New Subtypes of B-ALL Introduced in WHO-HAEM5

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B-ALL with iAMP21 and B-ALL with Ph-like features were upgraded from provisional to definite subtypes of ALL. B-ALL with *TCF3::HLF* fusion was included as a new subtype of B-ALL; all three of these subtypes have been discussed above. This research briefly describes the other new genetic subtypes of B-ALL in WHO-HAEM5.

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1. B-ALL with *DUX4* Rearrangement

B-ALL with *DUX4* rearrangement is one of the newer described subtypes of B-ALL. *DUX4*-rearranged B-ALL comprises 16% of the B-other cases or 4% of all pediatric B-ALL [1]. In B-ALL in AYA in Japan, *DUX4*, *ZNF384*, and *MEF2D* fusion genes account for about 40% of Ph-negative cases [2]. In B-ALL in Malaysia and Singapore, *DUX4*-rearranged B-ALL is the third-most-common subtype [3]. This leukemia has a favorable prognosis, similar to B-ALL, with high hyperdiploidy and *ETV6::RUNX1* fusion, despite the presence of high MRD levels [3][4].

The *DUX4* gene encodes a homeobox-containing protein and is located within a subtelomeric D4Z4 repeat region on 4q and 10q. The gene is present in 11–100 copies on each allele and is epigenetically silent in somatic tissues. The *DUX4* rearrangement occurs most frequently with *IGH* and less frequently with the *ERG* gene. In the *IGH*::*DUX4* fusion, a segment of the *DUX4* gene is relocated to *IGH*, leading to the overexpression of DUX4. This rearranged form of *DUX4* binds with a genetic region in the ETS-family transcription factor *ERG* (ETS-related gene), which leads to the expression of an *ERG* protein fragment that inhibits normal ERG function and causes leukemic transformation. *ERG* deletions are frequent secondary alterations in *DUX4*-rearranged B-ALL [1][2][5]. Also, *IKZF1* deletions co-occur with *ERG* deletions in *DUX4*-rearranged B-ALL. As the prognosis of *IKZF1* deletions depends on the co-occurring mutations in B-ALL, the usually adverse prognosis of *IKZF1* deletions can be overcome in these patients by chemotherapy based on MRD evaluation [6].

DUX4 rearrangements in B-ALL are complex and different from those in *CIC::DUX4* fusion-positive (non-Ewing) round-cell sarcoma (sarcoma described in [7]) [1]. The complexity of the genetic rearrangement is likely to be the reason why these abnormalities were not detected in the pre-genomics era. The gene expression profile for *DUX4*-rearranged B-ALL is distinctive [1]. Flow cytometry showed strong (aberrant) surface expression of CD371 on the leukemic cells in *DUX4*-rearranged B-ALL, which, when combined with the expression of CD2, diagnosed all cases

of this type of B-ALL [8]. CD371 is predominantly expressed on myeloid cells [8] and is not expressed on mature lymphocytes (see image in [9]). *DUX4*-rearranged leukemic cells may also express CD66c, and the co-expression of CD66c and CD2 was almost exclusively found in *DUX4* fusion-positive B-ALL [10]. An immunohistochemical stain for detecting *DUX4* fusions showed immunohistochemical positivity in five of six molecularly-positive cases and negativity in three of three molecularly-negative cases [11]. *DUX4*-rearranged B-ALL leukemic cells may switch to monocyte-like cells, which is a feature of CD371 expression [8][11], and this switch does not lead to a worse outcome [12].

The WHO-HAEM5 diagnostic criteria require RNA or DNA sequencing by NGS to diagnose this type of B-ALL. The desirable criteria include confirming the *DUX4* gene rearrangement, the presence of CD371 expression on leukemic cells by FCI, or both [9]. It is noteworthy that while RNA sequencing can diagnose *DUX4* fusions, the most extensive study of *DUX4*-rearranged B-ALL patients examined by whole-genome sequencing (WGS) in a single clinical trial in the U.K. showed that whole-transcriptome sequencing alone could not be relied upon to identify all *DUX4*-rearranged B-ALL cases in the absence of WGS. These investigators established an automated bioinformatics pipeline that improved the detection of *DUX4* fusions by WGS [13].

2. B-ALL with *ZNF384* Rearrangement

The zinc finger protein 384, *ZNF384*, gene is located on the chromosomal locus 12p13.31. The gene encodes for a zinc finger transcription factor that is ubiquitously expressed in the bone marrow and other tissues. The transcription factor appears to bind and regulate the promoters of the extracellular matrix genes [14]. *ZNF384* rearrangements may occur with at least ten different gene partners in about 5% of childhood B-ALLs, 10% of adult B-ALLs, and 48% of mixed-phenotype acute leukemia, B/myeloid-type [15][16].

In Japan, *ZNF384*-related fusion genes were identified in 4.1% of 291 B-ALL or about 9% of B-other ALL patients. All *ZNF384*-related gene fusions, including *TCF3::ZNF384* and *EP300::ZNF384*, showed weak or negative CD10 expression with aberrant CD13 and CD33 expression. But the clinical features differed depending on the specific fusion gene. Higher cell counts, younger age (median age five years), and more frequent relapses were present in *TCF3::ZNF384*-positive than in *EP300::ZNF384*-positive B-ALL patients. The latter group of B-ALL patients had a median age of 11 years [16][17]. FISH with break-apart probes or genomic sequencing (RNA or DNA) is required to diagnose the cryptic *ZNF384* rearrangement [9].

3. B-ALL with *MEF2D* Rearrangement

Myocyte-enhancer factor 2 (Mef2) transcription factors are necessary for early B-cell development [18]. *MEF2D*, located on 1q22, encodes one of these transcription factors. *MEF2D* was found to be rearranged in about 5% of pediatric B-ALL without recurring genetic abnormalities. *MEF2D* can rearrange with multiple genes (*BCL9*, *CSF1R*, *DAZAP1*, *HNRNPUL1*, and *SS18*), with *BCL9*, located on 1q21, being the most frequent.

MEF2D::BCL9-rearranged B-ALL presents at a median age of 14 years. Morphologically, the leukemic cells appear to be mature B-cell leukemia-like cells with high expression of HDAC [19]. They have a characteristic immunophenotype with weak or absent CD10, CD38 positivity, and cytoplasmic IgM positivity. The cytogenetic rearrangement is cryptic by karyotyping, and diagnosis requires FISH, gene expression profiling, or genomic sequencing. There is resistance to chemotherapy, with very early relapse in this high-risk leukemia [19][20][21].

4. B-ALL with *PAX5*alt and B-ALL with *PAX5* p.P80R

The *PAX5* gene encodes for a transcription factor that regulates numerous genes essential for normal B cell development. B-ALL with *PAX5*alt and B-ALL with *PAX5* p.P80R refer to two distinct types of B-ALL. Both of these types of B-ALL harbor molecular genetic abnormalities in *PAX5*, which lead to a loss of the normal PAX5 protein, initiating a precursor B lymphoblastic leukemia.

B-ALL with *PAX5* p.P80R is unique because this subtype of B-ALL is characterized by a single point mutation in PAX5 instead of the other types of abnormalities that are common in B-ALL, such as deletions and translocations. This point mutation, c.239C>G, p.P80R, causes a substitution of proline to arginine in the DNA-binding domain of *PAX5*. In a cohort of 170 adult B-ALL cases that were negative for the known genetic abnormalities in B-ALL, gene expression data profiling showed four clusters corresponding to B-ALL with rearranged *ZNF384*, *DUX4*, *KMT2A*, and *BCR::ABL1*-like features [22]. A fifth cluster in this study comprised 14 patients with *PAX5* p.P80R and lacked any fusion gene. Sanger sequencing identified 16 additional cases with *PAX5* p.P80R in another cohort [22]. Cytogenetics showed structural rearrangements of 9p or 7p, including dic(9;20) and der(7;9). The second allele was deleted or inactivated, leading to biallelic loss of PAX5 [22][23]. Mutations of genes in the RAS pathway were also present [22][23].

B-ALL with *PAX5*alt includes leukemia-causing genetic abnormalities other than *PAX5* p.P80R. This type of B-ALL has a gene expression profile distinct from that of B-ALL with *PAX5* p.P80R [23]. It comprises about 3–5% of childhood ALLs and 9.6% of adult B-ALLs.

In contrast, B-ALL with *PAX5* p.P80R comprises about 1% of childhood B-ALLs and up to 5% of adult B-ALLs. By FCI, B-ALL with *PAX5* p.P80R shows a pro-B immunophenotype, with low CD20 and high CD45 expression on the leukemic cells. The leukemic cells are CD13-negative, CD33-positive, and CD2-positive and show stronger intensity CD10 expression than in *KMT2A*-rearranged B-ALL. The prognosis of B-ALL with *PAX5* p.P80R is better than that of B-ALL with *PAX5*alt abnormalities [4][23][24]. The diagnosis of these subtypes requires genomic sequencing.

5. B-ALL with *MYC* Rearrangement

This rare leukemia occurs in <1% of children, 1–2% of AYA, and 2–3% of adult B-ALLs [9]. These cases have a precursor B-ALL immunophenotype, including no expression of surface immunoglobulins, but they harbor *MYC* rearrangement. According to gene expression profiling, these leukemias cluster with precursor B cells and other B-

ALLs, but not with Burkitt leukemia [25]. In adults, these leukemias are considered high-risk B-ALLs with poor prognoses [4]. Children with *MYC*-rearranged B-ALLs are usually treated with Burkitt lymphoma therapy, with a better outcome than adults with *MYC*-rearranged B-ALL [9].

6. B-ALL with *NUTM1* Rearrangement

NUTM1 rearrangement is more frequent in infants (about 3–5%) than in children (0.4–0.9%) with B-ALL, and this rearrangement has not yet been detected in adults with B-ALL [26].

The nuclear protein in the testes (NUT) is normally located in post-meiotic spermatogenic cells, wherein a global increase in hyperacetylation occurs for spermatogenesis. The NUT Midline carcinoma family member 1 (*NUTM1*) gene (also known as *NUT*), located on 15q14, was first discovered as a part of the fusion gene in a rare and aggressive carcinoma called NUT carcinoma [27][28]. NUT carcinoma harbors a reciprocal t(15;19)(q14;p13.1) translocation between *NUTM1* on chromosome 15q14 and the BET family gene *BRD4* on chromosome 19p13.1, leading to an in-frame *BRD4::NUT* fusion oncogene driven by the *BRD4* promoter [28]. Subsequently, with the increased evaluation of tumors by genomic sequencing approaches, the *NUTM1* gene was found to also be present with other fusion partner genes in different types of cancers, including sarcomas and B-ALL [29]. These fusions lead to aberrant NUTM1 overexpression, and the altered global chromatin acetylation might confer sensitivity to histone deacetylase inhibitors and possibly to bromodomain inhibitors for *NUTM1::BRD9* fusion cases [9].

Intriguingly, while NUT carcinoma is a highly aggressive cancer, *NUTM1*-rearranged B-ALL has a favorable prognosis. This type of B-ALL occurs in infants and comprises 21.7% to 30% of non-*KMT2A*-rearranged (or *KMT2A* germline) B-ALL in infants [26][30]. Among nine *NUTM1*-rearranged B-ALL patients with a median age of 8.8 months, *ACIN1* (n = 5), *CUX1* (n = 2), *BRD9* (n = 1), and *ZNF618* (n = 1) were identified as fusion partners [30]. Interestingly, this same study also identified other *KMT2A*-germline infant B-ALL patients with a median age of about 11 months who harbored *PAX5* fusion; those patients had a poor prognosis [30].

By immunophenotype, the leukemic cells in *NUTM1*-rearranged B-ALL may be CD10-positive or CD10-negative, in contrast with CD10-negative leukemic cells in *KMT2A*-rearranged B-ALL [26][30]. However, *KMT2A*-rearranged B-ALL may also be positive for CD10 [10], indicating that CD10 expression alone cannot be used to distinguish these two subtypes of ALL. The diagnosis can be made by FISH using a break-apart *NUTM1* probe or RNA or DNA sequencing [9][30].

7. B-ALL with *ETV::RUNX1*-like Features

This leukemia subtype comprises about 1–3% of childhood ALL [1] and about 2% of adult B-ALL [4]. Similar to Ph-like B-ALL, B-ALL with *ETV::RUNX1*-like features lacks the *ETV6::RUNX1* fusion, but the gene expression profile is similar to that of B-ALL with *ETV::RUNX1* fusion (see figure in [9]).

FCI shows the leukemia cells are CD24-positive and CD44-negative or low. However, note that this immunophenotype is not specific to this subtype of B-ALL and was also identified in B-ALLs with other genetic subtypes diagnosed by gene expression profiling [31]. Molecular analysis reveals combined *ETV6* and *IKZF1* alterations (rearrangements and deletions) in this type of leukemia [1]. Further, recent genomic studies showed biallelic *ETV6* inactivation [13] and the APOBEC mutational signature in *ETV6::RUNX1*-like childhood B-ALL patients [13][32]. Of note, B-ALL with *ETV6::RUNX1*-like features may also arise in patients with germline *ETV6* alterations [32].

References

1. Lilljebjörn, H.; Henningsson, R.; Hyrenius-Wittsten, A.; Olsson, L.; Orsmark-Pietras, C.; Von Palffy, S.; Askmyr, M.; Rissler, M.; Schrappe, M.; Cario, G.; et al. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. Nat. Commun. 2016, 7, 11790.
2. Yasuda, T.; Tsuzuki, S.; Kawazu, M.; Hayakawa, F.; Kojima, S.; Ueno, T.; Imoto, N.; Kohsaka, S.; Kunita, A.; Doi, K.; et al. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat. Genet. 2016, 48, 569–574.
3. Li, Z.; Lee, S.H.R.; Ni Chin, W.H.; Lu, Y.; Jiang, N.; Lim, E.H.H.; Coustan-Smith, E.; Chiew, K.H.; Oh, B.L.Z.; Koh, G.S.; et al. Distinct clinical characteristics of DUX4- and PAX5-altered childhood B-lymphoblastic leukemia. Blood Adv. 2021, 5, 5226–5238.
4. Paietta, E.; Roberts, K.G.; Wang, V.; Gu, Z.; Buck, G.A.N.; Pei, D.; Cheng, C.; Levine, R.L.; Abdel-Wahab, O.; Cheng, Z.; et al. Molecular classification improves risk assessment in adult BCR-ABL1-negative B-ALL. Blood 2021, 138, 948–958.
5. Zhang, J.; McCastlain, K.; Yoshihara, H.; Xu, B.; Chang, Y.; Churchman, M.L.; Wu, G.; Li, Y.; Wei, L.; Iacobucci, I.; et al. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat. Genet. 2016, 48, 1481–1489.
6. Stanulla, M.; Dagdan, E.; Zaliova, M.; Möricke, A.; Palmi, C.; Cazzaniga, G.; Eckert, C.; Te Kronnie, G.; Bourquin, J.P.; Bornhauser, B.; et al. IKZF1plus Defines a New Minimal Residual Disease–Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. J. Clin. Oncol. 2018, 36, 1240–1249.
7. Antonescu, C.R.; Owosho, A.A.; Zhang, L.; Chen, S.; Deniz, K.; Huryn, J.M.; Kao, Y.-C.; Huang, S.-C.; Singer, S.; Tap, W.; et al. Sarcomas With CIC-rearrangements Are a Distinct Pathologic Entity With Aggressive Outcome: A Clinicopathologic and Molecular Study of 115 Cases. Am. J. Surg. Pathol. 2017, 41, 941–949.

8. Schinnerl, D.; Mejstrikova, E.; Schumich, A.; Zaliova, M.; Fortschegger, K.; Nebral, K.; Attarbaschi, A.; Fiser, K.; Kauer, M.O.; Popitsch, N.; et al. CD371 cell surface expression: A unique feature of DUX4-rearranged acute lymphoblastic leukemia. Haematologica 2019, 104, e352–e355.
9. WHO Classification of Tumours Editorial Board. Hematolymphoid Tumours, 5th ed.; WHO Classification of Tumours Series; International Agency for Research on Cancer: Lyon, France, 2022; Volume 11, Available online: https://tumourclassification.iarc.who.int/home (accessed on 15 June 2023).
10. Ohki, K.; Takahashi, H.; Fukushima, T.; Nanmoku, T.; Kusano, S.; Mori, M.; Nakazawa, Y.; Yuza, Y.; Migita, M.; Okuno, H.; et al. Impact of immunophenotypic characteristics on genetic subgrouping in childhood acute lymphoblastic leukemia: Tokyo Children's Cancer Study Group (TCCSG) study L04-16. Genes Chromosom. Cancer 2020, 59, 551–561.
11. Siegele, B.J.; Stemmer-Rachamimov, A.O.; Lilljebjorn, H.; Fioretos, T.; Winters, A.C.; Cin, P.D.; Treece, A.; Gaskell, A.; Nardi, V. N-terminus DUX4-immunohistochemistry is a reliable methodology for the diagnosis of DUX4–fused B-lymphoblastic leukemia/lymphoma (N-terminus DUX4 IHC for DUX4 -fused B-ALL). Genes Chromosom. Cancer 2022, 61, 449–458.
12. Novakova, M.; Zaliova, M.; Fiser, K.; Vakrmanova, B.; Slamova, L.; Musilova, A.; Brüggemann, M.; Ritgen, M.; Fronkova, E.; Kalina, T.; et al. DUX4r, ZNF384r and PAX5-P80R mutated B-cell precursor acute lymphoblastic leukemia frequently undergo monocytic switch. Haematologica 2021, 106, 2066–2075.
13. Ryan, S.L.; Peden, J.F.; Kingsbury, Z.; Schwab, C.J.; James, T.; Polonen, P.; Mijuskovic, M.; Becq, J.; Yim, R.; Cranston, R.E.; et al. Whole genome sequencing provides comprehensive genetic testing in childhood B-cell acute lymphoblastic leukaemia. Leukemia 2023, 37, 518–528.
14. National Library of Medicine. Zinc Finger Protein 384 Gene. Available online: https://www.ncbi.nlm.nih.gov/gene/171017 (accessed on 19 March 2023).
15. Alexander, T.B.; Gu, Z.; Iacobucci, I.; Dickerson, K.; Choi, J.K.; Xu, B.; Payne-Turner, D.; Yoshihara, H.; Loh, M.L.; Horan, J.; et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. Nature 2018, 562, 373–379.
16. Hirabayashi, S.; Butler, E.R.; Ohki, K.; Kiyokawa, N.; Bergmann, A.K.; Möricke, A.; Boer, J.M.; Cavé, H.; Cazzaniga, G.; Yeoh, A.E.J.; et al. Clinical characteristics and outcomes of B-ALL with ZNF384 rearrangements: A retrospective analysis by the Ponte di Legno Childhood ALL Working Group. Leukemia 2021, 35, 3272–3277.
17. Shinsuke, H.; Kentaro, O.; Kazuhiko, N.; Hitoshi, I.; Yukihide, M.; Kohji, O.; Akinori, Y.; Kazuki, T.; Yuya, S.; Ai, Y.; et al. ZNF384-related fusion genes define a subgroup of childhood B-cell precursor acute lymphoblastic leukemia with a character-istic immunotype. Haematologica 2017, 102, 118–129.

18. Herglotz, J.; Unrau, L.; Hauschildt, F.; Fischer, M.; Kriebitzsch, N.; Alawi, M.; Indenbirken, D.; Spohn, M.; Müller, U.; Ziegler, M.; et al. Essential control of early B-cell development by Mef2 transcription factors. Blood 2016, 127, 572–581.
19. Suzuki, K.; Okuno, Y.; Kawashima, N.; Muramatsu, H.; Okuno, T.; Wang, X.; Kataoka, S.; Sekiya, Y.; Hamada, M.; Murakami, N.; et al. MEF2D-BCL9 Fusion Gene Is Associated With High-Risk Acute B-Cell Precursor Lymphoblastic Leukemia in Adolescents. J. Clin. Oncol. 2016, 34, 3451–3459.
20. Gu, Z.; Churchman, M.; Roberts, K.; Li, Y.; Liu, Y.; Harvey, R.C.; McCastlain, K.; Reshmi, S.C.; Payne-Turner, D.; Iacobucci, I.; et al. Genomic analyses identify recurrent MEF2D fusions in acute lymphoblastic leukaemia. Nat. Commun. 2016, 7, 13331.
21. Ohki, K.; Kiyokawa, N.; Saito, Y.; Hirabayashi, S.; Nakabayashi, K.; Ichikawa, H.; Momozawa, Y.; Okamura, K.; Yoshimi, A.; Ogata-Kawata, H.; et al. Clinical and molecular characteristics of MEF2D fusion-positive B-cell precursor acute lymphoblastic leukemia in childhood, including a novel translocation resulting in MEF2D-HNRNPH1 gene fusion. Haematologica 2019, 104, 128–137.
22. Passet, M.; Boissel, N.; Sigaux, F.; Saillard, C.; Bargetzi, M.; Ba, I.; Thomas, X.; Graux, C.; Chalandon, Y.; Leguay, T.; et al. Group for Research on Adult ALL (GRAALL). PAX5 P80R mutation identifies a novel subtype of B-cell precursor acute lymphoblastic leukemia with favorable outcome. Blood 2019, 133, 280–284, Erratum in Blood 2020, 135, 2011.
23. Gu, Z.; Churchman, M.L.; Roberts, K.G.; Moore, I.; Zhou, X.; Nakitandwe, J.; Hagiwara, K.; Pelletier, S.; Gingras, S.; Berns, H.; et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat. Genet. 2019, 51, 296–307.
24. Li, J.-F.; Dai, Y.-T.; Lilljebjörn, H.; Shen, S.-H.; Cui, B.-W.; Bai, L.; Liu, Y.-F.; Qian, M.-X.; Kubota, Y.; Kiyoi, H.; et al. Transcriptional landscape of B cell precursor acute lymphoblastic leukemia based on an international study of 1223 cases. Proc. Natl. Acad. Sci. USA 2018, 115, E11711–E11720.
25. Wagener, R.; López, C.; Kleinheinz, K.; Bausinger, J.; Aukema, S.M.; Nagel, I.; Toprak, U.H.; Seufert, J.; Altmüller, J.; Thiele, H.; et al. IG-MYC+ neoplasms with precursor B-cell phenotype are molecularly distinct from Burkitt lymphomas. Blood 2018, 132, 2280–2285.
26. Boer, J.M.; Valsecchi, M.G.; Hormann, F.M.; Antić, Ž.; Zaliova, M.; Schwab, C.; Cazzaniga, G.; Arfeuille, C.; Cavé, H.; Attarbaschi, A.; et al. Favorable outcome of NUTM1-rearranged infant and pediatric B cell precursor acute lymphoblastic leukemia in a collaborative international study. Leukemia 2021, 35, 2978–2982.
27. Rousseaux, S.; Reynoird, N.; Khochbin, S. NUT Is a Driver of p300-Mediated Histone Hyperacetylation: From Spermatogenesis to Cancer. Cancers 2022, 14, 2234.

28. French, C.A. Pathogenesis of NUT Midline Carcinoma. Annu. Rev. Pathol. 2012, 7, 247–265.
29. McEvoy, C.R.; Fox, S.B.; Prall, O.W.J. Emerging entities inNUTM1-rearranged neoplasms. Genes Chromosom. Cancer 2020, 59, 375–385.
30. Fazio, G.; Bardini, M.; De Lorenzo, P.; Grioni, A.; Quadri, M.; Pedace, L.; Abascal, L.C.; Palamini, S.; Palmi, C.; Buldini, B.; et al. Recurrent genetic fusions redefine MLL germ line acute lymphoblastic leukemia in infants. Blood 2021, 137, 1980–1984.
31. Zaliova, M.; Kotrova, M.; Bresolin, S.; Stuchly, J.; Stary, J.; Hrusak, O.; Kronnie, G.T.; Trka, J.; Zuna, J.; Vaskova, M. ETV6/RUNX1-like acute lymphoblastic leukemia: A novel B-cell precursor leukemia subtype associated with the CD27/CD44 immunophenotype. Genes Chromosom. Cancer 2017, 56, 608–616.
32. Brady, S.W.; Roberts, K.G.; Gu, Z.; Shi, L.; Pounds, S.; Pei, D.; Cheng, C.; Dai, Y.; Devidas, M.; Qu, C.; et al. The genomic landscape of pediatric acute lymphoblastic leukemia. Nat. Genet. 2022, 54, 1376–1389.