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Next Generation Evaluation and Treatment of Pediatric Acute Lymphoblastic Leukemia

Emily B. Heikamp, MD, PhD, MSc[1,2] and **Ching-Hon Pui, MD**[3,4]

[1]Department of Pediatrics, Section of Pediatric Hematology-Oncology, Baylor College of Medicine, Houston, Texas

[2]Texas Children's Cancer and Hematology Centers, Texas Children's Hospital, Houston, Texas

[3]Departments of Oncology and Pathology, St. Jude Children's Research Hospital, Memphis, Tennessee

[4]Department of Pediatrics, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee

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Advances in the diagnosis and treatment of pediatric acute lymphoblastic leukemia (ALL) are one of the greatest successes of modern medicine. Over the past 50 years, there has been a rapid increase in overall survival for pediatric ALL (Figure 1). Several factors have led to these remarkable improvements. First is the development of risk-adapted therapy based on both clinical and biologic presenting features, as well as early response to treatment[1]. Second, the effectiveness of molecularly targeted agents for specific genetic abnormalities has boosted outcomes for some high-risk groups[1]. Third, international collaboration among clinical trial networks has led to standardization of definitions and reporting of results that allows comparison of data across multiple national study groups to identify optimal treatment (**Table; available at** www.jpeds.com)[1–3]. Now, the long-term survival rate for pediatric ALL is approaching 90% in many high income countries, the highest of any type of leukemia in either children or adults[, 4]. These remarkable achievements notwithstanding, there remain a number of challenges in ALL pathology and treatment that need to be addressed. Relapse still occurs in 10–15% of patients, and death due to relapsed ALL remains one of the leading causes of cancer mortality in children. Conventional cytotoxic chemotherapy continues to be associated with both short- and long-term toxic effects and is unlikely to be modified substantially in the near future. Thus, it will be important to take

Corresponding Author: Emily.heikamp@bcm.edu.

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advantage of emerging molecular and immunologic insights to improve risk stratification and to devise targeted therapies to avoid over- or under-treatment.

In this review, we discuss advances in the diagnosis and treatment of pediatric ALL that are reshaping the landscape of this disease. In the future, all patients may undergo genetic sequencing of both cancer and germline genomes to increase the precision of risk stratification and hence the specificity of treatment. Patients with high-risk genetic subtypes or poor response to treatment, as measured by minimal residual disease (MRD), may benefit from molecularly targeted therapy or immunotherapy. With advances in identifying molecular lesions that are amenable to targeted therapy and in developing risk-adapted therapy for ALL, we believe that precision medicine will drive ALL treatment in the future.

Evaluation and Risk Stratification

Risk stratification of patients with pediatric ALL is used to determine the optimal type, intensity and duration of treatment. We will discuss risk stratification based on the following factors: (1) clinical presenting features, (2) leukemia genetic subtype (3) germline cancer predisposition, and (4) initial response to treatment as measured by MRD (Figure 2).

Clinical presenting features.

Age and white blood cell (WBC) count at presentation are used to risk stratify patients with pediatric ALL, according to National Cancer Institute (NCI) consensus criteria[5]. High-risk features include age less than 1 year or older than 10 years, and WBC>50,000 cells per cubic millimeter. Extramedullary involvement at sanctuary sites such as the central nervous system and testes and prolonged pre-treatment with corticosteroids are also considered high-risk features.

In addition to presenting features, genetic evaluation has important prognostic and therapeutic implications. Increasingly, genome sequencing technologies are being used to diagnose and guide therapy for pediatric ALL.

Next-generation sequencing (NGS).

Next-generation sequencing (NGS) is the latest genomic sequencing technology that enables high-throughput, massively parallel DNA sequencing[6]. In pediatric ALL, NGS is increasingly being used to comprehensively define the somatic genetic alterations and the role of inherited genetic variants in leukemogenesis, to monitor drug response and treatment toxicity, and to enhance the sensitivity of MRD detection compared with current methods[7–15]. Indeed, NGS of both host and cancer genomes is required to develop truly personalized risk-adapted therapy (Figure 2).

Genetic subtypes of ALL.

Pediatric ALL is a genetically heterogeneous disease, arising from the malignant transformation of hematopoietic cells at various stages of lymphoid development. Efforts to define the mutational landscape of pediatric ALL have revealed three major categories of genetic alterations: (1) chromosomal translocations, (2) duplications or deletions of large

segments of DNA, and (3) point mutations in oncogenes or tumor suppressors[16]. Based on genetic alterations, patients with B- and T-ALL may be stratified into high-, intermediate-, or low-risk categories (Figure 2).

High-risk subtypes.—Patients with high-risk disease should be identified early in therapy because they benefit from intensified induction and consolidative treatment. Among patients with B-ALL, a high-risk group harbor the "Philadelphia" chromosome (Ph), the product of a t(9;22) translocation that results in *BCR-ABL1* fusion, which can be treated with ABL1 tyrosine kinase inhibitors (TKI). Ph+ ALL generally occurs in older children and has a poor prognosis overall[17].

'Ph-like ALL' is another high-risk subtype of B-ALL characterized by a gene expression profile and a high frequency of *IKZF1* alterations similar to Ph+ ALL but lacking *BCR ABL1* fusion[14]. Among this clinically and biologically heterogeneous group, a wide range of genetic alterations in Ph-like ALL results in dysregulation of several cytokine receptors and kinase signaling pathways[12, 18]. Alterations in *IKZF1* are an independent risk factor associated with poor prognosis[18–22]. Additional treatment strategies are needed for this high-risk group, particularly for a subset of patients termed IKZF^{plus} with certain co-occurring mutations that confer the worst prognosis among patients with Ph-like ALL[23]. Notably, a subset of these IKZF1^{plus} patients with rapid early response had excellent outcomes, emphasizing the utility of MRD assessment in assigning risk of relapse, even among high-risk ALL.

Older children are also more likely to harbor rearrangements involving the *MEF2D* gene, a recently identified fusion partner that carries a high risk of relapse[24, 25]. For some high-risk groups, such as those with intrachromosomal amplification of chromosome 21 (iAMP21), intensification of conventional chemotherapy has led to a reduced risk of relapse[26–29]. Treatment outcome remains poor for infant ALL. Among infants with B-ALL, chromosomal translocations involving the *mixed lineage leukemia* (*MLL/KMT2A*) gene are common and are associated with high rates of induction failure and relapse[30].

Hypodiploid ALL with less than 44 chromosomes is another high-risk subtype of ALL[8, 31]. Of interest, low-hypodiploid ALL with 32 to 39 chromosomes is characterized by a high frequency of genetic alterations of *TP53* that are often inherited[31]. A recent study suggested that response-adapted treatment can improve outcomes in patients with lowhypodiploid ALL who attain MRD-negative status after remission induction, as these patients have a high cure rate with intensive chemotherapy[31].

Among patients with T-ALL, those with early T-cell precursors (ETP)-ALL have an especially poor response to induction therapy[32–34]. Patients in this high-risk group typically lack specific chromosomal rearrangements, but they share a distinct gene expression profile and immunophenotype of a subset of thymocytes that retain stem cell-like features[32]. Recent studies suggest that ETP-ALL patients may benefit from intensive consolidative treatment with cyclophosphamide, mercaptopurine and cytarabine and may not require HSCT[35, 36].

Intermediate-risk subtypes.—Patients with intermediate-risk disease require intensive chemotherapy to prevent relapse and are not candidates for treatment reduction. Approximately half of all cases of B-ALL would be classified as intermediate-risk, including those recently found to have translocations involving the *ZNF384* gene[24, 37]. T-ALL patients with abnormalities in the tumor suppressor gene *PTEN* have intermediate outcomes, though prognosis depends on the mechanism of *PTEN* inactivation[38–40]. *MLL* rearrangements have also been observed in T-ALL, but these patients have better outcomes than those with B-ALL and *MLL* rearrangements[41, 42].

Low-risk subtypes.—Patients with low-risk subtypes of pediatric ALL may be considered excellent candidates for treatment reduction to decrease the toxicity associated with intensive chemotherapy. However, such reduction should be applied judiciously to 'rapid early responders' with negative MRD and favorable leukemia genetic subtype so that the overall cure rate is not compromised. In a recent study, 'standard-risk' patients (defined by favorable age 1 to 10 years and WBC <50,000 cells per cubic millimeter) with unfavorable leukemia genetics who were 'rapid early responders' had worse outcomes when delayed intensification treatment was reduced[43]. We contend that only B-ALL patients with low-risk genetic features such as *ETV6-RUNX1* fusion (previously known as *TEL-AML1*), trisomies 4 and 10, or hyperdiploid ALL and rapid early response to treatment following 1–2 weeks of 3-drug remission induction are good candidates for treatment reduction[43]. In patients with T-ALL, those with *NOTCH/FBXW7* mutations have favorable outcomes[44–46].

Detecting minimal residual disease (MRD).

Risk-adapted therapy guided by MRD level measured during remission induction and consolidation treatment has contributed greatly to the improved outcome in pediatric ALL[47, 48]. Because it accounts for leukemic cell genetics, host pharmacogenetics, leukemia cell environment, and treatment efficacy, the MRD level has become an important prognostic factor in ALL[49]. High levels of MRD at the end of remission induction or persistent MRD after consolidative treatment are an indication for intensification of treatment or even HSCT.

Traditionally, MRD has been measured with multicolor flow cytometry or quantitative PCR (qPCR). Recent studies based on NGS showed enhanced sensitivity and specificity compared with standard methods of MRD detection in both B- and T-ALL[50, 51]. These results suggest that NGS may detect as few as 1 leukemic blast out of 1 million normal cells, corresponding to a 10-times greater sensitivity than qPCR and a 100-times greater sensitivity than flow cytometry[52, 53]. In this regard, negative MRD findings by NGS can identify a subgroup of 'rapid early responders' who appear to be at even lower risk of relapse with chemotherapy or after HSCT compared with those with negative MRD defined by flow cytometry or qPCR (with limits of <1 leukemic cell among 10,000 normal cells)[54–56].

Predicting treatment failure and toxicity.

More recently, NGS has revealed genetic variations in the host and cancer genome that may predict the risk of treatment failure and toxicity associated with chemotherapy (Figure 2). For example, patients with B-ALL harboring activating mutations in the *CREB binding protein* (*CREBBP*) gene have high rates of relapse associated with resistance to

glucocorticoids[57], and those with activating mutations in *NT5C2* or loss of function mutations in *PRPS1* are resistant to thiopurines such as mercaptopurine[58, 59]. Understanding how these mutations confer drug resistance may inform the design of optimal frontline or salvage therapy.

Genome-wide analyses have also uncovered genetic variations in the host germline genome that are associated with particular adverse outcomes of chemotherapy (Figure 2). Both *thiopurine methyltransferase* (*TPMT*) and *nudix hydrolase 15* (*NUDT15*) genetic polymorphisms, for example, have been associated with intolerance to thiopurine treatment; that is, patients with homozygous polymorphisms are at increased risk of life-threatening myelosuppression when exposed to conventional doses of thiopurines such as mercaptopurine[60, 61]. Similarly, patients with polymorphisms in the promoter region of the *centrosomal protein 72 (CEP72)* gene, which encodes a protein involved in microtubule assembly, have an increased risk of severe peripheral neuropathy when treated with vincristine[62]. More recent discoveries include genetic polymorphisms that are associated with increased risk of steroid-induced osteonecrosis and methotrexate-related mucositis[63–65]. As genome-wide analyses such as NGS become widely available, future treatment plans could utilize genomic technology to prospectively identify patients at high risk of treatment intolerance, in order to dose-adjust chemotherapy and minimize morbidity.

Cancer predisposition genes in pediatric ALL.

Epidemiologic studies have demonstrated different frequencies of pediatric ALL among various ethnic groups. Children of Hispanic or Native American ancestry have the highest incidence of ALL, followed by those of European descent, and finally by those of African descent[66]. Population-based genome-wide association studies have revealed ethnicity-specific polymorphisms that may account for these patterns. For example, the highest frequencies of polymorphisms in the *ARID5B*, *BMI1-PIP4K2A*, and *GATA3* genes were found among Hispanics[67–69]. These germline risk alleles can also influence treatment outcome, as illustrated by *GATA3* variants associated with Ph-like ALL and a poor outcome[69].

Recent studies revealed germline mutations in cancer predisposition genes associated with a high risk of developing ALL, such as *TP53*, *PAX5*, *ETV6*, and *IKZF1* in up to 5% of pediatric patients with ALL[70–75]. Such results have implications not only for the patients but also for their families, as close relatives may benefit from genetic testing, counseling and surveillance. Notably, patients with *TP53* germline variations also have increased risk of relapse and development of second cancers[76].

Personalized Treatment

Pediatric ALL is a highly disseminated and heterogeneous disease, warranting the current focus on personalized treatment. At most centers, therapy for this disease is tailored to the patient's features: (1) specific genetic subtype, (2) extent of disease, and (3) drug sensitivity as assessed by MRD after remission induction or consolidative treatment. Patients with high-risk genetic subtypes, disseminated disease involving sanctuary sites such as the central nervous system or testes, or a positive MRD finding after remission induction, typically

require more intensive chemotherapy to prevent recurrence. Although uniform treatment of large groups of patients has become a relic of the past, there is still a need for standardized, protocol-directed therapy, which currently proceeds in 3 phases: induction, consolidative therapy, and maintenance.

Conventional cytotoxic chemotherapy.

Initial treatment with induction chemotherapy eliminates 99.99% or more of leukemia cells. This phase of treatment most often begins with 4 weeks of vincristine, a corticosteroid (prednisone or dexamethasone), and asparaginase, with the addition of an anthracycline (doxorubicin or daunorubicin) for patients with higher-risk leukemia[77]. The next phase of treatment aims to further reduce submicroscopic leukemia, and is therefore termed consolidative therapy. The duration, intensity, choice of agent, and number of treatment courses used during this phase varies according to risk group and protocol, but consolidative therapy typically involves high-dose methotrexate, mercaptopurine, asparaginase, dexamethasone, and vincristine, with or without an anthracycline. For high-risk patients, cytarabine and cyclophosphamide may be added to post-induction consolidative therapy; however, these agents may not be necessary for low- or standard-risk patients, especially in light of their potential effects on future fertility[78]. The final phase of treatment, the so-called maintenance or continuation component, aims to eradicate any remaining leukemic or pre-leukemic cells and consists of antimetabolites (daily mercaptopurine and weekly methotrexate) with or without pulses of a corticosteroid plus vincristine. Dexamethasone improves survival in patients <10 years old; however, prednisone is used in lieu of dexamethasone for patients >10 years old in some protocols out of concern for increased risk of osteonecrosis associated with dexamethasone treatment in this age group[79]. Although one study showed that two-thirds of patients (including 16 of the 18 patients with *ETV6-RUNX1* B-ALL) could be cured with 1 year of maintenance treatment[80], this phase typically lasts for 2 to 2.5 years in virtually all contemporary protocols, as there are no reliable markers to identify patients who may be cured with abbreviated treatment.

It is quite possible that cytotoxic chemotherapy may one day be replaced by shorter treatments with targeted agents (Figure 3), but until the genes and pathways essential for leukemia cell survival can be targeted with certainty, the need for distinct phases of chemotherapy will likely persist.

Targeted therapy.

Next-generation sequencing has revolutionized the treatment of pediatric ALL by revealing genetic alterations that are amenable to targeted therapy. Indeed, initiatives such as the St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project (PCGP) and the Therapeutically Applicable Research to Generate Effective Therapies (TARGET) Project have uncovered a number of novel genetic alterations in pediatric ALL[81, 82]. Thus far, trials of promising targeted therapies have significantly improved outcomes for some high-risk groups, such as patients with Ph+ ALL and subsets of those with Ph-like ALL with *ABL*-class fusion transcripts. Novel immunotherapeutic approaches, including chimeric antigen receptor-based cellular therapies have also cured a substantial portion of patients with highly refractory leukemia, some of whom had relapsed after HSCT

(Figure 3). A representative selection of immunologic and genetically based treatment strategies are described below.

ABL1 tyrosine kinase inhibitors in Ph+ ALL.

The first successful use of precision medicine in childhood ALL began with the discovery that Ph+ B-ALL with the *BCR-ABL1* fusion were sensitive to the ABL1 tyrosine kinase inhibitors (TKIs)[83–86]. Once associated with dismal prognosis despite HSCT[17], the outcome for Ph+ ALL has significantly improved since the ABL1 TKI imatinib was incorporated into an intensive chemotherapy regimen[83–86]. Dasatinib, a second-generation ABL1 TKI targeting multiple kinases, has comparable safety and efficacy to imatinib, and reduced the need for HSCT in a recently completed phase II clinical trial (NCT01460160)[87, 88]. Ponatinib, a third-generation ABL1 TKI, is more effective than earlier generations of ABL1 TKIs in adults; however, due to the associated toxicities,[89] it should be used and dosed judiciously in children.

ABL1 TKIs and Janus kinase (JAK) inhibitors in Ph-like ALL.

Ph-like ALL is characterized by a wide range of genetic alterations that dysregulate several cytokine receptor and kinase signaling pathways, including *CRLF2* rearrangement in half of cases and translocation of non-receptor tyrosine kinases (predominantly *ABL*-class and *JAK*)[90]. Patients with *ABL*-class fusions (including *ABL1, ABL2, CSF1R, PDGFRB* and *PDGFRA*) respond clinically to ABL1 TKIs, whereas in preclinical models mutations activating the JAK-STAT pathway have been amenable to treatment with JAK inhibitors (e.g., ruxolitinib)[12]. Ongoing prospective studies are testing whether incorporating a TKI targeting kinase alterations into intensive chemotherapy regimens will improve outcome in patients with Ph-like ALL (NCT02723994, NCT03117751)[91, 92].

BCL2 inhibitors.—Preclinical studies have shown that a new class of drugs targeting the transcription factor BCL2 holds promise for *MLL* (*KMT2A*)-rearranged ALL and Ph +ALL[93, 94]. The BCL2 inhibitors venetoclax and navitoclax work by forcing leukemic cells to undergo apoptotic programmed cell death[93]. A phase II clinical trial of venetoclax in adults with relapsed or refractory chronic lymphocytic leukemia demonstrated a response rate of approximately 80%[95]. Pediatric clinical trials of venetoclax are currently underway for children with relapsed or refractory ALL (NCT03236857)[96].

FMS-like tyrosine kinase 3 (FLT3) inhibitors.—*MLL*-rearranged ALL displays constitutive activation of FMS-like tyrosine kinase (FLT3), and a subset harbor genetic alterations in this gene[97, 98]. In *MLL*-rearranged ALL, *FLT3* alterations are associated with a poor prognosis[99, 100]. A phase III trial of the FLT3 inhibitor lestaurtinib (CEP-701) in combination with cytotoxic chemotherapy showed no benefit over chemotherapy alone (NCT00557193)[101, 102]. Phase I/II trials have been conducted for the FLT3 inhibitors sorafenib[103], midostaurin[104], and quizartinib (AC220)[105] demonstrating safety and tolerability, but further trials are needed to determine efficacy.

Nucleoside analogs.—Nucleoside analogs are currently in clinical trials for B-ALL and TALL. A phase II trial of the purine analog clofarabine in combination with

cyclophosphamide and etoposide for relapsed B-ALL demonstrated an overall response rate of 44%[106]. For newly-diagnosed T-ALL, a recent phase III trial of the purine analog nelarabine in combination with intensive chemotherapy demonstrated improved disease-free survival without excessive toxicity[107]. In the future, incorporating nelarabine into upfront therapy for T-ALL may become standard of care.

Immunotherapy.

Chimeric antigen receptor T cells (CAR-T cells).—For patients with relapsed B-ALL, the most significant advance in the past decade has been the development of immunotherapies using chimeric antigen receptor-T cells (CAR-T cells). These genetically engineered autologous T cells are able to recognize and kill leukemic B cells bearing their target antigen[108]. The most commonly used CAR consists of an extracellular immunoglobulin domain that recognizes CD19 and an intracellular T-cell signaling domain that activates T cells to kill CD19+ leukemia cells (Figure 3). Because normal B-cells also express CD19, these patients also develop B-cell aplasia and require monthly intravenous immunoglobulin replacement therapy[109]. Unlike chemotherapy, where the therapeutic window is limited by the pharmacokinetics of drug clearance, CAR-T cells can persist for months or years *in vivo*, depending on the costimulatory molecule used, to provide long-term immune surveillance against leukemia cells[110].

The first pediatric phase I trial of CD19-directed CAR-T cell therapy (CTL019) demonstrated complete remissions in 93% of multiply relapsed B-ALL patients, two-thirds of whom had prior HSCT[111, 112]. Remarkably, relapse-free survival rates at 6 and 12 months were 76% and 55%, respectively[111, 112]. In patients who relapsed, the leukemic cells evaded immunotherapy by two mechanisms: (1) CAR-T cells did not persist, and (2) the leukemia re-emerged as a CD19 negative clone[111, 113]. To circumvent the problem of CD19 escape, CAR-T cells targeting another B-ALL associated antigen (CD22) have been developed[114]. In addition, tandem CARs recognizing both CD19 and CD22 on leukemic B cells is another strategy currently in preclinical development[115]. Phase II trials of CAR-T cell therapy are currently underway.

In 2017, the FDA designated CD19-directed CAR-T cells a “Breakthrough Therapy,” and approved CTL019 for relapsed pediatric and adult B-ALL. Given the therapeutic results reported thus far, it seems reasonable to predict that CAR-T cell-based immunotherapy will eventually be incorporated into frontline treatments for high-risk pediatric ALL, and possibly could replace HSCT for patients with relapsed or refractory ALL.

Bi-specific T cell engagers (BiTEs).—Currently, autologous CAR-T cell therapy has several limitations, including a lengthy and costly manufacturing process that sometimes results in failure to produce these genetically engineered cells. Therefore, some patients with rapidly progressive leukemia are unable to receive CAR-T cell therapy[116]. An alternative immunotherapeutic class of drugs called bi-specific T-cell engagers (BiTEs) can eliminate these obstacles. BiTEs contain 2 domains: (1) a CD19 or CD20 recognition domain that binds to leukemic B cells, and (2) a T cell-receptor recognition domain that binds and activates T cells to kill leukemic B cells[116, 117]. These bi-specific antibodies can be used in

patients for whom no T cells are available, and are available immediately as “off the shelf” products.

The most potent drug of this class — blinatumomab — had a response rate of 39% in a phase I/II trial of patients with relapsed or refractory B-ALL[117]. Another study demonstrated durable remissions in pediatric patients who had undergone HSCT[118]. However, in patients with overt or multiple relapses, blinatumomab by itself did not induce durable remissions, and instead was used as a bridge to HSCT[117]. Ongoing clinical trials are testing whether blinatumomab in combination with intensive chemotherapy can improve outcomes in patients with newly diagnosed B-ALL and persistent MRD after remission and consolidative therapy, in the absence of HSCT.

Conclusions

Future progress in pediatric ALL research will be driven not only by advances in science and technology, but also by greater international collaboration among investigators to standardize risk group classification, definition of treatment response, and toxicity criteria. Innovations in genomic sequencing can be expected to aid in diagnosis, identify targetable lesions, and guide risk stratification to optimize therapy, and novel therapies will likely become available for various disease subtypes. At the same time, efforts to optimize immunotherapy for relapsed and refractory disease should yield clear breakthroughs in this challenging research area. Whether immunotherapy and molecular targeting strategies will ultimately replace cytotoxic chemotherapy for ALL remains unclear, although recent observations of durable complete remissions among patients responding to targeted therapies after failing chemotherapy or hematopoietic stem cell transplantation (HSCT) suggest a major impact for this approach in the future. Finally, as more attention is directed toward smaller subsets of patients with drug-resistant leukemia, the importance of collaborative international research will grow considerably so that therapeutic gains in high income countries can be translated to patients in middle or low income countries[119]. Finally, increasing our understanding of the biology of ALL and factors that predispose patients to leukemia may lead to preventive measures to decrease the risk of ALL in the future.

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List of abbreviations

ALL	acute lymphoblastic leukemia
B-ALL	B-cell acute lymphoblastic leukemia
BiTEs	bi-specific T cell engagers
CAR-T	chimeric antigen receptor T cells
ETP-ALL	early T cell precursor acute lymphoblastic leukemia

FLT3	FMS-like tyrosine kinase 3
HSCT	hematopoietic stem cell transplantation
JAK	Janus kinase
NGS	next-generation sequencing
MRD	minimal residual disease
MLL	mixed lineage leukemia
Ph+ ALL	Philadelphia chromosome positive-acute lymphoblastic l6eukemia
Ph-like ALL	Philadelphia chromosome-like acute lymphoblastic leukemia
T-ALL	T-cell acute lymphoblastic leukemia
TKI	tyrosine kinase Inhibitor
WBC	White blood cell

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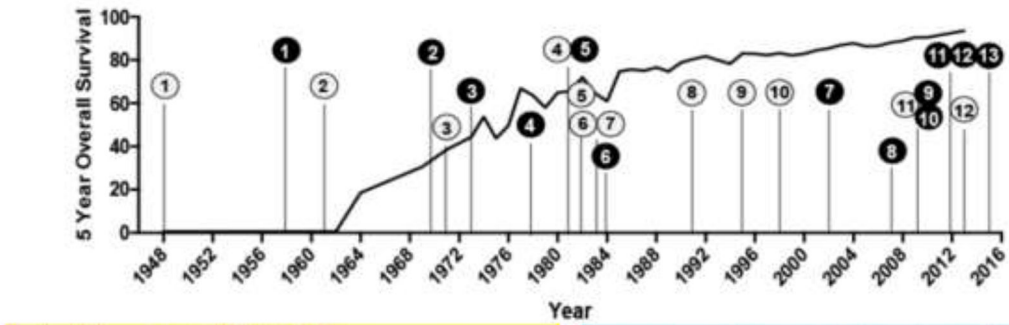

Landmark Advances in Treatment for Pediatric ALL		
1	1948	"Transient remissions" induced by aminopterin
2	1961	First use of antimetabolites mercaptopurine and methotrexate
3	1971	Combination chemotherapy and effective CNS-directed therapy cure approximately 50% of patients
4	1981	Re-induction treatment improves outcomes
5	1982	Triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine may effectively substitute for prophylactic cranial irradiation in some patients
6	1983	Postremission weekly high-dose asparaginase improves outcome
7	1983	Intermediate-dose methotrexate with leucovorin rescue decreases systemic and testicular relapses
8	1991	Dexamethasone is more effective than prednisone in preventing CNS relapse
9	1995	Inherited genetic polymorphisms in gene encoding thiopurine methyltransferase influence mercaptopurine toxicity
10	1998	Individualized methotrexate dose improves outcome
11	2009	Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients; imatinib improves outcome in Philadelphia chromosome-positive ALL
12	2013	First trial of chimeric antigen receptor (CAR)-T cell therapy

Landmark Advances in Understanding the Biology of Pediatric ALL		
1	1958	First cytogenetic study in ALL
2	1970	First report of Philadelphia chromosome-positive ALL
3	1973	First identification of T-cell ALL by spontaneous rosette formation with sheep erythrocytes
4	1978	Classification of ALL by chromosome number >50 (hyperdiploidy) is associated with prolonged remission duration
5	1981	Immunologic monitoring of residual leukemia
6	1984	First identification of immunophenotype-specific chromosomal translocations: t(11;14) in T-cell ALL and t(1;19) in pre-B ALL
7	2002	First genome-wide profiling of gene expression
8	2007	First genome-wide study of changes in DNA copy number
9	2009	Germline genetic variants associated with the development of ALL
10	2009	Recognition of Philadelphia chromosome-like "Ph-Like" ALL
11	2012	First whole-genome sequencing study to identify driver mutations in early T-cell precursor ALL
12	2012	Use of next-generation sequencing to enhance detection of minimal residual disease
13	2015	Whole genome analysis identified germline genetic mutations in predisposition genes

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Figure 1: Landmark advances in pediatric Acute Lymphoblastic Leukemia (ALL).

5-year overall survival data for pediatric ALL from the Surveillance, Epidemiology, and End Results (SEER) Program[120] is overlaid with landmark advances in the treatment (white; left table) and in understanding the biology of pediatric ALL (black; right table).

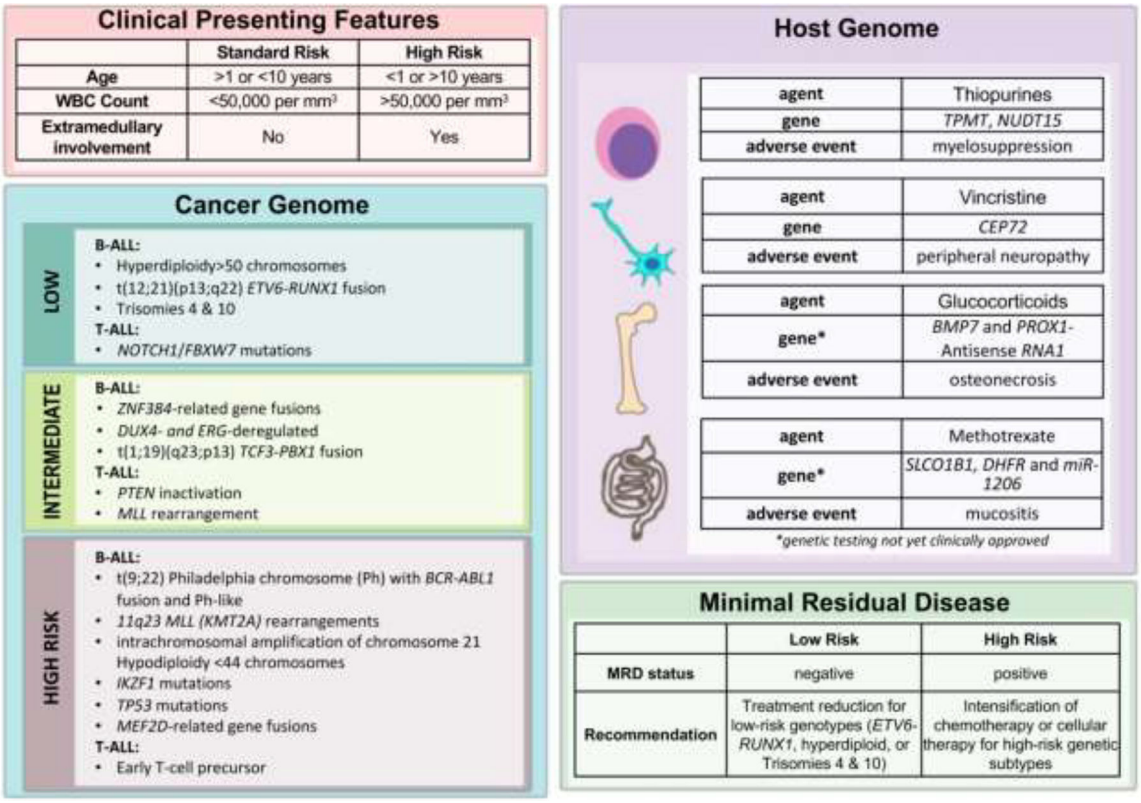

Figure 2: Factors influencing risk stratification and outcome for patients with ALL.

Clinical presenting features, leukemia cell genetics (cancer genome), host germline genome and minimal residual disease should be considered when determining risk-adapted therapy. Advances in whole genome sequencing of both host (germline) and cancer (leukemia) genomes has deepened our understanding of genetic factors that determine risk (high-, intermediate-, and low-risk) and influence treatment response and toxicity of cytotoxic chemotherapy agents.

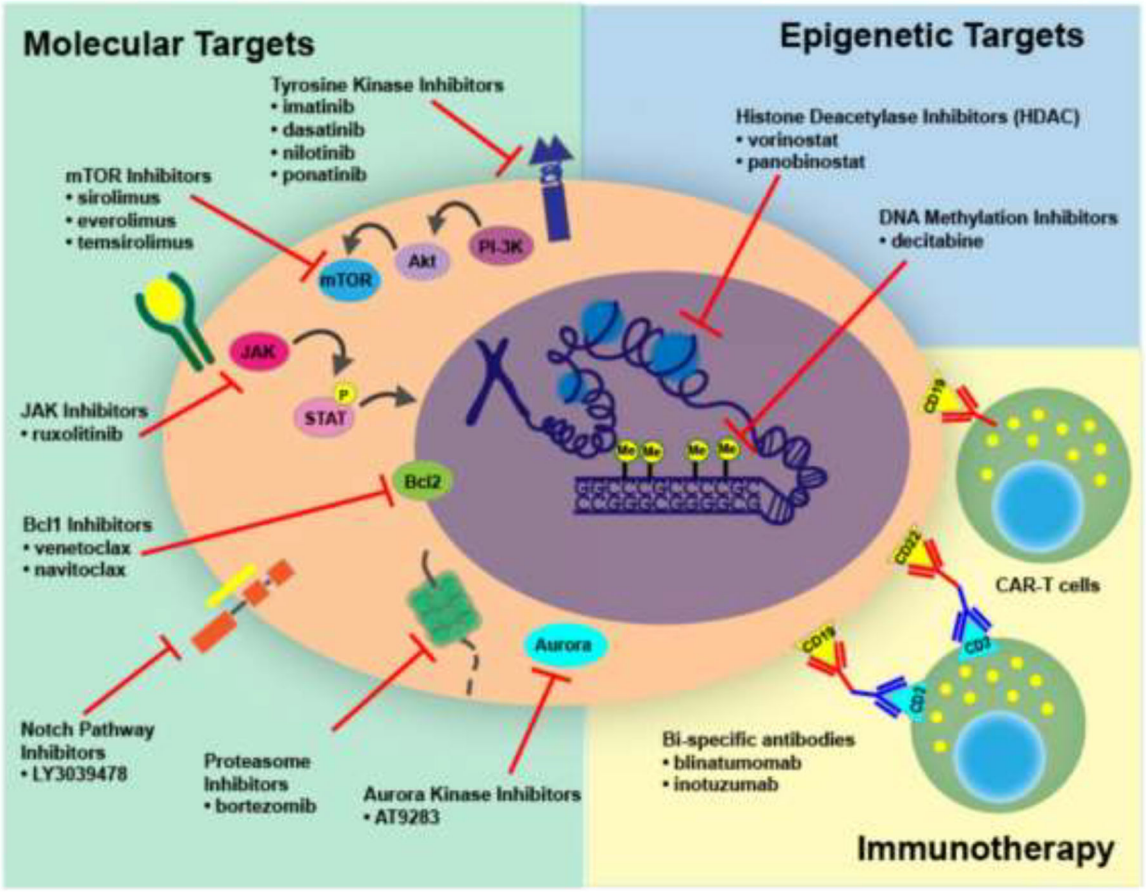

Figure 3: Mechanisms of therapy (molecular, epigenetic, and immunologic) for pediatric ALL.
Precision medicine has revolutionized treatment of pediatric ALL by providing novel molecular and epigenetic targets, in addition to immunotherapeutic approaches to cure patients with relapsed/refractory disease.

Table I;

online: Results of Recent Major Clinical Trials of Pediatric ALL

Study group	Trial design	Number of patients	5-Year EFS	5-Year OS	Main finding of the study
Induction Chemotherapy					
AIEOP-BFM ALL 2000[121]	Randomized trial	3727	83.9% (Dexamethasone) 80.8% (Prednisone)	90.3% (Dexamethasone) 90.5% (Prednisone)	Dexamethasone was superior to prednisone, and led to a significant reduction in the rate of relapse, but increased treatment-related mortality.
COG AALL0232[79]	Randomized trial	3,154	91.2 ± 2.8% (DH) 83.2 ± 3.4% (DC) 82.1 ± 3.5% (PC) 80.8 ± 3.7% (PH) 75.2 ± 1.1% (overall)	96.3 6 1.9% (DH) 92.3 6 2.4% (DC) 92.3 6 2.5% (PC) 92.7 6 2.4% (PH) 85.0 ± 0.9% (overall)	Among high-risk patients, high-dose methotrexate (H) led to superior EFS and OS compared to Capizzi escalating-dose methotrexate (C), with no increase in toxicity. Dexamethasone (D) was more effective than prednisone (P) and led to improved EFS and OS in younger children, but led to higher risk of osteonecrosis in children >10 years old without improvement in EFS or OS.
DFCI 05–001[122]	Randomized trial	551	90% (PEG-asparaginase) 89% *(E. coli* asparaginase) 85 ± 1.5% (overall)	96% (PEG-asparaginase) 94% *(E. coli* l asparaginase) 91 ± 1% (overall)	PEG-asparaginase had similar toxicity and efficacy as native *E coli* l-asparaginase.
EORTC-CLG 58951[123]	Randomized trial	1947	81.5% (Dexamethasone) 81.2% (Prednisone) 82.6 ± 0.9% (overall)	87.2% (Dexamethasone) 89.0% (Prednisone) 89.7± 0.7% (overall)	Given during remission induction, dexamethasone led to a significant reduction in the rate of relapse, and had similar toxicity compared to prednisone.
Delayed Intensification/Consolidation Chemotherapy					

IC-BFM 2002[124]	Randomized trial among 15 countries on 3 continents	5197	74 ± 1% (overall)	82 ± 1% (overall)	International collaborative clinical trials among middle income countries are feasible, but improved supportive care is necessary to prevent excessive mortality from intensive chemotherapy.
NOPHO ALL2008[125]	Nonrandomized trial	1908	89%±1% (1–9 years old) 80±3% (10–17 years old) 74±4% (18–45 years old)	94±1% (1–9 years old) 87±2% (10–17 years old) 78±3% (18–45 years old)	Pediatric-based treatment protocols are tolerable and effective for young adults. There was no benefit to EFS for individualized 6-mercaptopurine dosing during consolidation therapy.
Risk stratification					
CoALL 97[126]	Nonrandomized trial	667	80 ± 3% (PVA score 3+4) 73 ± 3% (PVA score 5–7) 63 ± 8% (PVA score 8+9) 76.7 ± 1.7% (overall)	85.4 ± 1.4% (overall)	MRD was a superior prognostic indicator when compared with *in vitro* drug sensitivity testing based on PVA score (sensitivity to prednisolone, vincristine and asparaginase) for risk-stratification of patients.
DCOG ALL10[127]	Nonrandomized trial	865	93 ± 2% (standard-risk) 88 ± 2% (intermediate-risk) 78 ± 8% (high-risk) 87 ± 1.2% (overall)	99 ± 1% (standard-risk) 92.3 ± 4% (intermediate-risk) 82.1 ± 12% (high-risk) 91.9 ± 1.0% (overall)	Based on MRD risk stratification, chemotherapy was safely reduced in low-risk groups without compromising survival, and intensification of therapy improved EFS in intermediate- and high-risk groups.
JCCLSG ALL2000[128]	Nonrandomized trial	321	82.5 ± 2.6% (MRD) 74.7 ±5.7% (clinical) 79.7± 2.4% (overall)	91.4 ± 1.9% (MRD) 85.3 ± 4.5% (clinical) 89.2 ± 1.8% (overall)	MRD was a superior prognostic indicator when compared to clinical presenting features for

					risk-stratification of patients.
Ma-Spore 2003[129]	Nonrandomized trial	556	93.2 ± 4.1 % (standard-risk) 91.2 ± 4.9% (intermediate-risk) 51.8 ± 10.0% (high-risk) 83.2 ± 3.5% (overall)	82.1 ± 3.3% (standard-risk) 92.1 ± 3.3% (intermediate-risk) 67.7 ± 11% (high-risk) 75.2 ± 3.1% (overall)	Using risk stratification based on MRD as well as clinical and genetic features, chemotherapy was safely reduced in low-risk groups without compromising survival.
MRC UKALL 2003[130]	Randomized trial	3126	82.8± 4.7% (standard) 89.6 ± 3.7% (intensified) 87.3 ± 1.4% (overall)	88.9± 3.9% (standard) 92.9± 3.1% (intensified) 91.6 ± 1.2% (overall)	Intensification of therapy for MRD positive high-risk patients leads to better EFS but not OS, compared to standard therapy. Intensified therapy was also associated with more adverse events.
Adjuvant therapy to prevent CNS relapse					
Study group	**Trial design**	**Number of patients**	**5-Year EFS**	**5-Year OS**	**Main finding of the study**
SJCRH Total Therapy XV[48,131]	Nonrandomized trial	498	96.3 ± 2.6% (low-risk) 92.3 ± 4.5%(standard-risk) 74.7 ± 15.3% (high-risk) 79.7 ± 2.9% (overall)	98.7 ± 1.3% (low-risk) 92.5 ± 3.0% (standard-risk) 67.9 ± 12.8% (high-risk) 93.5 ± 1.9% (overall)	With effective MRD-guided systemic chemotherapy, optimal triple intrathecal therapy, and risk adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted from the treatment all patients with pediatric ALL.
TPOG ALL 2002[132]	Randomized trial	1366	85.2 ±2.7% (one course) 89.8 ± 2.3% (two courses) 74.3 ± 1.2% (overall)	91.6 ± 2.1% (one course) 93.7 ± 1.8% (two courses) 81.6 ± 1.1% (overall)	There was no difference in EFS or OS in standard risk patients who received one versus two course of re-induction chemotherapy

Abbreviations: AIEOP, Associazione Italiana di Ematologia Pediatrica; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; CoALL, Cooperative ALL (study group); COG, Children's Oncology Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute (consortium); DFS, disease-free survival; EFS, event-free survival; EORTC-CLG, European Organisation for Research and Treatment of Cancer-Children's Leukemia Group; IC-BFM, Intercontinental BFM; i.m., intramuscular; i.v., intravenous; IR, JCCLSG, Japanese Children's Cancer and Leukemia Study Group; Ma-Spore, Malaysia-Singapore; MRC UKALL, Medical Research Council United Kingdom Acute

Lymphoblastic Leukemia; MRD, minimal residual disease: N/A, not applicable; NOPHO, Nordic Society of Pediatric Hematology and Oncology; OS, overall survival; SJCRH, St Jude Children's Research Hospital; TPOG, Taiwan Pediatric Oncology Group.

[▽] Results for 6-year EFS and OS are shown.