

Artificial intelligence applications in pediatric hematology and oncology: current advances and future perspectives

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ABSTRACT: In pediatrics, hematology and oncology, artificial intelligence (AI) is increasingly being studied as a way to retrieve clinically meaningful information from complex and heterogeneous biomedical data. This narrative review critically reviews the current use of AI, machine learning, and deep learning in the management of malignancies and solid tumors in children, as well as benign hematological disorders, highlighting their translational potential. Applications that are emerging include automated blood and bone marrow morphology, medical imaging and digital pathology, disease classification, measurable residual disease evaluation, risk stratification, treatment-response and relapse prediction, toxicity evaluation, and survival modelling. The evidence is more robust for use in acute lymphoblastic leukemia, and less so in acute myeloid leukemia and lymphoma in children with hematological malignancies. AI-based imaging and radiomics are more extensively studied in central nervous system tumors than in other pediatric solid tumors, for which the evidence remains less mature. While there has been some progress in encouraging performance across multiple applications, the majority of studies are retrospective, single centre or relatively small in size with limited external validation and prospective testing. There are many obstacles to clinical translation, such as small pediatric populations, disease rarity and heterogeneity, data fragmentation, algorithmic bias, explainability, and workflow integration issues and concerns. The development of multimodal and longitudinal AI, foundation models, federated learning, and dynamic prediction systems combining clinical, imaging, pathology and multi-omics data are anticipated to be key areas of future progress. The role of AI in the field of pediatric hematology-oncology will be determined not just by algorithmic performance, but by strong evidence supporting the benefit of human-AI collaborations within the clinical decision-making process in terms of improved patient outcomes, clinical safety and equity.

KEYWORDS: Machine learning; deep learning; pediatric hematology; pediatric oncology; childhood cancer; leukemia; precision medicine

INTRODUCTION

Pediatric hematology and oncology include a wide range of clinically and biologically distinct, malignant and nonmalignant disorders including but not limited to acute leukemias, lymphomas, central nervous system and extracranial solid tumors, hemoglobinopathies, bone marrow failure syndromes, cytopenias and coagulation disorders. Childhood cancers are relatively rare compared to cancers in adults, but have a significant impact as they are early in life and can have long term consequences in survivors. Leukemias and brain tumours are among the most prevalent childhood cancers, affecting around 400,000 children and adolescents aged 0-18 years of age annually in the world (World Health Organization [WHO], 2026). In addition to the above, hematological malignancies, mainly acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and lymphomas, account for a large share of childhood mortality, and nonmalignant hematological diseases are also a major cause of childhood mortality [1-3].

There have been significant improvements in diagnosis, risk-adapted therapy, supportive care and molecular characterization which have greatly improved outcomes. Access to treatment for paediatric cancer is excellent in high income countries, with over 80% of children being cured, especially those with childhood ALL [2, 4]. Biologically distinct subgroups have been characterized through molecular methods and provide new possibilities

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for targeted and immune-based therapies such as blinatumomab (an anti-CD19/anti-CD3 bispecific T-cell bispecific antibodies) and Chimeric Antigen Receptor T-cell (CAR-T) therapy, which could potentially be a cure to selected high-risk hematological diseases (HRHDs); hematopoietic stem-cell transplantation (HSCT) is also potentially curative for some HRHDs [5, 6]. However, relapse, resistance to treatment and the presence of acute and chronic side effects are still significant issues. Pediatric hematology-oncology is therefore becoming more personalized with strategies that take into account both the biology of the disease and molecular characteristics, response to treatment, toxicity risk, as well as patient-specific factors [7].

There is also some inequality in progress. In many high income countries, the cure rates are > 80%, while in many LMIC countries, the cure rates are < 30% due to differences in timely diagnosis, access to treatment, supportive care, and relapse and toxicity management [8-10]. These inequities are also seen in nonmalignant hematological diseases like sickle cell disease [11]. Therefore, the ability of emerging precision-medicine approaches to be accessible, generalizable, and to provide a clinical benefit that's equitable must not be overlooked, in addition to the technical performance.

Precision medicine has greatly improved the ability to characterize pediatric diseases at the level of the biology of the disease. Molecular profiling can help narrow down diagnoses, help to uncover clinically relevant subgroups, and uncover potential actionable alterations. Integration of molecular and clinical information has proven to be feasible and clinically relevant in large-scale sequencing programs and the multinational INFORM registry in pediatric malignancies [12]. A methodological paradox arises with increasing biological resolution, however, as the number of potentially informative variables increases and already rare pediatric disease events are broken into smaller and smaller molecular classes.

At the same time, pediatric hematology-oncology has become data-driven. In the modern era, a range of information can be obtained from EHRs, laboratory values, blood and bone marrow morphology, flow cytometry, cytogenetics, MRD, radiological imaging, digital pathology, treatment data, and genomic, transcriptomic and other omics data [13-15]. The challenge has now become not only generating data but extracting clinically meaningful information and, in order to better diagnose, to better stratify risk, to better choose treatment, and to be able to predict outcome, to integrate diverse data sources.

One promising way to tackle this complexity is through the use of artificial intelligence (AI), such as machine learning (ML) and deep learning (DL). AI can provide complementary tools to conventional biostatistics for extracting insights from nonlinear relationships, high-dimensional molecular profiles, images, free text, longitudinal measurements, and complex interactions among variables [16, 17]. AI has therefore been studied for disease detection and classification, automated cellular morphology, imaging and digital pathology, risk stratification, prognosis, prediction of treatment response and relapse, toxicity prediction and assessment, and clinical decision support [18]. The potential applications of multimodal AI and multi-omics methods are especially notable, as medical decisions are rarely made based on a single information source, and a combination of morphology, immunophenotyping, molecular data, imaging, treatment history and longitudinal response may be necessary for most cases.

To effectively contextualize these technologies, it is essential to distinguish between artificial intelligence (AI), machine learning (ML), and deep learning (DL) [19]. AI is the overarching concept of computational systems performing tasks that typically require human perception and decision-making. ML is a subset of AI where algorithms automatically learn relationships from data rather than relying on predefined rules, while DL is a further specialized branch of ML utilizing multi-layered neural networks to extract abstract representations directly from highly complex, unstructured data without manual feature engineering [19]. In pediatric oncology, clinical decisions are inherently multidimensional, relying on the careful synthesis of electronic health records, laboratory values, multi-omics profiles, and digital pathology. Consequently, the performance of medical AI cannot be judged by algorithmic accuracy alone; metrics such as sensitivity, specificity, model calibration, and true clinical utility are critical because misclassifications in vulnerable pediatric populations carry severe consequences. Furthermore, while multimodal AI networks are technically promising, deploying complex network architectures alone is insufficient [20]. To be clinically viable, AI systems must be supported by rigorous external validation, transparent failure mode assessments, and seamless human-AI workflow integration [21]. When AI models inevitably encounter edge cases or make errors, they must be utilized strictly as explainable decision-support tools rather than autonomous decision-makers, ensuring that expert clinical judgment remains central to patient care [21]. Finally, emerging trends such as generative AI, foundation models, and synthetic data generation offer novel pathways to overcome data scarcity, enhance model explainability, and improve algorithmic fairness in rare pediatric hematological diseases [21].

Adults can't be directly applied to kids. Pediatric diseases are unique with biological, molecular, physiologic, therapeutic, reference, and outcome perspectives. Moreover, children are also underrepresented in many biomedical datasets, which puts them at risk of suboptimal performance when adult-derived models are applied to children [22]. In addition to these challenges, many pediatric diseases are rare, datasets are small and sparse, institutional variation is present, data is missing, and there is class imbalance, overfitting and little external validation [17]. Thus, good prediction in the retrospective data set is not necessarily reflected in clinical utility.

Therefore, translating the findings of computational performance to clinical benefit continues to be a major challenge. To ensure responsible implementation, external and prospective validation, calibration and failure mode assessment, generalizability evaluation, transparent reporting, and human-AI interaction and workflow integration [23] are needed. Ethical and governance issues also arise when applying the techniques to children, including consent and assent, privacy, fairness, explainability, accountability, and algorithmic bias [24]. These factors are especially relevant in situations where recommendations by AI can affect the intensive chemotherapy, transplantation, investigational treatment, and/or treatment de-escalation.

Against this background, the literature remains fragmented across diseases, data modalities, and clinical applications. This narrative review therefore provides a critical and integrated synthesis of AI, ML, and DL applications across pediatric hematology and oncology, encompassing benign hematological disorders, hematological malignancies, solid tumors, HSCT, diagnosis and classification, imaging and digital pathology, risk stratification, prognosis, treatment-response, relapse and toxicity prediction, precision medicine, and multimodal and multi-omics integration. Rather than cataloguing algorithms, the review distinguishes applications supported by credible validation from those that remain technically promising but clinically unproven. Particular attention is given to pediatric-specific data limitations, external validity, explainability, fairness, privacy, regulatory and workflow considerations, and emerging approaches including multimodal and federated learning, generative AI, foundation models, synthetic data, and digital twins [24]. By connecting technological capabilities with the evidence required for responsible implementation, this review aims to clarify the current clinical value, major translational gaps, and future potential of AI in precision pediatric hematology and oncology. The overall landscape of multimodal data sources, major disease domains, and AI-supported applications across the pediatric hematology-oncology care continuum is summarized in Figure 1.

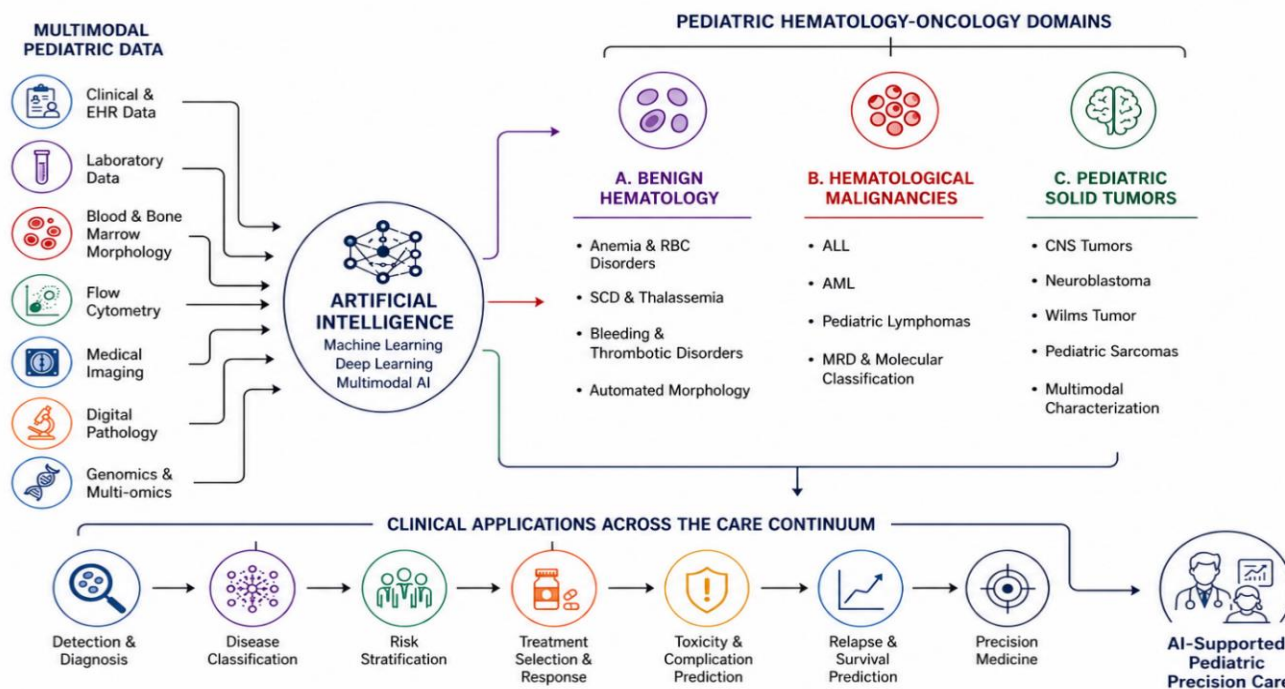


Figure 1. Artificial intelligence landscape across pediatric hematology and oncology. Multimodal pediatric data, including clinical and electronic health record (EHR) data, laboratory measurements, blood and bone marrow morphology, flow cytometry, medical imaging, digital pathology, and genomic and multi-omics data, can be integrated using artificial intelligence (AI) approaches to support applications across benign hematology, hematological malignancies, and pediatric solid tumors. Applications span detection and diagnosis, disease classification, risk stratification, treatment selection and response prediction, toxicity and complication prediction, relapse and survival prediction, and precision medicine, ultimately supporting AI-assisted pediatric precision care.

ARTIFICIAL INTELLIGENCE IN MEDICINE: CONCEPTS AND METHODOLOGICAL FRAMEWORK

Artificial intelligence, machine learning, and deep learning

Artificial intelligence (AI) is the broadest term, encompassing computational systems for tasks such as perception, language processing, pattern recognition, and decision support. Machine learning (ML) is a subset of AI in which algorithms learn relationships from data rather than relying solely on explicitly programmed rules; deep learning (DL) is a subset of ML based on multilayer neural networks that learn increasingly abstract representations. The hierarchy is therefore $AI \rightarrow ML \rightarrow DL$, and the terms are not interchangeable. Many biomedical studies described generically as “AI” are more precisely conventional ML applications [25]. This distinction also separates data-driven ML from rule-based expert systems, in which decision logic is predefined. Traditional regression models and manually constructed clinical scores use prespecified variables and functional forms, whereas many ML methods flexibly capture interactions and nonlinearities. Flexibility does not imply superiority: a systematic review found no consistent performance advantage of ML over logistic regression for clinical prediction, emphasizing that complexity should match the data and clinical question [26].

In pediatric hematology-oncology, this distinction is particularly consequential because many datasets are small, imbalanced, retrospective, and single-center; a recent systematic review of pediatric hematologic malignancy models also identified limited external validation [17]. Conventional ML has nevertheless been explored for relapse prediction in childhood acute lymphoblastic leukemia (ALL) [27], while more recent ensemble-learning approaches have been developed for treatment-related complications such as tumor lysis syndrome [28]. Relevant tasks include blood-cell classification, leukemia detection, digital pathology, imaging, genomics, risk stratification, prognosis, and prediction of response or toxicity; method choice depends on data modality, dimensionality, sample size, interpretability, and intended use.

In the context of computational technologies, artificial intelligence (AI) is the broad discipline of simulating human intelligence [19]. Machine learning (ML), a subset of AI, focuses on algorithms that learn from data without explicit programming, whereas deep learning (DL) is a specialized branch of ML that uses multi-layered neural networks to automatically extract complex features directly from raw data, such as medical images or genomics, eliminating the need for manual feature engineering [19]. While multi-network and multimodal AI systems offer advanced capabilities, their architectural complexity alone is insufficient for clinical adoption; they require rigorous external validation and clear evidence of clinical utility to ensure reliability across diverse pediatric populations [20]. Furthermore, to mitigate the risks associated with inevitable algorithmic errors, AI must be implemented within a human-in-the-loop framework, serving as an explainable decision-support tool rather than an autonomous decision-maker, ensuring that final clinical judgments remain with healthcare professionals [21]. Finally, addressing the persistent challenge of data scarcity in rare pediatric diseases, emerging trends in generative AI—such as foundation models and synthetic data generation—provide promising solutions to improve model robustness and fairness [29].

Major learning paradigms and algorithms

Supervised learning uses labeled examples to map predictors to an outcome. Classification addresses categorical endpoints such as diagnosis, relapse, or toxicity, whereas regression predicts continuous quantities; time-to-event extensions support survival prediction. Common pipelines may compare logistic regression, decision trees, random forests, support vector machines, k-nearest neighbors, gradient boosting—including XGBoost or CatBoost—and neural networks. The objective is reproducible prediction of a clinically relevant target, not selection of the most complex algorithm [30].

Unsupervised learning instead searches for structure without a predefined outcome label. Clustering methods such as k-means and hierarchical clustering can identify groups of patients, tumors, or molecular profiles, while principal component analysis and learned representations reduce dimensionality and reveal dominant patterns. In pediatric oncology [31] used k-means clustering of MRI radiomic features to identify pediatric low-grade glioma

subgroups associated with key molecular markers, illustrating how unsupervised methods can generate biologically testable patient partitions without being diagnostic tools in themselves.

Semi-supervised learning combines limited labeled data with larger unlabeled datasets, whereas self-supervised learning derives supervisory signals from the data themselves before task-specific fine-tuning. Both are attractive in rare pediatric diseases, where expert annotation of imaging, digital pathology, blood or marrow morphology, and genomic data is costly. In pediatric low-grade glioma, self-supervised transfer learning improved molecular-subtype classification and was evaluated on an independent external cohort, an example of label-efficient learning, not routine deployment [32].

Reinforcement learning (RL) learns policies through sequential interactions in which actions are linked to future rewards. Conceptually, it could support adaptive dosing, supportive-care strategies, or multistep treatment decisions; however, healthcare RL is highly sensitive to confounding, reward specification, off-policy evaluation, and safety constraints [33]. Direct evidence in pediatric hematology-oncology remains sparse, and RL should therefore be regarded as an investigational framework rather than an established clinical approach.

Deep learning architectures relevant to pediatric hematology-oncology

Artificial neural networks consist of interconnected computational units that transform input variables through learned weights; deep neural networks contain multiple representation layers and can approximate complex nonlinear relationships. Their principal advantage is representational flexibility, particularly for high-dimensional unstructured data, but they generally require more data and computational resources and can be harder to interpret than simpler models [34].

Convolutional neural networks (CNNs) exploit spatially local patterns and have become central to image-based biomedical AI. Relevant pediatric hematology-oncology tasks include leukocyte and blast recognition on peripheral smears, bone-marrow cell classification, digital pathology, radiologic tumor detection, segmentation, and disease classification. In hematopathology, a deep neural network trained on a large bone-marrow image dataset achieved high cell-type discrimination, demonstrating the feasibility of automated morphology while also highlighting the need to test performance across laboratories, scanners, staining practices, and patient populations before pediatric clinical extrapolation [35].

Recurrent neural networks (RNNs), including gated variants such as long short-term memory networks, were designed to model ordered sequences and are therefore relevant to longitudinal electronic health records (EHRs), serial laboratory values, treatment trajectories, and time-varying toxicity signals. Large-scale EHR work has shown that deep sequential models can learn directly from temporally ordered clinical data, although transportability and workflow integration remain distinct problems from retrospective prediction accuracy [25].

Transformers use attention mechanisms to model long-range dependencies and permit highly parallel representation learning. In medicine they now underpin language models, structured-EHR models, vision transformers, genomic sequence models, and multimodal systems. Med-BERT demonstrated how transformer pretraining on large structured EHR datasets can support downstream disease prediction [36]. In pediatric neuro-oncology, a vision-transformer-based MRI classifier incorporating age information has been evaluated for pediatric brain-tumor classification, illustrating the architecture's direct relevance while not establishing clinical utility [37].

Model development, validation, and performance evaluation

A clinically credible AI pipeline includes data acquisition → preprocessing → feature selection → model development → internal validation → external validation → prospective evaluation → clinical implementation. Preprocessing should address missing data, coding consistency, scaling, feature selection, and carefully controlled augmentation. Class imbalance is particularly important in rare pediatric outcomes because high accuracy may hide poor detection of minority cases [38]. Pediatric datasets are often small relative to the number of predictors, increasing the risk of overfitting. Sample-size planning should therefore consider outcome frequency, candidate parameters, expected model performance, and precision [39]. Cross-validation and bootstrapping help assess internal performance but cannot replace independent validation. Training data are used to fit the model, validation

data for tuning, and test data for final evaluation. Data leakage occurs when information from outside the intended training process influences model development, producing overly optimistic results [40]. External validation across different hospitals, populations, time periods, or devices is essential for assessing generalizability [41]. Common classification metrics include accuracy, sensitivity, specificity, precision, F1-score, and AUROC. For imbalanced datasets, precision-recall measures may be more informative than AUROC [42]. Survival models often use the concordance index. Calibration assesses whether predicted risks agree with observed outcomes [43]. Decision-curve analysis evaluates whether predictions provide clinical benefit across decision thresholds [44]. Ultimately, strong retrospective performance is insufficient; models require external validation, prospective evaluation, and evidence of meaningful clinical benefit before implementation.

Explainability, interpretability, and clinical trust

Interpretability refers to how easily a model or its predictions can be understood, while explainability uses methods to clarify complex model behavior. In high-stakes medicine, inherently interpretable models may be preferable when they achieve similar performance to black-box models [45]. Common explainability methods include SHAP, LIME, and Grad-CAM. SHAP estimates feature contributions, LIME explains individual predictions using local surrogate models, and Grad-CAM highlights image regions influencing CNN predictions. However, explanations do not prove causality, biological validity, fairness, robustness, or safety. In pediatric hematology-oncology, explainability should support error analysis, bias detection, and clinician review, while trust should ultimately depend on validated performance and clinical evidence [46].

ARTIFICIAL INTELLIGENCE IN BENIGN PEDIATRIC HEMATOLOGY

Anemia and red blood cell disorders

Direct pediatric evidence remains limited and is concentrated in screening and morphology [15]. Combined elastic light scattering with machine learning to distinguish healthy children, iron-deficiency anemia, and thalassemia minor from red-cell optical/morphologic signatures, illustrating a low-volume screening concept. In children with severe malaria anemia, deep learning quantified disease-associated erythrocyte morphologies on blood films, extending automated phenotyping beyond routine indices [47]. By contrast, CBC-only models separating iron-deficiency anemia from β -thalassemia trait have largely been developed in general clinical cohorts rather than explicitly pediatric populations [48, 49]; their pediatric transportability therefore remains unproven.

Hemoglobinopathies: sickle cell disease and thalassemia

For sickle cell disease, recent pediatric studies increasingly target complications rather than diagnosis. OCT-based machine learning detected sickle maculopathy in a retrospective pediatric cohort [50], while automated vascular extraction and machine learning applied to pediatric MRA characterized CNS vasculopathy and clinical risk groups [51]. These are promising imaging biomarkers, but neither demonstrates prospective treatment benefit. Experimental morphology platforms can classify sickled red cells from microfluidic images with high technical performance, although clinical samples were not developed as a pediatric decision tool [52]. Similarly, AI-derived RBC morphology plus XGBoost/logistic regression showed strong discrimination for thalassemia and subtypes, including IDA-versus-thalassemia separation, in a general hematology population rather than a pediatric validation cohort [53]. Robust pediatric AI evidence for transfusion-related prediction remains insufficient.

Table 1. Major artificial intelligence and machine learning approaches relevant to pediatric hematology and oncology

AI approach	Basic principle	Typical data type	Representative/potential pediatric hematology-oncology application	Key strengths	Major limitations	Reference(s)
Conventional supervised ML	Learns a labeled predictor–outcome relationship for classification or regression	Clinical variables, laboratory data, omics, engineered imaging features	Relapse, toxicity, response, and risk prediction; childhood ALL relapse prediction provides a direct example	Effective for structured data; accommodates multiple candidate algorithms; often feasible with modest computing resources	Performance depends strongly on sample size, labeling, preprocessing, and validation; not inherently superior to regression	[27, 30]
Random forests	Ensembles multiple decision trees generated from resampled observations/features	Tabular clinical, laboratory, genomic, radiomic data	Potential component of pediatric leukemia relapse/toxicity modeling; direct pediatric ALL studies have compared multiple conventional ML approaches	Models nonlinearities and interactions; relatively robust; variable-importance measures available	Can overfit small datasets; probabilities may require calibration; importance measures can be misleading	[27]
Support vector machines	Finds a decision boundary with maximal class separation, optionally using nonlinear kernels	Tabular, high-dimensional molecular, engineered image features	Potential classification of leukemia, molecular profiles, or treatment outcomes; application should be independently validated in pediatric cohorts	Useful in high-dimensional settings; flexible kernels	Sensitive to tuning and scaling; limited direct interpretability; performance may deteriorate with distribution shift	[30]
Gradient boosting, including XGBoost/CatBoost	Sequentially combines weak learners to correct preceding prediction errors	Primarily structured clinical/laboratory data	CatBoost has been studied for tumor lysis syndrome prediction in childhood ALL; XGBoost is a related boosting implementation	Strong performance on heterogeneous tabular data; handles complex interactions	Overfitting and miscalibration remain possible; hyperparameter-dependent; retrospective accuracy does not establish benefit	[28]
Artificial/deep neural networks	Stacked nonlinear transformations learn complex input–outcome relationships	Structured data, images, signals, multimodal data	Potential nonlinear risk, response, or multimodal prediction; especially useful when representation learning is required	Highly flexible; scalable to complex, high-dimensional inputs	Data- and computation-intensive; optimization and interpretability challenges; often unnecessary for small tabular cohorts	[34]
Convolutional neural networks	Learns spatial features through convolutional filters	Blood/bone-marrow images, histopathology, MRI/CT/PET	Blood- and marrow-cell morphology, digital pathology, tumor detection and segmentation; large-scale marrow morphology evidence exists, but pediatric-specific transportability requires validation	Automated feature learning; strong image-recognition capability	Domain shift from staining, scanner, acquisition, or institution; annotation burden; black-box behavior	[35]
Recurrent/sequential neural networks	Models temporal dependencies across ordered observations	Longitudinal EHRs, laboratory series, treatment	Potential/emerging: prediction from serial counts, chemotherapy courses, toxicity trajectories, or	Represents temporal context and variable-length sequences	Missingness and irregular sampling are difficult; temporal leakage and	[25]

		trajectories	longitudinal EHRs; not established in routine pediatric hemato-oncology		changing practice patterns can bias models	
Transformers	Attention-based representation learning captures long-range dependencies	Text, structured EHRs, images, genomics, multimodal data	Direct pediatric example: MRI-based pediatric brain-tumor classification with a vision transformer; also potentially applicable to EHRs and genomics	Parallelizable; supports pretraining and multimodal learning; strong representation capacity	Computationally demanding; data hungry; potentially poorly calibrated or opaque; clinical validation remains essential	[36, 37]
Unsupervised learning	Discovers latent structure without outcome labels through clustering or dimensionality reduction	Radiomics, omics, phenotypes, high-dimensional clinical data	Direct pediatric example: radiomic clustering of pediatric low-grade gliomas associated with molecular markers	Does not require outcome labels; useful for hypothesis generation and subtype discovery	Clusters may be unstable or clinically artificial; association with biology does not establish clinical usefulness	[31]
Self-supervised learning	Generates supervisory signals from unlabeled data before task-specific fine-tuning	Imaging, pathology, morphology, genomics, text	Direct pediatric example: label-efficient molecular subtyping of pediatric low-grade glioma from MRI with external testing	Reduces dependence on expert labels; facilitates transfer learning in data-scarce settings	Requires sufficiently representative unlabeled data; pretrained representations can inherit dataset bias; downstream validation remains necessary	[32]
Natural language processing	Extracts or transforms information contained in clinical language	Notes, pathology/radiology reports, discharge summaries, literature	Potential/emerging in pediatric hemato-oncology: EHR phenotyping, information extraction, cohort identification, documentation, and research support	Can convert unstructured text into analyzable information	Documentation bias, privacy concerns, local terminology, and transportability across institutions	[54]
LLMs/foundation models	Large pretrained models are adapted or prompted for multiple language or multimodal tasks	Text; increasingly images, EHRs, laboratory and multimodal data	Emerging and not clinically validated in pediatric hemato-oncology: summarization, knowledge retrieval, communication support, trial matching, and decision-support augmentation	Broad task adaptability; few-/zero-shot capability; natural-language interface	Hallucinations, inconsistency, bias, privacy, accountability, uncertain calibration, and sparse pediatric prospective evidence	[55, 56]
Explainable AI approaches	Generates global or local explanations for otherwise complex predictions	Tabular ML, images, multimodal models	SHAP-assisted interpretation of pediatric ALL risk models; Grad-CAM/saliency approaches for morphology or imaging models	Supports model interrogation, error analysis, and clinician review	Explanation fidelity and stability may be limited; explanations do not prove causality, fairness, robustness, or safety	[28]

Bleeding, coagulation, and other benign hematological disorders

Evidence in bleeding and cytopenic disorders is small but clinically oriented. In 944 children with newly diagnosed immune thrombocytopenia (ITP), registry-based machine learning predicted chronicity with AUROC 0.737 [57]. A prospective 286-child ITP study reported XGBoost AUROC 0.886 for moderate-to-severe bleeding, but used a single-center internal split [58]; urinary-metabolomic prediction of rituximab response involved only 37 children, emphasizing proof-of-concept status [59]. In hemophilia A, a model in Chinese boys estimated physical-activity-related bleeding risk, but the narrow cohort limits generalizability [60]. Pediatric thrombosis is more advanced: a real-time EHR model was derived and validated for hospital-acquired VTE [61], yet its subsequent randomized implementation did not reduce VTE, despite good discrimination [62]. Pediatric AI evidence for other coagulation disorders and cytopenias remains sparse.

Automated hematological morphology and laboratory decision support

Automated morphology may be the nearest-term laboratory application. A prospective pediatric study of 372 individuals and approximately 500,000 annotated cells achieved high sensitivity/specificity for several leukocyte and erythrocyte classes, but was positioned as a prediagnostic decision-support tool rather than an outcomes-validated system [63]. General hematology platforms such as RedTell and Bio-Net further demonstrate scalable segmentation, feature extraction, and RBC/WBC/platelet detection, but provide indirect, not pediatric clinical-utility, evidence [64, 65]. Overall, benign pediatric hematology remains predominantly at proof-of-concept or technical-validation stages; meaningful translation requires multicenter pediatric datasets, external and prospective validation, calibrated handling of rare-class imbalance, workflow integration, and demonstration that model-guided care improves clinically important outcomes.

Table 2. Representative artificial intelligence studies in benign pediatric hematology.

Condition / application	AI method	Data type	Study population	Key finding /clinical relevance	References
Iron-deficiency anemia/thalassemia-minor screening	Machine-learning classification of elastic light-scattering signatures	Optical signatures reflecting RBC morphology	Pediatric	Demonstrated feasibility of rapid, low-volume morphology-based anemia screening without conventional smear interpretation	[15]
Severe malaria anemia morphology	Deep learning/image analysis	Digitized peripheral blood films	Pediatric children with severe malaria anemia	Demonstrated that AI can capture erythrocyte phenotypes associated with severe pediatric anemia beyond visible parasitemia	[47]
Sickle-cell maculopathy	Logistic regression, KNN, random forest	Optical coherence tomography	Pediatric SCD cohort	Supported automated extraction of an SCD complication phenotype from routinely acquired imaging	[50]
Sickle-cell CNS vasculopathy	Automated computer vision with clustering, classification, and event-based modeling	Magnetic resonance angiography	Pediatric sickle cell anemia	Extracted vessel-level information, including small-vessel features not represented by conventional radiologic scoring	[51]
Sickle RBC morphology	Deep learning integrated with microfluidics	Images of RBCs adhered to laminin in microfluidic assays	General/experimental SCD samples; not pediatric-specific	Cell classification accuracy was 96.0 ± 0.3%, demonstrating strong technical automation of a labor-intensive assay	[52]
Thalassemia screening and subtype classification	XGBoost and logistic regression using AI-extracted RBC features	Automated RBC morphology	General hematology; not pediatric-specific in the reported validation	LR AUROC 0.98 for thalassemia vs control and 0.88 for IDA vs thalassemia; supports morphology-driven screening	[53]
ITP chronicity	Multiple machine-learning approaches	Baseline clinical/laboratory registry variables	Pediatric, 944 children/adolescents	AUROC 0.737; demonstrates scalable prognostic modeling in a comparatively large international pediatric ITP cohort	[57]
ITP bleeding risk	Seven ML algorithms; XGBoost best-performing	Clinical and laboratory variables	Pediatric, prospectively collected cohort of 286 patients	XGBoost AUC 0.886; potentially relevant for early risk stratification	[58]

ITP rituximab response	Machine learning with metabolomic feature selection	Urinary metabolomics	Pediatric, 37 steroid-nonresponsive patients	A seven-metabolite model achieved AUC 0.85 ± 0.13 , suggesting a possible precision-treatment biomarker	[59]
Hemophilia A activity-related bleeding	Machine-learning survival/risk modeling	Clinical, treatment, activity, joint, and pharmacokinetic variables	Pediatric, Chinese boys with hemophilia A	Illustrates individualized activity-related bleeding prediction as a potential aid to prophylaxis/activity planning	[60]
Hospital-acquired pediatric VTE	Real-time EHR prognostic model embedded in model-guided thromboprophylaxis workflow	Longitudinal EHR clinical data	Pediatric, 17,427 randomized hospitalizations	In the randomized trial, model C-statistic was 0.799, but HA-VTE was not reduced (0.7% control vs 0.9% intervention; $P=.10$), directly demonstrating the gap between predictive accuracy and clinical utility	[62]
Automated pediatric peripheral-blood morphology	AI image classifier with expert annotations and data augmentation	Digitized peripheral blood smears	Pediatric, 372 individuals; ~500,000 annotated cell objects	For benign RBC phenotypes, sensitivity was 80% for sickle cells and 81% for target and pencil cells, with 99% specificity for sickle and pencil cells; supports prediagnostic laboratory assistance	[63]
Interpretable RBC morphology platform	Mask R-CNN segmentation, quantitative feature extraction, decision-tree classifiers	RBC microscopy images	General hematology/research; not pediatric-specific	Demonstrates interpretable, reusable morphology infrastructure that could support pediatric laboratory workflows	[64]

ARTIFICIAL INTELLIGENCE IN PEDIATRIC HEMATOLOGICAL MALIGNANCIES

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) has the most developed pediatric AI evidence base. Deep learning on Giemsa-stained bone-marrow whole-slide images can distinguish ALL from AML/nonleukemic marrow and retain, with external attenuation, signals for B/T lineage and ETV6::RUNX1 [66]. In flow cytometry, supervised learning has automated childhood B-ALL MRD across three laboratories, standardizing an early-response endpoint [67], while transformer models support event-level population identification without manual gating [68]. Molecular classifiers address unresolved disease: ALLIUM integrated methylation and expression to classify 17 subtypes in Nordic pediatric cohorts [69], whereas ALLCatchR generalized transcriptomic subtyping to independent mixed-age cohorts, predominantly pediatric in validation [70]. Prognostic models exploit multidimensional information: relapse prediction generalized to an independent childhood ALL cohort [27] (Pan et al., 2017); random-survival forests identified genomic predictors of event-free survival in high-risk pediatric ALL [71]. and methylation profiling added relapse-risk information to clinical-genetic variables [72]. PREPARE-ALL, developed in 2,252 children across five Indian centers, improved relapse sensitivity versus clinicians but retained modest specificity/positive predictive value, illustrating the gap between prediction and treatment utility [73].

Acute myeloid leukemia

Pediatric AML evidence is substantially smaller. UMAP-HDBSCAN enabled flow-cytometric MRD detection, but MRD-positive test data came from only 10 children [74]. Analysis of 696 diagnostic and 194 relapsed pediatric AML methylomes identified recurrence-associated signatures without independent external validation [75]. Conversely, an infant-AML transcriptomic score derived from four Children's Oncology Group trials underwent external validation and refined existing risk stratification [76]. Post-transplant relapse models integrating chimerism and clinical variables remain single-center and cross-validated [77]. Pediatric AI for diagnostic morphology and treatment-response prediction remains limited; adult AML studies are indirect.

Pediatric lymphomas

Direct pediatric lymphoma evidence remains sparse and imaging-centric. CT radiomics has differentiated pediatric DLBCL from Hodgkin lymphoma in a small single-center cohort [78], while PET/CT radiomics improved T-cell lymphoma identification over SUV-derived features [79]. In Hodgkin lymphoma, a longitudinal PET/CT network trained on Children's Oncology Group trial data and externally tested on a second trial cohort improved interim residual-disease detection and PET quantification [80]. Pediatric AI evidence for Burkitt lymphoma pathology, molecular classification, and prognosis is minimal.

Table 3. Representative artificial intelligence studies in pediatric hematological malignancies

Disease/ application	Study population	AI/ML method	Clinical task	Main finding/performance	Reference s
ALL / digital morphology	Pediatric (Tier 1); ALL, AML, and nonleukemic marrow; independent pediatric cohort included	Deep-learning WSI model	Leukemia discrimination; B/T lineage; ETV6::RUNX1 prediction	ALL vs AML/nonleukemic marrow AUC 0.99; external B/T AUC 0.72 and ETV6::RUNX1 AUC 0.69	[66]
ALL / flow-cytometric MRD	Pediatric (Tier 1); 337 day-15 B-ALL bone-marrow samples from three laboratories	Supervised Gaussian-mixture-model framework	Automated MRD quantification	Median F1 $\approx$ 0.92 under matched conditions and >0.85 in cross-system testing	[67]
ALL / molecular classification	Pediatric (Tier 1); 1,131 Nordic ALL cases; additionally evaluated in 281 previously molecularly undefined BCP-ALL cases	Multimodal classifier (ALLIUM)	Molecular subtype assignment	Classified 17 subtypes; assigned a single revised subtype to 81.5% of previously undefined BCP-ALL cases	[69]
ALL / transcriptomic classification	Mixed age (Tier 2); training n=1,869; independent validation n=1,018, approximately 75% pediatric	Supervised ALLCatchR classifier	BCP-ALL molecular subtyping	95.7% classification accuracy in independent hold-out cohorts	[70]
ALL / relapse prediction	Pediatric (Tier 1); childhood ALL derivation cohort n=336; independent dataset n=84	Comparative multivariable ML	Relapse prediction	Demonstrated that nonlinear multivariable modeling could predict relapse in an independent childhood ALL dataset	[27]
ALL / survival prediction	Pediatric (Tier 1); high-risk pediatric ALL; held-out test n=47	Random survival forest	Event-free survival prediction and biomarker discovery	Held-out time-dependent ROC AUC 92.9%; test error 12.47%	[71]
ALL / mortality and relapse	Pediatric (Tier 1); 161 children aged <16 years	Ten comparative ML algorithms	Mortality and relapse prediction	Test accuracy ranged approximately 64–74% for mortality and 64–84% for relapse across models	[81]
ALL / relapse prediction	Pediatric (Tier 1); n=2,252, five Indian centers; 565 relapses	XGBoost	Relapse prediction	Sensitivity 68.5% versus approximately 31–36% for clinicians; PPV 31.3%, specificity 50.3%	[73]
AML / flow-cytometric MRD	Pediatric (Tier 1); 10 AML patients contributing 66 MRD-positive flow files	UMAP + HDBSCAN anomaly detection	Automated blast/MRD identification	With 15 control samples, mean/median F1 0.514/0.595; preprocessing improved mean/median F1 to 0.557/0.680	[74]
AML / epigenomic relapse characterization	Pediatric (Tier 1); 696 newly diagnosed and 194 relapsed AML profiles	Boruta, LASSO, LightGBM, Monte-Carlo feature selection; decision tree/random forest	Identification of recurrence-associated methylation signatures	Convergent feature-selection approaches identified methylation loci/genes associated with diagnosis-versus-relapse status	[75]
AML / prognostic stratification	Pediatric (Tier 1); infant AML; derivation data n=213, internal validation n=127, external validation n=63	Machine-learning-derived infant prognostic score	EFS/risk prediction and treatment stratification	Added prognostic information to conventional pediatric AML stratification and re-stratified 43% of infants	[76]
ALL/AML / post-HSCT relapse	Pediatric (Tier 1); 63 ALL and 46 AML patients	Random forest with interpretable ML	Relapse within 24 months after HSCT	Cross-validated accuracy 85% for ALL and 81% for AML; sensitivity 85% and 75%, respectively	[77]
AML / administrative cohort phenotyping	Pediatric (Tier 1); n=2,558 manually reviewed development cases; subsequent cohort n=3,016	SVM and random forest	AML case identification and chemotherapy-regimen ascertainment	Development patient-identification sensitivity/PPV 0.97/0.97; external chart-based testing also supported regimen identification	[82]

Lymphoma / CT radiomics	Pediatric (Tier 1); 66 children: 16 DLBCL and 50 Hodgkin lymphoma; 139 lesions	Radiomics with LR/QDA and other classifiers	DLBCL versus Hodgkin lymphoma differentiation	Best combined radiomics/LDH QDA model AUC 0.845	[78]
Lymphoma / PET/CT radiomics	Pediatric (Tier 1); 110 children with lymphoma/leukemia-lymphoma subtypes; training n=77	Radiomics with LR, SVM, neural network, AdaBoost	Identification of T-cell lymphoma	Patient-level PET/CT LR AUC 0.863 and accuracy 0.779; exceeded SUV/CT-only modeling	[20]
Hodgkin lymphoma / longitudinal response imaging	Pediatric (Tier 1); 297 patients from COG AHOD1331/AHOD0831; internal n=200, external n=97	Longitudinally aware segmentation network (LAS-Net)	Lesion segmentation, residual-disease detection, quantitative response assessment	Interim residual-disease F1 0.61; baseline Dice 0.77; PET metrics strongly correlated with physician measurements	[80]

ARTIFICIAL INTELLIGENCE IN PEDIATRIC SOLID TUMORS

Central nervous system tumors

Among pediatric solid tumors, CNS applications have the strongest evidence. Multicenter multiparametric-MRI segmentation in 244 children achieved external whole-tumor Dice 0.88, although outcome benefit was not tested [83]. In medulloblastoma, three-center radiomics (n=109) retained independent-site AUCs of 0.70–0.73 for SHH and 0.76–0.80 for group 4 [84]. Beyond imaging, M-PACT classified pediatric CNS tumors from CSF cfDNA methylomes with 92% benchmarking and 88% validation accuracy, but requires prospective validation [85]. A two-center diffuse-midline-glioma MRI-radiomics pipeline externally predicted 12-month survival with 81% baseline accuracy [86]. Ependymoma evidence is comparatively sparse; a broad mixed-age pathology model included ependymal classes but did not report pediatric-specific performance [87]. Overall, technical validity exceeds demonstrated treatment utility.

Neuroblastoma, Wilms Tumor, and Pediatric Sarcomas

Extracranial evidence is narrower. In high-risk neuroblastoma, FDG-PET/CT skeletal radiomics improved EFS discrimination over clinical variables (validation C-index 0.754 vs. 0.579), but validation was an internal split [88]. Wilms-tumor CT radiomics predicted stage I versus non-stage I disease (test AUC 0.81) without external validation [89]. A multicenter osteosarcoma study found MRI CNN-derived volume change predicted $\geq 90\%$ necrosis with 80% accuracy in a 20-case validation set spanning two centers, one external [90]. Pediatric rhabdomyosarcoma radiomics remains limited to small internal diagnostic studies, and comparably validated Ewing-sarcoma models were not identified [91].

Multimodal ai in pediatric solid tumors

Multimodal models increasingly combine imaging with clinical, pathology, and omics data. In 396 pLGGs, clinical+MRI deep learning outperformed clinical- or MRI-only EFS models (Ctd 0.85 vs. 0.72 and 0.79) on held-out testing [92]. Pathology–transcriptomic fusion also improved pediatric brain-tumor prognostication over unimodal models, but independent external validation was adult-only [93]. Multimodality therefore remains experimental, constrained by rarity, incomplete paired data, scanner/protocol heterogeneity, and limited prospective validation.

ARTIFICIAL INTELLIGENCE ACROSS THE PEDIATRIC CANCER CARE CONTINUUM

Diagnosis, risk stratification, and treatment response

Across diagnoses, AI's most credible near-term role is decision support rather than autonomous treatment selection. An externally validated RNA-seq ensemble classified 52 pediatric tumor types with 98% precision and 77% recall in KidsFirst, complementing pathology for rare entities [94]. Genomics-based digital drug assignment identified actionable options in 72/100 high-risk pediatric cancers and informed tumor-board choices, but did not establish outcome improvement [95]. Evidence that AI adds prospective benefit beyond established clinical risk systems remains limited.

Toxicity, complications, relapse, and survivorship

In 4,423 febrile-neutropenia episodes, XGBoost predicted bloodstream infection and septic shock (AUROC 0.87/0.88), but from one center [96]. A prospective 399-child cohort predicted delayed chemotherapy-induced nausea/vomiting with AUC 0.815 without external validation [97].

In survivors, clinical+genetic random forests improved anthracycline-cardiotoxicity AUC from 0.59 to 0.72, while longitudinal symptom trajectories improved future HRQoL AUCs to 0.75–0.85 [98, 99]. Relapse, late-effect, and survival prediction may benefit from longitudinal EHR and multimodal data, but prospective impact studies and cross-system transportability remain exceptional; routine outcome-improving pediatric AI utility has not yet been demonstrated.

Challenges, clinical translation, and ethical considerations

While there is progress in all areas of paediatric haematology-oncology, there has been limited impact of artificial intelligence (AI) in the clinical routine. One obvious limitation is the small, unbalanced, single-center datasets of pediatric disorders that are often rare, and are prone to overfitting and poor performance across institutions, populations, treatment protocols, imaging systems and laboratory platforms. Therefore, internal cross-validation or high discrimination may not be sufficient to confirm the clinical readiness, robust implementation needs independent multicenter external validation, clinical failure modes assessment, including calibration, prospective evaluation, and evidence of improved patient-important outcomes via AI-supported decision making. Barriers to data quality and interoperability include electronic health records, imaging, digital pathology, laboratory measurements, and molecular data that are collected according to different standards, in addition to missingness and temporal variation in clinical care.

These methodological restrictions are coupled with significant ethical issues in the child domain. Protecting sensitive longitudinal and genomic data, consent and assent processes that are age-appropriate, and governance mechanisms for secondary data use are necessary for the development of AI, and underrepresentation of certain subgroups of disease, demographics or geography could create algorithmic inequities. Explainability can help guide clinical interpretation and model failure detection, but should not be seen as a sign of causality, fairness, or safety.

There is also a lack of accountability when algorithm-driven recommendations can affect high stakes clinical decisions, like escalating or de-escalating treatment, or transplanting. Thus, clinically responsible pediatric AI must be used alongside, not in place of, expert clinical judgement, and should be tested in actual clinical settings for usability, human–AI interaction, and unintended consequences. Multicenter data collaboration, transparent reporting, privacy preserving methods, post-deployment monitoring, and regulatory frameworks that take into account algorithm performance and the unique vulnerability and longterm interests of children will be needed to make progress towards trustworthy implementation. The process of developing an AI to one that is clinically trusted will be mapped out and summarized in Figure 2, along with the pediatric-specific, ethical, and implementation challenges that will impact the transition.

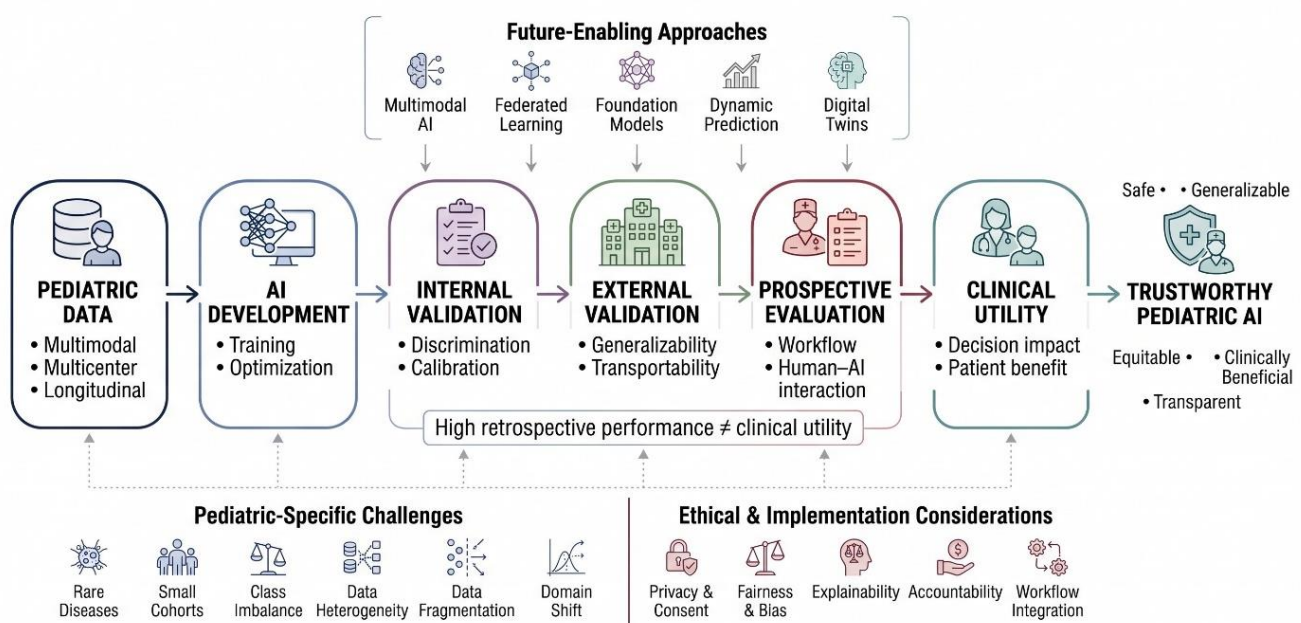


Figure 2. Translational pathway toward trustworthy artificial intelligence in pediatric hematology-oncology.

CONCLUSIONS AND RECOMMENDATIONS

Artificial intelligence is emerging as a potentially valuable tool across pediatric hematology and oncology, with applications spanning automated morphology, imaging, disease classification, risk stratification, toxicity prediction, and multimodal precision medicine. However, the current evidence remains heterogeneous, and strong retrospective performance has rarely translated into demonstrated improvements in clinical outcomes. Progress toward routine implementation will require representative multicenter pediatric datasets, rigorous external and prospective validation, transparent model development, and integration into clinically meaningful workflows. To achieve this without centralizing sensitive pediatric data, federated learning provides a highly recommended framework for secure, multicenter model development.

Looking forward, AI in pediatric hematology-oncology is expected to evolve from single-task, single-modality algorithms toward comprehensive, multimodal, and longitudinal systems. Dynamic models that continuously update predictions based on treatment response, measurable residual disease, and molecular changes will offer significantly greater clinical value than static baseline models. Furthermore, foundation models, generative AI, and eventually digital twins will facilitate complex information integration, trial matching, and molecularly guided drug discovery. Ultimately, rather than replacing clinical expertise, the most realistic and beneficial trajectory for AI is toward a validated human–AI collaboration. The true clinical relevance of these technologies must be determined not by algorithmic sophistication alone, but by prospective evidence that they support safer, more precise, equitable, and evidence-based care for children.

DECLARATIONS

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Competing interests

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