

Marker	Typical interpretation	Main caveat
CD71	Highly sensitive marker of erythroid precursors.	Not specific; also reflects cellular proliferation.
E-cadherin	Highlights immature erythroid precursors in marrow and tissue.	Best interpreted with a broader erythroid panel.
CD36	Supports erythroid differentiation.	Can also be expressed in monocytes and megakaryocytic cells.
Glycophorin A/hemoglobin	Confirm erythroid maturation when positive.	May be weak or absent in very immature PEL.
GLUT1	Sensitive adjunctive erythroid marker.	Must be interpreted in tissue context.
CD34/CD117	Variable stem/progenitor-associated expression.	Absence of CD34 does not exclude PEL.
MPO, CD41, CD61, CD42b	Help exclude myeloid or megakaryoblastic mimics.	Partial or aberrant expression requires integrated interpretation.

Cytogenetic and Molecular Pathophysiology in Pediatric Pure Erythroid Leukemia

Genetics and pathophysiology are difficult to separate in PEL because the morphology reflects disrupted erythroid development. Pediatric PEL can be conceptualized as a state in which a clone retains erythroid identity, acquires self-renewal, and fails to complete terminal maturation. Normal erythroid differentiation depends on coordinated transcriptional and chromatin-regulatory networks that progressively establish erythroid identity and maturation.[44-46] Distinct lesions may converge on this phenotype through different roles. NUP98 and NFIA fusions function as transcriptional drivers that impose self-renewal or maturation arrest,[9,28,47] while TP53 loss can provide genomic tolerance and survival advantage.[13,14] EPOR/JAK2 activation often appears to function as a proliferative cooperating pathway, particularly in TP53-altered disease.[48] GATA1s is a driver of trisomy 21-associated myeloid disease, but its main relevance to PEL is as a developmental comparator and diagnostic mimic. These relationships are summarized in Figure 3.

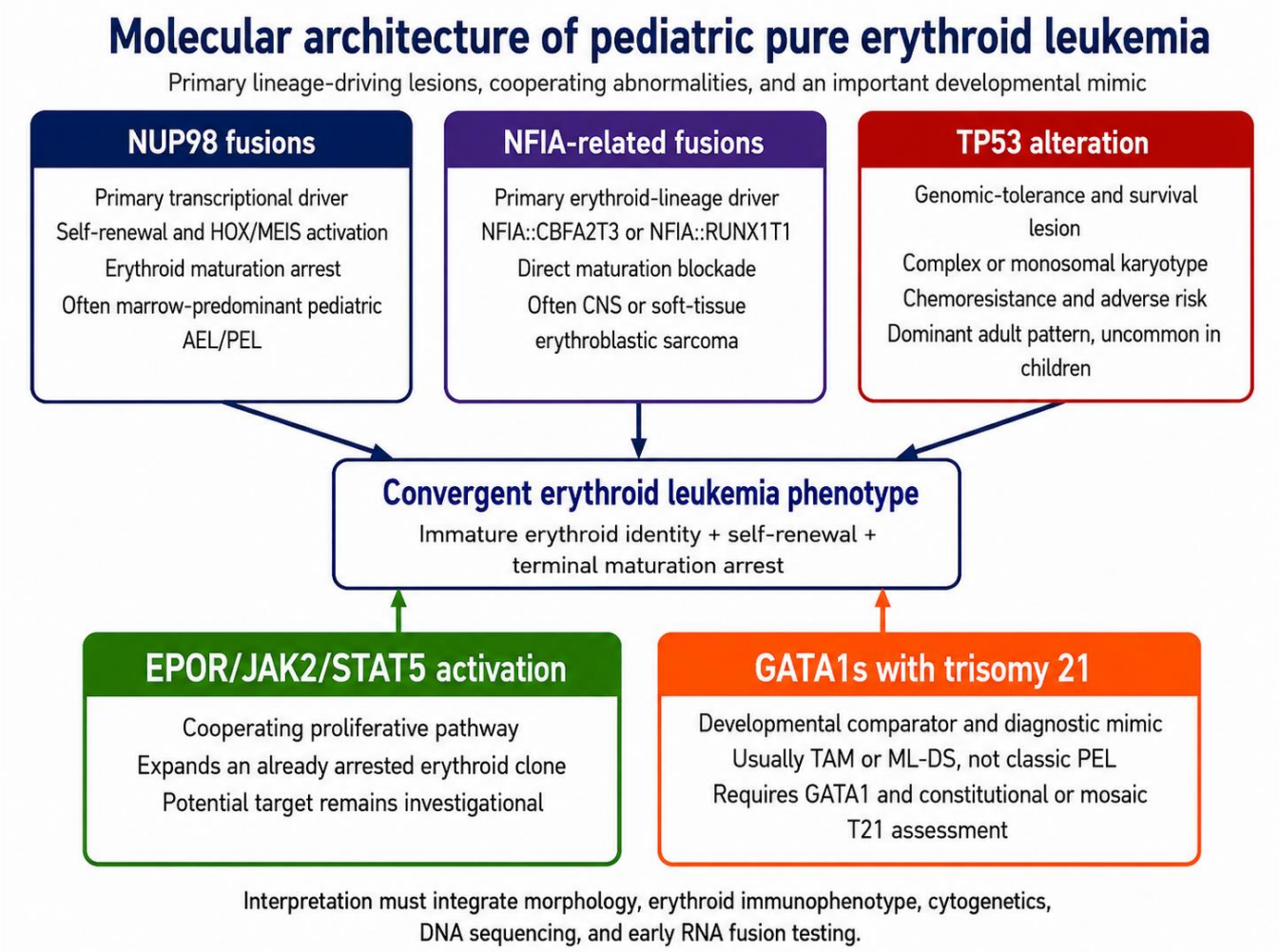

Figure 3: Molecular architecture of pediatric pure erythroid leukemia. Primary lineage-driving lesions, cooperating abnormalities, and the trisomy 21/GATA1s developmental mimic converge on an immature erythroid phenotype through distinct mechanisms.

NUP98 and NFIA fusions are shown as primary transcriptional or lineage-driving lesions; TP53 alteration provides genomic tolerance and adverse-risk biology; EPOR/JAK2/STAT5 activation acts as a cooperating proliferative pathway; and GATA1s with trisomy 21 indicates TAM or ML-DS rather than classic PEL.

TP53-altered PEL remains the best-defined adult model and should still be assessed in children. TP53 normally regulates DNA-damage response, cell-cycle arrest, senescence, and apoptosis. Adult series link the pure erythroid phenotype to adverse cytogenetics, treatment resistance, and poor outcome.[10-12] Biallelic TP53 loss allows erythroid progenitors with chromosomal damage to survive rather than undergo elimination, creating conditions for complex karyotypes, chromosome 5q or 7q losses, and therapy resistance.[13,14] Abnormal p53 immunohistochemistry can help distinguish TP53-altered PEL from reactive erythroid hyperplasia.[49] Mechanistically, TP53 loss may permit damaged erythroid-committed progenitors to proliferate despite failed maturation. Experimental AML data indicate that the antileukemic effect of venetoclax combined with cytarabine and the anthracycline idarubicin is TP53-dependent; this supports a role for TP53 status in chemotherapy response but does not establish a PEL-specific or pediatric PEL-specific resistance mechanism.[50]

NUP98 fusions offer a pediatric-relevant mechanism of fusion-driven erythroid leukemogenesis. Rearranged NUP98 proteins can alter transcriptional regulation, activate stem-cell and HOX/MEIS-associated programs, maintain chromatin accessibility at self-renewal loci, and impair maturation. In an erythroid progenitor, this may preserve erythroid identity while preventing normal terminal differentiation. The practical implication is important: NUP98-rearranged pediatric AEL/PEL may be missed if testing relies only on morphology, conventional karyotype, or DNA-only panels. Early RNA-based fusion testing should be strongly considered in suspicious pediatric cases because relevant rearrangements may be missed by morphology, conventional karyotyping, or DNA-only panels.[9,47,51]

NFIA-related fusions provide one of the clearest routes to an erythroid maturation-arrest phenotype. NFIA participates in erythroid transcriptional regulation, whereas CBFA2T3/ETO2 and RUNX1T1/ETO are transcriptional corepressor partners involved in hematopoietic differentiation. Clinical reports have described NFIA::CBFA2T3 and NFIA::RUNX1T1 in infant or

CNS erythroblastic sarcoma/PEL-like disease.[15,16] Cytogenetic and sequencing studies have also linked CBFA2T3 rearrangements and other rare fusions to acute erythroid leukemia.[17-19] Recent pediatric reports extend the NFIA-associated erythroid tumor spectrum.[20,21] Experimental data show that NFIA-ETO2 blocks erythroid maturation and, with mutant TP53, induces PEL in model systems. This supports a two-component model in which the fusion imposes an abnormal erythroid transcriptional state and maturation block, while cooperating lesions enhance survival or clonal fitness. Clinically, this helps explain why NFIA-rearranged tumors can present as erythroblastic sarcoma or PEL-like disease with strong erythroid markers, few conventional myeloblasts, and occasional CNS involvement.[28]

GATA1 and Down syndrome should be discussed as a distinct developmental pathway rather than a classic PEL subtype. In constitutional trisomy 21, acquired exon 2 GATA1 mutations generate the short GATA1s isoform and initiate transient abnormal myelopoiesis, while additional cohesin, epigenetic, or signaling lesions can support progression to myeloid leukemia of Down syndrome.[30-39] These disorders usually show megakaryoblastic or mixed megakaryocytic-erythroid differentiation rather than a monomorphic proerythroblast proliferation. Their importance in a PEL review is therefore diagnostic: neonates or infants with circulating blasts, nucleated erythroid cells, dyserythropoiesis, CD36 or CD117 expression, or marrow erythroid expansion require assessment for constitutional or mosaic trisomy 21 and GATA1 mutation.[30,31,52]

A GATA1s-positive trisomy 21-associated myeloid proliferation should be classified and treated within the TAM or ML-DS framework rather than relabeled as PEL. This distinction separates a biologically and therapeutically defined pediatric entity from fusion-driven or TP53-associated erythroid leukemia.

EPOR/JAK2/STAT5 activation and epigenetic dysregulation may act as cooperating mechanisms. EPOR and JAK2 amplification can increase erythropoietin-receptor pathway signaling, giving erythroid progenitors survival and proliferative advantages.[48] If the same clone carries a transcriptional lesion that blocks maturation, enhanced signaling may expand an already arrested erythroid compartment. Similarly, abnormalities in chromatin regulators may stabilize a leukemic erythroid transcriptional program and reduce responsiveness to normal differentiation cues. Integrated genomic studies have identified molecular subgroups of acute erythroid leukemia,[47,51] while transcriptomic and model-based work has shown how transcriptional and epigenetic abnormalities can function as drivers rather than bystanders.[53,54]

Clinical correlations remain provisional because pediatric datasets are small and depend heavily on one cooperative-group reclassification study, small series, and individual reports.[9,15,16,20-27] Limited existing evidence suggests that marrow replacement by immature erythroid cells produces anemia, thrombocytopenia, neutropenia, infection risk, bleeding, and transfusion dependence, while some fusion-defined pediatric tumors are predominantly extramedullary or CNS-based and have little circulating or marrow disease at presentation. Diagnostic reporting should therefore document karyotype complexity, TP53 mutation and allelic status, copy-number abnormalities, NUP98 or NFIA-related fusions, EPOR/JAK2 pathway alterations, GATA1 mutation when trisomy 21-associated disease is possible, and the method used to detect cryptic rearrangements.[1,2,9,10,13,30,31,48,52]

Table 4: Genetic lesions and mechanisms that may produce a pediatric pure erythroid leukemia phenotype.

Genetic lesion or pathway	Mechanistic effect	How it can generate PEL biology	Practical implication
Biallelic TP53 alteration	Loss of DNA-damage checkpoint, apoptosis, and genome surveillance.	Permits expansion of genomically damaged erythroid progenitors with complex karyotype and maturation failure.	Assess TP53 mutation, deletion, VAF, copy-number status, and p53 IHC pattern.
NUP98 fusions	Aberrant transcriptional activation and persistence of stemness programs.	Maintains self-renewal in an immature erythroid progenitor and blocks terminal differentiation.	Use RNA-based fusion testing when pediatric PEL is suspected.
NFIA::CBFA2T3 / NFIA::RUNX1T1	Disruption of erythroid transcriptional regulation and corepressor networks.	Produces an erythroid maturation block and may present as erythroblastic sarcoma/PEL.	Consider in pediatric extramedullary erythroid tumors and CNS disease.
GATA1s with trisomy 21	Altered megakaryocyte-erythroid differentiation in fetal hematopoiesis.	Usually causes TAM/ML-DS rather than classic PEL, but can mimic erythroid leukemia.	Test GATA1 and evaluate constitutional/mosaic trisomy 21 when clinically relevant.

Genetic lesion or pathway	Mechanistic effect	How it can generate PEL biology	Practical implication
EPOR/JAK2/STAT5 activation	Enhanced erythroid survival and proliferative signaling.	Expands the arrested erythroid compartment when paired with differentiation blockade.	Look for copy-number gains or pathway activation in comprehensive genomic testing.

Genotype-Phenotype Heterogeneity and Prognostic Stratification

Available pediatric evidence supports several recurring genotype-phenotype patterns, but these patterns should not be interpreted as validated therapeutic subgroups. TP53-altered, complex-karyotype PEL is the dominant adult pattern and appears uncommon in children. NUP98-rearranged disease is enriched in pediatric AEL and PEL, while NFIA-related fusions are repeatedly associated with infants or young children, CNS or soft-tissue erythroblastic sarcoma, and occasionally minimal marrow involvement.[9,15,16,20-28] CIC-rearranged and other fusion-defined cases further expand this spectrum, but the evidence remains limited to isolated or small reports.[19,24]

Prognostic interpretation should combine genotype, morphology, disease distribution, and response. The five PEL cases in the Children's Oncology Group series had 5-year overall and event-free survival of approximately 20%, but the sample was too small for reliable partner-specific analysis.[9] NUP98::KDM5A was associated with poor outcome in the available pediatric AEL cohort, while NFIA-fusion reports show heterogeneous outcomes ranging from early death to durable remission after AML-directed treatment and, in selected cases, transplantation.[9,15,20,26,27] These data support explicit risk communication but do not support a definitive pediatric PEL risk score.

Table 5: Genotype-phenotype patterns, reported treatment response, and provisional clinical implications in pediatric pure erythroid leukemia and erythroblastic sarcoma.

Molecular pattern	Typical age or context	Clinical distribution	Outcome signal	Reported treatment and response	Clinical implication	Evidence strength
Biallelic TP53 alteration with complex or monosomal karyotype	Predominantly adults; uncommon pediatric pattern	Usually marrow-dominant PEL; severe cytopenias; frequent genomic complexity	Extremely poor adult survival; pediatric estimate unavailable	Adult PEL series reported no responses among patients receiving hypomethylating agents, HMA-venetoclax, intensive chemotherapy, or supportive/other therapy; pediatric response data are unavailable.[10]	Document allelic status and copy-number loss. Manage within a high-risk AML framework; clinical-trial referral should be considered	Strong adult evidence; limited pediatric evidence[10-14]
NUP98 fusion, including NUP98::KDM5A or NUP98::NSD1	Children and adolescents; partner-specific age variation	Usually marrow AEL/PEL. NUP98::KDM5A often occurs in young children and can show erythroid or megakaryoblastic morphology	High induction MRD and relapse risk in pediatric AML. The PEL subset had poor survival; partner-specific estimates remain unstable	Standard induction response is often poor. A 10-patient pediatric NUP98-rearranged AML cohort reported 20% complete remission after first induction. Selected patients achieved remission with BCL-2-, FLT3-, or CDK6-containing combinations, but the evidence was not PEL-specific.[55]	Perform early RNA testing. Apply a high-risk pediatric AML framework and evaluate co-lesions such as FLT3-ITD. Targeted agents remain trial-based	Cooperative-group, pediatric AML cohort, and preclinical evidence[9,55-59]
NFIA::CBFA2T3 or NFIA::RUNX1T1	Infants and young children	Often CNS or soft-tissue dominant. In the mixed pediatric erythroblastic sarcoma dataset, CNS and soft-tissue involvement each occurred in 9/20 cases (45%), although this estimate was not NFIA-specific. Marrow involvement may be minimal or delayed	Heterogeneous case outcomes, including early death and durable remission	AML-directed chemotherapy, CNS-directed therapy, and HSCT have produced mixed results, from early death to reported remissions lasting 27 to 28 months in individual cases.[15,20,26,27]	Reserve tissue or fluid for RNA sequencing. Complete CNS staging. Consider AML-directed systemic and CNS therapy, with HSCT guided by response and overall risk	Recurrent case reports, small series, comparative pathology, and mechanistic evidence[15,16,20,21,23,25-28]

Molecular pattern	Typical age or context	Clinical distribution	Outcome signal	Reported treatment and response	Clinical implication	Evidence strength
CIC rearrangement or other rare fusion	Neonatal or infant cases reported	Extramedullary or mixed marrow and mass presentation	Poor early outcome reported in isolated cases	Cytarabine-based treatment was followed by poor early outcome in the reported pediatric case. No reproducible subtype-specific response pattern is available.[24]	Use broad RNA fusion testing and consider registry enrollment. No subtype-specific regimen has been established	Case-report level[19,24]
EPOR/JAK2 amplification or activation	Mainly TP53-altered adult AEL or PEL; pediatric frequency uncertain	Marrow-dominant erythroid proliferation with activated STAT5 signaling	Very poor outcome in TP53-altered cohorts	Ruxolitinib activity has been demonstrated in vitro and in xenograft models only; pediatric clinical response data are unavailable.[48]	Document the pathway alteration. JAK inhibition should remain limited to a clinical trial or research framework	Comparative genomic and preclinical evidence[48]
GATA1s with constitutional or mosaic trisomy 21	Neonates and young children with Down syndrome biology	TAM or ML-DS, usually megakaryoblastic or mixed megakaryocytic-erythroid disease	Favorable under ML-DS protocols in many young children; not comparable with PEL	TAM and ML-DS often respond to disease-specific pediatric management, but these treatment outcomes should not be extrapolated to PEL.[30-39,52]	Classify as TAM or ML-DS. Use GATA1 and trisomy 21 testing to prevent misdiagnosis	Established disease-specific evidence; mimic rather than PEL[30-39,52]

Differential Diagnosis

The differential diagnosis should begin with non-neoplastic erythroid expansion. Severe vitamin B12 or folate deficiency, copper deficiency, hemolysis, recent bleeding, erythropoietin exposure, marrow recovery after chemotherapy, congenital dyserythropoietic anemia, and viral or inflammatory marrow stress may produce erythroid hyperplasia and dyserythropoiesis. These conditions usually retain a spectrum of erythroid maturation, lack leukemia-defining clonal genetics, and improve when the underlying cause is corrected. Neoplastic mimics include myelodysplastic neoplasm with erythroid predominance, AML with myelodysplasia-related genetics, acute megakaryoblastic leukemia, minimally differentiated AML, acute undifferentiated leukemia, lymphoblastic leukemia or lymphoma, plasma-cell neoplasms, and metastatic pediatric small round-cell tumors. Acute megakaryoblastic leukemia is especially difficult because erythroid and megakaryocytic programs share developmental ancestry and Down syndrome-associated disease occupies this lineage boundary. A broad panel and genomic testing reduce diagnostic error. PEL should be diagnosed only when immature erythroid lineage is convincingly demonstrated and competing diagnoses have been actively excluded.[5,8,43] The principal differential diagnoses are summarized in Table 6.

Table 6: Differential diagnosis of pediatric pure erythroid leukemia.

Entity	Reason for overlap	Clues against PEL
Megaloblastic anemia/reactive erythroid hyperplasia	Erythroid expansion and dyserythropoiesis.	Nutritional or regenerative context; absent clonal leukemia genetics.
MDS with erythroid predominance	Cytopenias, dysplasia, erythroid-rich marrow.	Less monomorphic proerythroblast proliferation; classification depends on blasts and genetics.
Acute megakaryoblastic leukemia	Shared megakaryocyte-erythroid progenitor biology.	Strong CD41/CD61/CD42b or AMKL-defining genetics.
Minimally differentiated AML	MPO-negative immature blasts.	Lacks convincing erythroid marker pattern.
Lymphoblastic lymphoma/leukemia or sarcoma	Blastoid morphology or mass lesion.	Lineage-defining lymphoid markers or non-hematopoietic tumor profile.

Practical Diagnostic Approach

The practical work-up should proceed as an integrated sequence rather than as a descriptive recap. First, establish the clinical trigger and obtain adequate marrow, biopsy, peripheral blood, tissue, and CSF specimens when indicated. Second, determine whether the dominant abnormal population shows immature erythroid morphology with maturation arrest. Third, prove erythroid lineage with a panel that includes sensitive and maturation-associated erythroid markers while actively excluding myeloid, lymphoid, monocytic, megakaryocytic, and non-hematopoietic mimics. The morphology and immunophenotype criteria are summarized in Tables 3 and 6.

Genetic testing should proceed in parallel with phenotyping. Conventional karyotype and copy-number assessment identify complex, monosomal, 5q, 7q, 17p, EPOR, or JAK2 abnormalities. DNA-based NGS should include TP53 and relevant myeloid genes, but a negative DNA panel does not exclude fusion-driven PEL. Early RNA-based fusion testing is strongly recommended in suspicious pediatric cases because NUP98, NFIA, CIC, and other rearrangements may be cryptic.[9,15-19,24,28] GATA1 mutation and constitutional or mosaic trisomy 21 assessment should be ordered early when neonatal presentation, Down syndrome, or megakaryocytic-erythroid ambiguity is present.[30,31,52] The distinction between likely drivers and cooperating lesions, together with provisional genotype-phenotype patterns, is summarized in Tables 4 and 5.

The final report should state the WHO and ICC classification basis, the quantitative and architectural evidence for erythroid predominance, the immunophenotypic evidence for erythroid lineage, the genetic lesion and TP53 allelic status, the marrow and CNS or extramedullary distribution, the major excluded mimics, and the baseline MRD target. Suggested wording is: "acute erythroid leukemia or pure erythroid leukemia, with [genetic abnormality], [TP53 allelic status], and [marrow, CNS, or extramedullary status]." The report should also qualify the evidence strength of unusual fusion-defined interpretations and should link the diagnosis to the treatment and MRD framework summarized in Tables 7 and 8. Figure 4 integrates the diagnostic, genotypic, treatment, and MRD steps into one workflow.

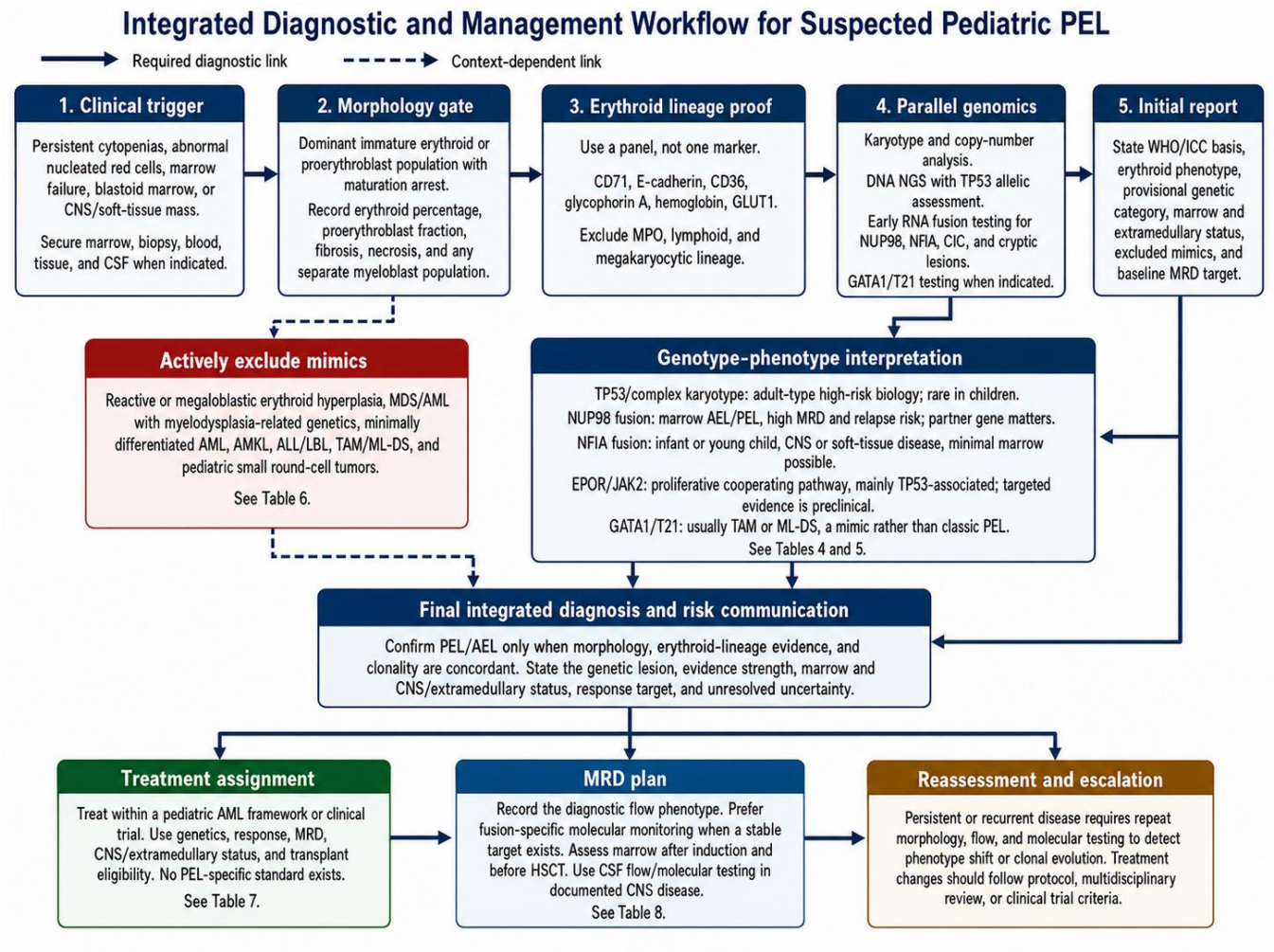

Figure 4: Integrated diagnostic and management workflow for suspected pediatric pure erythroid leukemia. Thick solid arrows indicate required diagnostic links, while dashed arrows indicate context-dependent exclusion or staging steps. The workflow cross-references morphology, molecular subtype, differential diagnosis, treatment, and MRD tables.

Treatment and Prognosis

No prospective pediatric PEL trial and no accepted PEL-specific regimen have been reported. Children are generally treated within a contemporary pediatric AML protocol or clinical trial, using protocol-defined cytarabine- and anthracycline-based induction followed by risk-adapted consolidation.[9,15,20-27,56] This approach reflects the absence of an alternative evidence-based standard rather than proof that all molecular subtypes respond equally. Reported CNS or other extramedullary cases have generally received systemic AML therapy plus protocol-directed intrathecal treatment. Local radiotherapy or surgery has been used selectively for diagnostic tissue acquisition, neurologic compromise, or local control.

The role of allogeneic hematopoietic stem-cell transplantation (HSCT) in first complete remission is unresolved for PEL itself. Current pediatric AML practice uses adverse genetics, induction response, MRD, primary refractory disease, and relapse status to determine transplant eligibility.[56,57] The Children's Oncology Group AEL series was too small to establish a PEL-specific transplant benefit, and the reported transplanted patients belonged to the erythroid or myeloid subgroup rather than the five-case PEL subset.[9] Limited case evidence describes durable remission after HSCT in selected NFIA::CBFA2T3-associated disease, but selection and publication bias prevent routine recommendation for every NFIA-fusion case.[15,26]

Genotype-directed therapy remains investigational. NUP98-rearranged AML is associated with poor induction response and high MRD, and co-occurring FLT3-ITD should be treated according to pediatric AML protocol or clinical-trial criteria.[55,56] Menin inhibition suppresses NUP98-fusion leukemia in preclinical and patient-derived models, but PEL-specific clinical efficacy has not been established.[58,59] A small retrospective pediatric NUP98-rearranged AML study reported responses with combinations containing BCL-2, FLT3, or CDK6 inhibitors, but only 10 NUP98-rearranged patients were included and the findings do not define a standard regimen.[55] EPOR/JAK2-amplified AEL shows ruxolitinib sensitivity in vitro and in xenograft models, but no validated pediatric clinical strategy exists.[48] Adult TP53-altered PEL responds poorly to intensive chemotherapy, hypomethylating agents, or hypomethylating-agent and venetoclax combinations, so adult data should not be used to promise benefit in children.[10]

Prognosis is adverse but heterogeneous. In the largest pediatric cooperative-group analysis, the five PEL cases had 5-year overall survival and event-free survival of approximately 20%.[9] Pediatric erythroblastic sarcoma series also show poor aggregate survival, but mixed adult and pediatric cohorts, variable definitions, and frequent publication of severe extramedullary cases limit direct comparison.[25] Potential adverse features include PEL morphology, complex or monosomal karyotype, biallelic TP53 alteration, NUP98::KDM5A, induction failure, persistent MRD, relapse, and disseminated CNS or soft-tissue disease. These features should guide risk communication and trial referral, but they do not yet constitute a validated pediatric PEL prognostic model.

Table 7: Current treatment framework and evidence limitations in pediatric pure erythroid leukemia.

Clinical situation	Current approach	Potential escalation	Evidence limitation
Newly diagnosed marrow PEL	Enroll in a pediatric AML protocol or trial. Use protocol-defined intensive induction and response assessment	Risk-adapted consolidation; HSCT assessment for adverse genetics, persistent MRD, or poor response	No PEL-specific prospective trial[9,56]
CNS or extramedullary erythroblastic sarcoma	Systemic AML therapy plus protocol-directed intrathecal treatment. Obtain marrow and complete staging	Individualized HSCT and local control when clinically required	Evidence comes mainly from NFIA-fusion case reports and small series[15,16,20,21,25-27]
NUP98-rearranged disease	Treat as high-risk pediatric AML. Test for cooperating lesions, including FLT3-ITD	Clinical trial for FLT3, menin, BCL-2, or other genotype-directed therapy when appropriate	Targeted evidence is preclinical or small retrospective pediatric AML data, not PEL-specific[55-59]
TP53-altered complex-karyotype disease	High-risk AML management and early clinical-trial referral	HSCT considered only after response and multidisciplinary risk assessment	Adult PEL outcomes are extremely poor; pediatric evidence is sparse[10-14]
EPOR/JAK2-amplified disease	Standard AML treatment while documenting pathway alteration	JAK inhibition only within a clinical trial or exceptional research framework	Ruxolitinib activity is preclinical[48]
Relapsed or refractory disease	Repeat morphology, flow, cytogenetics, DNA and RNA testing; use relapse AML protocol or trial	HSCT or cellular and targeted therapy according to response and availability	No established salvage regimen for pediatric PEL

Measurable Residual Disease Monitoring

MRD is a central prognostic tool in pediatric AML, but no PEL-specific threshold or validated assay has been established.[60,61] Morphology alone is inadequate because its conventional detection limit is approximately 5%, early erythroid regeneration can mimic residual disease, and PEL may persist in extramedullary sites despite a morphologically negative marrow. Morphology should therefore describe response and marrow recovery but should not serve as the sole MRD method.

Multiparameter flow cytometry should use the diagnostic sample to define a leukemia-associated immunophenotype and should also apply a different-from-normal strategy at follow-up.[60,61] A PEL-oriented panel can include CD71, CD36, CD117, CD34, CD45, glycophorin A or another erythroid marker suitable for flow, and exclusion markers for myeloid, lymphoid, monocytic, and megakaryocytic differentiation. Practical limitations include fragility of erythroblasts, cell loss during red-cell

lysis, hemodilution, variable CD34 or CD117 expression, and phenotypic shifts after treatment. The first marrow pull should be reserved for MRD when feasible, and the flow result should be interpreted with biopsy findings and regeneration status.

Molecular MRD is potentially more specific in fusion-defined pediatric disease. When the genomic breakpoint is known, patient-specific RT-qPCR, digital PCR, or validated RNA- or DNA-based sequencing can track NUP98, NFIA, or another stable fusion. A negative broad DNA panel at diagnosis does not provide a molecular MRD target, and a mutation such as TP53 should be interpreted with allelic context and paired with flow because persistence may not always represent the same active leukemic population. Assay sensitivity, specimen type, target stability, and the quantitative reporting threshold should be stated in the laboratory report.[60]

For documented CNS disease, CSF cytology should be combined with flow cytometry and, when technically validated, fusion-specific molecular testing. The reported use of CSF flow and NFIA::CBFA2T3 RNA detection shows diagnostic and monitoring feasibility, but current evidence is limited to individual cases and no standardized CSF MRD threshold or schedule exists.[27] Reasonable AML-based time points include diagnosis, the end of induction courses, pre-HSCT assessment, post-HSCT surveillance when a stable molecular target exists, and any clinical suspicion of relapse. Treatment adjustment should follow the applicable pediatric AML protocol or multidisciplinary trial criteria rather than an unvalidated PEL-specific MRD cutoff.

Table 8: MRD modalities, practical limitations, and proposed use in pediatric pure erythroid leukemia.

Method	Strength	PEL-specific limitation	Suggested use	Evidence
Morphology	Widely available; documents cellular recovery and overt persistence	Low sensitivity; regeneration and dyserythropoiesis can mimic disease; misses isolated CNS or tissue disease	Use with, not instead of, flow or molecular testing	General AML practice; no PEL validation
Multiparameter flow cytometry	Rapid, quantitative, applicable without a known fusion	Fragile erythroblasts, lysis-related cell loss, hemodilution, variable antigen expression, overlap with regenerating erythroid precursors	Record baseline phenotype. Use first-pull marrow, LAIP plus different-from-normal analysis, and a broad exclusion panel	Pediatric AML prognostic evidence; PEL-specific data limited[60,61]
Fusion-specific RT-qPCR or digital PCR	High analytic specificity and sensitivity when the breakpoint is known	Requires a stable, assayable fusion and laboratory validation; partner-specific assays are not universally available	Preferred adjunct for NUP98-, NFIA-, or other fusion-defined disease when technically feasible	Biologically strong; direct pediatric PEL monitoring data are case-based[9,27]
NGS-based MRD	Tracks multiple variants and clonal evolution	Sensitivity and turnaround vary. Persistent mutations may not equal active PEL. RNA fusion detection requires adequate material	Use when validated and when no quantitative PCR assay exists; report limit of detection and target stability	Consensus AML methodology, indirect for PEL[60]
CSF cytology, flow, and molecular testing	Directly assesses documented CNS disease	Low cell count, sample degradation, no standardized PEL threshold, and negative CSF does not exclude parenchymal disease	Use at diagnosis and follow-up in CNS-associated cases according to protocol and clinical status	Limited case evidence[20,27]

Critical Appraisal and Evidence Gaps

The evidence base has major structural limitations. The largest pediatric study included only five PEL cases, while most NFIA-, CIC-, and other fusion-defined observations come from single cases or small series.[9,15,16,20-27] Classification changes from FAB AML-M6 through successive WHO and ICC systems create substantial case-mixing and prevent direct comparison of older survival data. Publication bias likely favors unusual extramedullary presentations, molecularly solved cases, and severe outcomes. Conversely, children who respond well without extensive molecular testing may be underrepresented. The search was restricted to PubMed and English-language full-text publications. Studies indexed only in other databases, non-English reports, and grey literature may therefore have been missed. Initial database retrieval and exclusion counts were not prospectively archived; Figure 1 is a reconstructed audit of the final deduplicated source library rather than a prospectively logged PRISMA flow.

Treatment and MRD conclusions require similar caution. No randomized or prospective PEL-specific therapeutic trial has been reported, HSCT selection is confounded by response and genetic risk, and targeted-therapy evidence is largely preclinical or derived from broader NUP98-rearranged pediatric AML.[48,55-59] Flow-cytometric and molecular MRD methods have not been validated specifically for fragile erythroid blasts or CNS erythroblastic sarcoma. Future progress requires international registry-based case capture, harmonized WHO and ICC annotation, central morphology and immunophenotype review,

paired DNA and RNA sequencing, standardized marrow and CSF MRD collection, and prospective reporting of treatment exposure and outcome.

Conclusions

Pediatric PEL is a rare, high-risk erythroid-lineage leukemia that requires integrated diagnosis and deliberate exclusion of reactive erythroid hyperplasia, myelodysplastic neoplasms, AML with myelodysplasia-related genetics, acute megakaryoblastic leukemia, and Down syndrome-associated myeloid proliferations. The adult model of biallelic TP53 alteration and complex karyotype remains important, but childhood disease includes NUP98-, NFIA-, CIC-, and other fusion-defined presentations with distinct marrow and extramedullary patterns. No PEL-specific pediatric treatment standard or validated prognostic score exists. Current management should follow a high-quality pediatric AML protocol or clinical trial, with HSCT decisions based on genetics, treatment response, MRD, relapse status, and disease distribution. MRD should combine flow cytometry with fusion-specific molecular monitoring when available, while CSF-based monitoring remains case-supported and unstandardized. The immediate priorities are transparent evidence grading, early RNA fusion testing, genotype-aware reporting, harmonized MRD methods, and international prospective registration.

List of Abbreviations

AEL, acute erythroid leukemia; AI, artificial intelligence; AMKL, acute megakaryoblastic leukemia; AML, acute myeloid leukemia; AML-M6, acute myeloid leukemia M6; ARID1A, AT-rich interaction domain 1A; ATM, ataxia telangiectasia mutated; BCL-2,B-cell lymphoma 2; CBFA2T3, CBFA2/RUNX1 partner transcriptional co-repressor 3; CDK6, Cyclin-dependent kinase 6; CIC, capicua transcriptional repressor; CNS, central nervous system; COG, Children's Oncology Group; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; EFS, event-free survival; EPOR, erythropoietin receptor; ES, erythroblastic sarcoma; FAB, French-American-British; FISH, fluorescence in situ hybridization; FLT3, FMS-like tyrosine kinase 3; GATA1, GATA binding protein 1; GATA1s, short isoform of GATA1; GLUT1, glucose transporter 1; HMA, hypomethylating agent; HOX/MEIS, homeobox and myeloid ecotropic viral integration site transcriptional programs; HSCT, hematopoietic stem-cell transplantation; ICC, International Consensus Classification; IHC, immunohistochemistry; JAK2, Janus kinase 2; KIT, KIT proto-oncogene receptor tyrosine kinase; LAIP, leukemia-associated immunophenotype; MDS, myelodysplastic neoplasms; MEDLINE, Medical Literature Analysis and Retrieval System Online; ML-DS, myeloid leukemia of Down syndrome; MPO, myeloperoxidase; MRD, measurable residual disease; NFIA, nuclear factor I A; NGS, next-generation sequencing; NUP98, nucleoporin 98; OS, overall survival; PB, peripheral blood; PEL, pure erythroid leukemia; RNA, ribonucleic acid; RT-qPCR, reverse-transcription quantitative polymerase chain reaction; RUNX1T1, RUNX1 partner transcriptional co-repressor 1; SANRA, Scale for the Assessment of Narrative Review Articles; SREBF1, sterol regulatory element-binding transcription factor 1; STAT5, signal transducer and activator of transcription 5; TAM, transient abnormal myelopoiesis; TP53, tumor protein p53; VAF, variant allele frequency; WHO, World Health Organization.

Authors' Contributions

Conceptualization, methodology, investigation, data curation, visualization, project administration, and writing—original draft: YY. Validation, formal analysis, and supervision: RP. Writing—review and editing: YY and RP. All authors have read and agreed to the submitted version of the manuscript.

Availability of Data and Materials

All literature-derived data discussed in this narrative review are available in the cited publications. The original image files for Figure 2 are retained by the corresponding author and are not publicly deposited, because they derive from clinical material and remain subject to applicable ethical and privacy restrictions. The source files may be provided confidentially to the editorial office by the corresponding author upon request.

Ethical Approval

This narrative review did not involve prospective human-subject research or collection of new research data. Figure 2 comprises anonymized, previously unpublished bone marrow aspirate images obtained during routine clinical care and supplied by the authors. No additional research procedure was performed for the purposes of this review. The ethical basis for publication of these clinical images is the written informed consent for publication obtained from the patient's parent/legal guardian, as stated below.

Consent for Publication

Figure 2 contains anonymized, previously unpublished patient-derived bone marrow aspirate images obtained during routine clinical care and supplied by the authors. The images contain no directly identifying patient information. Written informed consent for publication of the anonymized clinical images was obtained from the patient's parent/legal guardian.

Conflict of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AI-declaration

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