Genomic Alterations in ALL

Subjects: Oncology

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Acute lymphoblastic leukemia (ALL) is the most successful paradigm of how risk-adapted therapy and detailed understanding of the genetic alterations driving leukemogenesis and therapeutic response may dramatically improve treatment outcomes, with cure rates now exceeding 90% in children.

Keywords: B-ALL ; DUX4 ; IKZF1 ; PAX5 ; Ph-like ; ZNF384 ; NUTM1 ; T-ALL ; NOTCH1 ; BCL11B ; transcriptome ; genome

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent childhood tumor and despite cure rates now exceeding 90% in children, outcomes for older children and adults remain poor with cure rates below 40% in those over the age of 40 [1][2][3], despite pediatric-inspired chemotherapy regimens [4]. This discrepancy is in part attributable to the different prevalence of genetic alterations across age. ALL may be of B- (B-ALL) or T-lymphoid (T-ALL) lineage, and comprises over thirty distinct subtypes characterized by germline and somatic genetic alterations that converge on distinct gene expression profiles [5][6][7][8][9][10][11][12]. These subtypes are defined by disease-initiating recurrent chromosomal gains and losses (hyper- and hypodiploidy, and complex intrachromosomal amplification of chromosome 21); chromosomal rearrangements that deregulate oncogenes or encode chimeric fusion oncoproteins, importantly often including cryptic rearrangements not identifiable by conventional cytogenetic approaches, such as *DUX4* and *EPOR* rearrangements; subtypes defined by single point mutations (e.g., PAX5 P80R or IKZF1 N159Y); subtypes defined by enhancer hijacking (e.g., *BCL11B*-rearrangements in T-ALL and lineage ambiguous leukemia) [5]; and subtypes that “phenocopy” established subtypes, with similar gene expression profile but different founding alterations (e.g., *BCR-ABL1*-like ALL and *ETV6-RUNX1*-like ALL) [7][13][14][15]. Secondary somatic DNA copy number alterations and sequence mutations are also important in leukemogenesis and treatment response, and their nature and prevalence vary according to the ALL subtype [6]. Multiple genes are associated with predisposition to ALL, including polymorphic variants in *ARID5B, BAK1, CDKN2A*, *CDKN2B*, *CEBPE*, *ELK3*, *ERG*, *GATA3*, *IGF2BP1*, *IKZF1*, *IKZF3*, *LHPP*, *MYC*, *PTPRJ*, *TP63* and the *BMI1-PIP4K2A* locus or rare mutations in *PAX5*, *TP53*, *IKZF1* and *ETV6* [16]. Several are associated with ALL subtype, for example, variants in *GATA3* have been associated with an increased risk of Philadelphia- like (Ph-like) ALL in patients of Hispanic ancestry [17], variants in *TP63* and *PTPRJ* with *ETV6-RUNX1* ALL [18] and in *ERG* with *TCF3-PBX1* ALL and African American ancestry [19][20]. A variant in the deubiquitinase gene *USP7* has been instead associated with risk of T-lineage ALL [19].

2. B-Cell Precursor Acute Lymphoblastic Leukemia

2.1. Previously Established Subtypes with Recurring Chromosomal Abnormalities

Prior the advent of next generation sequencing (NGS), classification of ALL has been relied on conventional karyotyping, fluorescence in situ hybridization (FISH) and targeted-molecular analyses for the identification of recurring chromosomal abnormalities including aneuploidy, chromosomal rearrangements and/or known gene fusions (**Figure 1**).

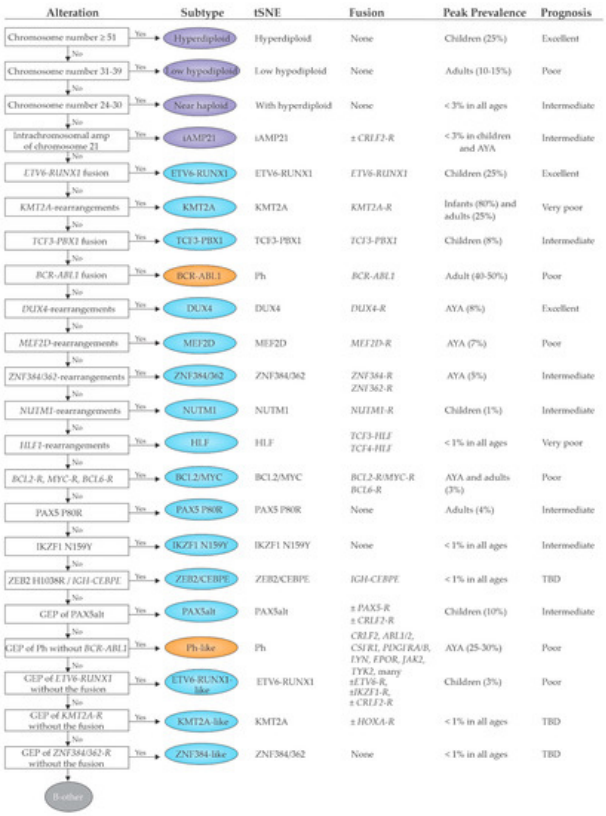

Figure 1. This schematic algorithm for B-ALL subtyping was modified from the figure originally published in Paietta E. et al. Molecular Classification Improves Risk Assessment in Adult BCR-ABL1-negative B-ALL. Blood Prepublished Apr 25 2021; doi:10.1182/blood.2020010144 [21]. This figure describes each B-ALL subtype according to the specific genetic alterations and gene expression profile. Moreover, for each subtype peak prevalence and prognosis are shown. Subtypes are colored according to defining genetic alteration: gross chromosomal abnormalities (purple), transcription factor rearrangements (blue), other transcription factor alterations (blue), and kinase alterations (orange). Abbreviations: AYA, adolescent and young adult; tSNE, t-distributed stochastic neighbor embedding; TBD: to be defined; -R: rearranged.

2.2. Emerging B-ALL Subtypes Defined by Genome Sequencing Studies

NGS approaches, particularly whole transcriptome sequencing (WTS), have enabled several research groups the identification of a large number of novel genetic alterations. These include cryptic rearrangements not identifiable by conventional approaches; novel subtypes that “phenocopy” established subtypes sharing similar gene expression profile but having different founding alterations; and subtypes defined by a single point mutation.

2.3. Prognostic Implications

The frequent and wide use of genomics to profile the landscape of ALL has allowed a tailored refinement of risk in association with standard criteria, such as minimal residual disease (MRD) levels [22] (**Figure 1**). In childhood B-ALL, *ETV6-RUNX1*, high-hyperdiploid, and *DUX4*-rearranged B-ALL are categorized as favorable due the highest overall survival rates and the lowest relapse rates, despite elevated early MRD in *DUX4*-rearranged cases. *BCR-ABL1*, *BCR-ABL1*-like, *ETV6-RUNX1*-like, *KMT2A*-rearranged, and *MEF2D*-rearranged ALL show high levels of MRD and the worst event-free survival rates and thus are categorized to be unfavorable subtypes. The remaining subtypes including *TCF3-PBX1*, *PAX5*alt, iAMP21, hypodiploid, *ZNF384*-rearranged, *NUTM1*-rearranged, and *PAX5* P80R ALL have intermediate risk [23]. These prognostic groups have been mostly confirmed in a historic, non-MRD risk adapted trial (UKALLXII/ECOG-ACRIN E2993, NCT00002514) in adolescents and adult B-ALL cases [21] according to the following risk assignment: standard risk genotypes: *DUX4*-rearranged, *ETV6-RUNX1*/-like, *TCF3-PBX1*, PAX5 P80R, high-hyperdiploid; high-risk genotypes: Ph-like, *KMT2A-AFF1*, low-hypodiploid/near-haploid, *BCL2/MYC*-rearranged; and intermediate-risk genotypes: *PAX5*alt, *ZNF384*/-like, and *MEF2D*-rearranged.

3. T-Cell Acute Lymphoblastic Leukemia (T-ALL)

3.1. Genomic Overview of T-ALL

T-ALL leukemic cells express a subset of T-cell makers (CD3, cyCD3, CD2, CD5, CD7, CD8) and arises from immature T-cell progenitors [24][25]. Pediatric T-ALL accounts for 10–15% of newly diagnosed pediatric ALL and is characterized by higher incidence in boys, high initial white blood cell counts, mediastinal mass, central nervous system infiltration, and

slightly worse prognosis compared to B-ALL [26]. The majority of T-ALL cases may be subclassified into subtypes according to the aberrant expression and dysregulated pathways of transcription factors and oncogenes induced by leukemia-initiating alterations involving basic helix–loop–helix (bHLH) factors (*TAL1*, *TAL2*, *LYL1*), homeobox genes (*TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *NKX2-1*, *NKX2-5*, *HOXA*), *LMO1*, *LMO2*, *MYB*, *BCL11B* and *SPI1* (**Figure 2**) [5][27][28]. These subtypes are defined with expression profiles by WTS or microarray, however, almost half of these leukemia-initiating alterations in T-ALL show intergenic breakpoints that can be missed by WTS but rescued by whole genome sequencing (WGS) [27][28]. Epigenomic analyses have also identified novel leukemia-initiating alterations in non-coding regions [5][29][30].

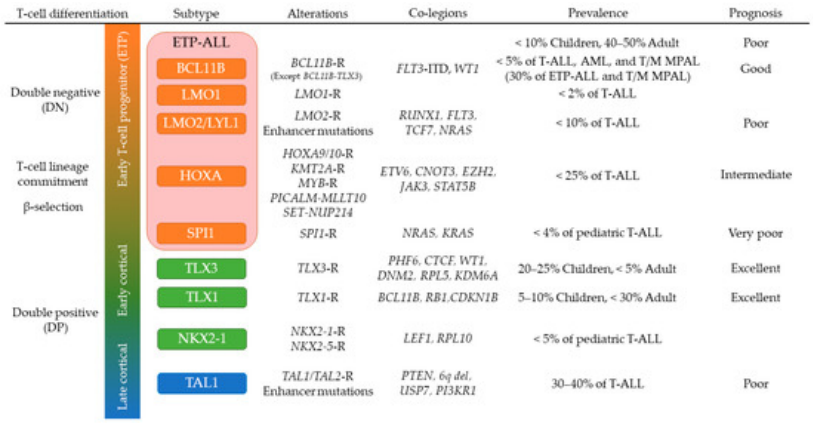

Figure 2. T-cell differentiation and T-ALL subtyping. This schema describes differentiation stages of each T-ALL subtype according to the specific genetic alterations leading to aberrant expression of rearranged or mutated genes. Prevalence and prognosis of each subtype are shown. Subtypes are colored according to corresponding normal T-cell differentiation stage: early T-cell precursor (ETP, red and orange), early stages of cortical thymocytes maturation (green), and late stages of cortical thymocytes maturation (blue). Abbreviations: T-ALL: T-cell acute lymphoblastic leukemia; T/M MPAL: T/myeloid mixed phenotype acute leukemia; -R: rearranged.

NOTCH1 activating mutations and deletion of *CDKN2A/CDKN2B* loci (9p21) are found in over 70% of T-ALL cases and considered as secondary but core events in leukemogenesis [27][28][31]. Concurrent somatic mutations and copy number alterations are frequently observed in T-ALL leading to dysregulation of several cellular pathways, including JAK-STAT signaling (*IL7R*, *JAK1*, *JAK3*, *DNM2*), Ras signaling (*NRAS*, *KRAS*, and *NF1*), PI3K-AKT signaling (*PTEN*, *AKT1*, *PIK3CA PIK3CD*), epigenetic regulation (*PHF6*, *SUZ12*, *EZH2*, *KDM6A*), transcription factors and regulators (*ETV6*, *GATA3*, *RUNX1*, *LEF1*, *WT1*, *BCL11B*), and translation regulators (*CNOT3*, *RPL5*, *RPL10*) [27][28][32][33]. Accumulation of these aberrant expression and dysregulated pathways disrupt the normal T-cell differentiation, proliferation, and survival, and results in T-ALL with unique gene expression signatures reflecting the point of differentiation arrest during T-cell development [25][32]. In addition to expression profiles, DNA methylation signatures are also associated with immunophenotypic profiles and normal T-cell development differentiation stage [34][35].

3.2. T-ALL in Early Stages of Cortical Thymocyte Maturation

T-ALL with CD1a$^+$, CD4$^+$, and CD8$^+$ immunophenotype includes several subgroups, such as rearrangements of *TLX1*, *TLX3*, *NKX2-1*, reflecting a differentiation arrest in early stages of cortical thymocyte maturation and confers a relatively favorable prognosis [36][37]. These subgroups almost commonly harbor *NOTCH1* and *CDKN2A* alterations. Dysregulated expression of HOX transcription factor genes is mostly induced by chromosomal translocations and inversions that juxtapose these genes to enhancers in the *TCR* and *BCL11B* regulatory regions [27][38]. Importantly, *BCL11B* rearrangements (*BCL11B-TLX3*) in this subgroup are mechanistically distinct from those identified in *BCL11B*-rearranged lineage ambiguous leukemias, in that in the *BCL11B-TLX3* leukemia, the *BCL11B* enhancer is used for aberrant expression of *TLX3* at the cost of the loss of expression of *BCL11B*, leading to complete difference in expression profiles [5][38][39]. Instead, *TLX3* rearranged T-ALL (including *BCL11B-TLX3*) shares gene expression signatures, DNA methylation profiles, somatic mutations (*BCL11B*, *WT1*, *PHF6*, *DNM2*), and downstream targets (JAK-STAT, epigenetic regulators) with *TLX1* rearranged T-ALL [27][28][34][35][37]. Some of overlapping genomic features with *TLX1/TLX3* rearranged T-ALL, including *NUP214-ABL1* (TKIs) and JAK-STAT pathway (ruxolitinib, a JAK-STAT inhibitor), can be targetable and have been incorporated into ongoing clinical trials [40].

3.3. TAL1-Driven T-ALL with Late Stages of Cortical Thymocyte Maturation

Deregulation of the *TAL1* oncogene is a feature of T-ALL that typically exhibits a late cortical thymocyte immunophenotype (CD4$^+$, CD8$^+$, CD3$^+$) and comprises approximately 40% of T-ALL [27][28]. This T-ALL subtype includes *TAL1* and *TAL2*

rearranged cases and is further classified into two subgroups by expression profiles whose one expresses *PTCRA* (pre-TCR) suggesting LCK activation that correlated with dasatinib sensitivity [28][37][41]. During normal T-cell differentiation, *TAL1* expression is transcriptionally silenced along with T-cell lineage commitment to proceed appropriate *TCR* rearrangements and differentiation [25]. *TAL1* overexpression is induced by several mechanisms: (1) chromosomal translocations with *TCRA/D*; (2) sub-microscopic interstitial deletion (*STIL-TAL1*); (3) disruption of insulated neighborhoods by losing CTCF binding sites [42]; and (4) somatic indels in a noncoding intergenic regulatory element upstream of *TAL1* to generate aberrant MYB binding site (*MuTE*) [29]. The latter two mechanisms have benefited of NGS technologies for their identification. Dysregulated *TAL1* expression inhibits the function of E-protein dimers by forming TAL1-E-protein heterodimer [43]. Furthermore, TAL1 forms the central node of the core regulatory circuit to coordinately regulate downstream target genes with several hematopoietic transcription factors including *GATA3*, *RUNX1*, *MYB*, and the ETS family genes, which is active in normal hematopoietic stem cell (HSC) and progenitor cells [44][45], and RUNX1 inhibition is reported to impair the growth of T-ALL but not normal hematopoietic cells [46]. However, although TAL1 functions as a master transcription factor related to T-cell differentiation and leukemogenesis of T-ALL, only 30% of transgenic mice develop T-ALL after a latent period, indicating that additional abnormalities are required for leukemogenesis [47]. Expression of *Lmo2* accelerates the onset of leukemia in *Tal1* transgenic mice, and *LMO1/LMO2* are commonly expressed in human *TAL1*-driven T-ALL [48][49]. Other cooperative genes and noncoding RNAs in *TAL1*-driven T-ALL include *ARID5B*, *ARIEL*, and *MYC*, driving aberrant expression of *TAL1* [50][51]. In addition, PI3K-AKT pathway genes including *PTEN* are frequently mutated in this subgroup [27][28], which associates with glucocorticoid resistance and can be reversed by the inhibition of this pathway [52]. Several cell cycle regulators including *CDK6* and *CCND3* are regulated by TAL1 complex [44] and may be potential targets of therapeutic intervention [53].

3.4. Early T-Cell Precursor (ETP) ALL and Mixed Phenotype Acute Leukemia

ETP-ALL is often referred to as a subtype of T-ALL as it exhibits an immunophenotype analogous to the earliest stages of T-cell development (cytoplasmic $CD3^+$, $CD7^+$; $CD8^-$, $CD1a^-$, $CD5^{weak}$), and with expression of myeloid and/or stem-cell markers [36][54]. However, the genomic alterations and gene expression profile of ETP-ALL are more similar to a hematopoietic stem cell than a T cell precursor, suggesting that ETP-ALL could be included in a subgroup of immature acute leukemias of ambiguous lineage (ALAL), originating from a hematopoietic progenitor at a maturational stage prior to initiation of a definitive program of T cell differentiation. Consistent with this, recent studies have defined a subgroup of *BCL11B*-deregulated ALAL, that includes one third of ETP-ALL and T/myeloid mixed phenotype acute leukemia (T/M MPAL) cases with a very distinct expression profile [5]. *BCL11B*-deregulated ALAL is characterized by structural variations of the region containing *BCL11B* at 14q32 including translocations and high-copy amplification generating a distal neo-enhancer, that each leads to aberrant expression of *BCL11B*, in the case of the rearrangements by hijacking super-enhancers active in CD34+ hematopoietic stem and progenitor cell (HSPCs) [5][39]. *FLT3* activating mutations were found in 80% of *BCL11B*-deregulated ALAL, and concurrent expression of *BCL11B* and *FLT3-ITD* on HSPC exhibited synergistic effects on activating T-cell directed differentiation to express cytoplasmic CD3 while blocking myeloid differentiation [5]. Other genomic features of ETP-ALL include a subgroup of aberrant expression of *PU.1* (*SPI1* fusions), *HOXA* genes (rearrangements of *HOXA* genes, *KMT2A* rearrangements, *PICALM-MLLT10*, *SET-NUP214*) and mutations of multiple cellular pathways (Ras signaling, JAK-STAT signaling, and epigenetic regulators) and transcription factors related to T-cell development [27][28][55]. Especially, T-ALL with *SPI1* fusions represents unique expression profiles with high relapse rate [5][28]. Again, several of these genomic mutations were shared with T/M MPAL, including biallelic *WT1* alterations, mutations of hematopoietic transcription factors (*ETV6*, *RUNX1*, *CEBPA*) and activating mutations of signaling pathways (JAK-STAT, *FLT3*, Ras) [56][55], supporting that they are similar entities in the spectrum of immature leukemias and both might have sensitivity to FLT3 and/or JAK inhibition [57].

3.5. NOTCH1 Activating Mutations in T-ALL

NOTCH1 encodes a highly conserved ligand-dependent transcription factor. The NOTCH1 signaling pathway plays an important role in the commitment of T-cell lineage specification and for further T-cell development [25][58]. In T-ALL, *NOTCH1* activating mutations are found in more than 70% of cases and is considered an oncogene involved in leukemogenesis [27][28]. Aberrant activation of NOTCH1 pathway in T-ALL is mostly induced by (1) ligand-independent activation (somatic mutations, indels and large deletions that disrupt the negative regulatory region), or (2) impairment of the proteasomal degradation of intracellular domain of NOTCH1 (truncation of the PEST domain, *NOTCH1* mutations in 3′ untranslated region, and *FBXW7* mutations) [59][60][61][62][63][64]. These two types of *NOTCH1* activating mutations have synergistic effects and more than 20% of T-ALL cases harbor both types of alterations [59]. However, most *NOTCH1* activating mutations found in human T-ALL are considered as a weak tumor initiator event. Co-existence of both types of *NOTCH1* mutations in hematopoietic progenitors tends to induce a transient preleukemic $CD4^+/CD8^+$ double positive cells and takes 10 to 15 weeks to fully transform into T-ALL, suggesting that they are alone incompletely leukemogenic [65][66][67]. In addition, more than 40% of T-ALL cases harbor subclonal *NOTCH1* activating mutations and their heterogeneity at

diagnosis was reported by several studies [27][28][68]. Furthermore, *NOTCH1* activating mutations are considered to be acquired as a late secondary event in leukemogenesis [31][68][69].

A key target of NOTCH1 is the *MYC* oncogene that shares several overlapping target genes with NOTCH1 to promote cell proliferation and dysregulate anabolic pathways in T-ALL [67][70][71]. NOTCH1 controls T-cell-specific distal enhancer of *MYC* ("NMe"), resulting in the NOTCH1-MYC regulatory circuit [67][70][71]. In addition, pre-TCR signaling also correlates with NOTCH signaling, leading to LCK signaling and robust cell growth at DN3 stage in the T-cell development, which can be targetable by dasatinib [41][72].

Due to the high prevalence and importance of *NOTCH1* activating mutations in T-ALL, targeted therapy on NOTCH1 pathway has been a major interest. This includes γ-secretase inhibitors (GSIs), ADAM inhibitors, SERCA inhibitors, and monoclonal antibodies [73]. Among them, GSIs, that block the activation process of NOTCH receptors by inhibiting proteolytic cleavage, have been tested in preclinical and Phase 1 studies [74][75]. However, the usage of GSIs in T-ALL is still in a developing phase due to gastrointestinal toxicity and insufficient antitumor responses that mostly induce transient growth arrest rather than cell death [76][77]. To overcome these problems, combination with other agents have been explored including glucocorticoids that showed synergistic effects by reversing glucocorticoid resistance [78]. Inhibition of mTORC1 signaling and PKCδ signaling are also promising combination strategies to restore GSIs sensitivity in resistant cells [79][80].

4. Implications for Diagnosis

The revolution in genomic characterization of ALL has created important opportunities and challenges for the clinical implementation of sequencing-based approaches for diagnosis and management of ALL (**Table 1**). This is particularly true for B-ALL, where many of the recently identified subtypes are associated with prognosis (even in the context of MRD-based risk-adapted therapy) [22][21] and where molecular characterization is needed to identify patients suitable for targeted therapy (an exemplar being Ph-like ALL). This is currently less compelling for T-ALL where identification of founding lesions driving T-ALL subtypes are of biological and mechanistic interest but are not typically used to risk stratify or guide therapy, exceptions possibly being kinase inhibition for JAK-STAT alterations and *ABL1* rearrangements, identification of alterations in Ras, *PTEN*, *NOTCH1* and/or *FBXW7* that have been found to be associated with outcome in some studies [81], and LCK dependence for dasatinib therapy [41]. The challenge is clinical implementation of appropriately comprehensive diagnostic approaches to identify all key genomic features. Despite the mutationally sparse genome of ALL, there is striking diversity of the nature of underlying driver alterations, including sequence mutations, DNA copy number alterations, and structural variations, many of which may involve the non-coding genome. Accurate subtyping is also challenged by the inability of conventional cytogenetic and targeted molecular approaches to identify several types of driver (e.g., *DUX4*-rearrangement) and the importance of identifying phenocopies (e.g., *ETV6-RUNX1*-like, and Ph-like ALL). Thus, moving forward, optimal clinical diagnostics require genomic approaches. The choice of approach in part rests on how clinical information will be used. If comprehensive subtyping and identification of all potentially clinically relevant genomic alterations is desirable, a combination of DNA and RNA-based technologies is required. For example, the combination of WGS and WTS enables the identification of sequence mutations, DNA copy number alterations, aneuploidy and structural variants (from WGS) together with identification of fusion chimeras, mutant allele expression, and gene expression profiling (from WTS). The use of one or both approaches is becoming increasingly widely used, and at St Jude Children's Research Hospital, three platform sequencing (WGS, WTS and exome sequencing) is clinical standard of care, informs clinical decision making in ALL [40], and retrieves more actionable clinical information than any single platform alone [82]. WGS is offered using a paired non-tumor sample to aid identification of somatic variants and provides the opportunity to return clinically relevant germline findings. Moreover, this comprehensive approach enables a more streamlined workflow [83][84][85], provided the demands of analysis and interpretation can be met.

Table 1. Clinical implementation of high-throughput sequencing.

Platform	Capability	Cost	Detectable Subtypes	Difficult Subtypes
WTS (RNAseq)	Fusion chimeras Gene expression profiling Mutant allele expression Alternative splicing analysis (BCR/TCR rearrangements) (Sequence mutations) (Copy number analysis)	Moderate	B-ALL ETV6-RUNX1; KMT2A; TCF3-PBX1; BCR-ABL1; DUX4; MEF2D; ZNF384/362 NUTM1; HLF; BCL2/MYC; PAX5alt; ZEB2/CEBPE; -like subtypes	B-ALL Aneuploidies
			T-ALL HOXA (*KMT2A*-R, *PICALM-MLLT10*, *SET-NUP214*); SPI1; NKX2-1; TAL1 (*STIL-TAL1*)	T-ALL BCL11B; TLX1/3; LMO1/2; HOXA (others); TAL1 (others); T-other
WGS	Sequence mutations Structural variants Copy number analysis (BCR/TCR rearrangements) (GWAS)	High	B-ALL Aneuploidies; ETV6-RUNX1; KMT2A; TCF3-PBX1; BCR-ABL1; DUX4; MEF2D; ZNF384/362; NUTM1; HLF; BCL2/MYC; PAX5 P80R; IKZF1 N159Y; ZEB2/CEBPE; Sequence and structural alterations in Ph-like ALL	B-ALL -like subtypes; Part of PAX5alt
			T-ALL BCL11B; TLX1/3; LMO1/2; HOXA; SPI1; NKX2-1; TAL1	T-ALL T-other
WES	Sequence mutations (coding) Structural variants (coding) Copy number analysis	Moderate	B-ALL (Aneuploidies) PAX5 P80R IKZF1 N159Y Sequence mutations in Ph-like ALL (e.g., JAK1/2/3, Ras)	Most of other B-ALL and T-ALL subtypes

Platform	Capability	Cost	Detectable Subtypes	Difficult Subtypes
Targeted sequencing (DNA and/or RNA)	Fusion chimeras (targeted) Gene expression (targeted) Sequence mutations (targeted) Structural variants (targeted) (Copy number analysis)	Low	Targeted alterations	Non-targeted alterations

The parenthesis in “Capability” indicates analyses in development. Abbreviations: WTS: whole transcriptome sequencing; BCR: B-cell receptor; TCR: T-cell receptor; WGS: whole genome sequencing; GWAS: genome wide association study; WES: whole exome sequencing; -R: rearranged.

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