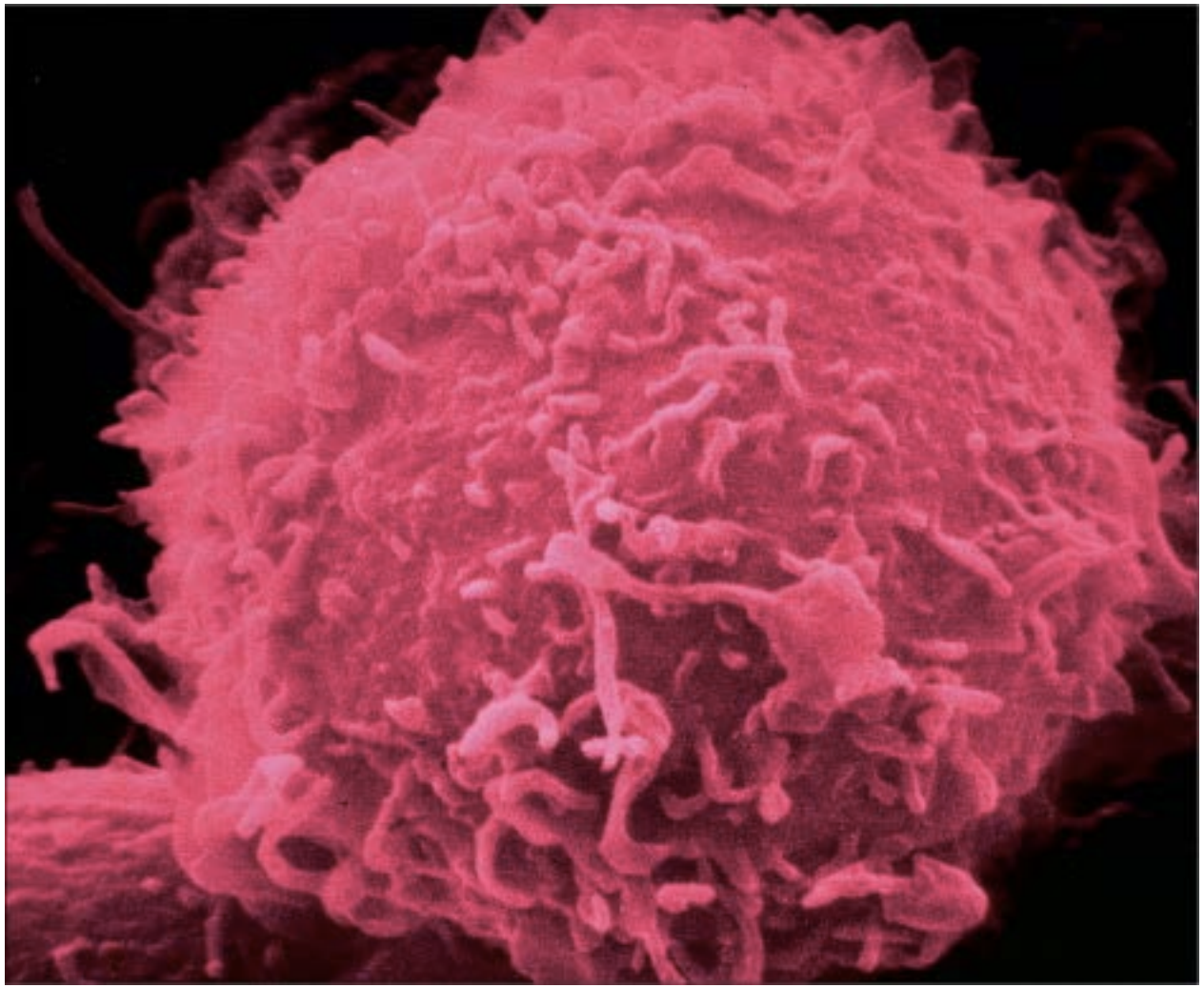
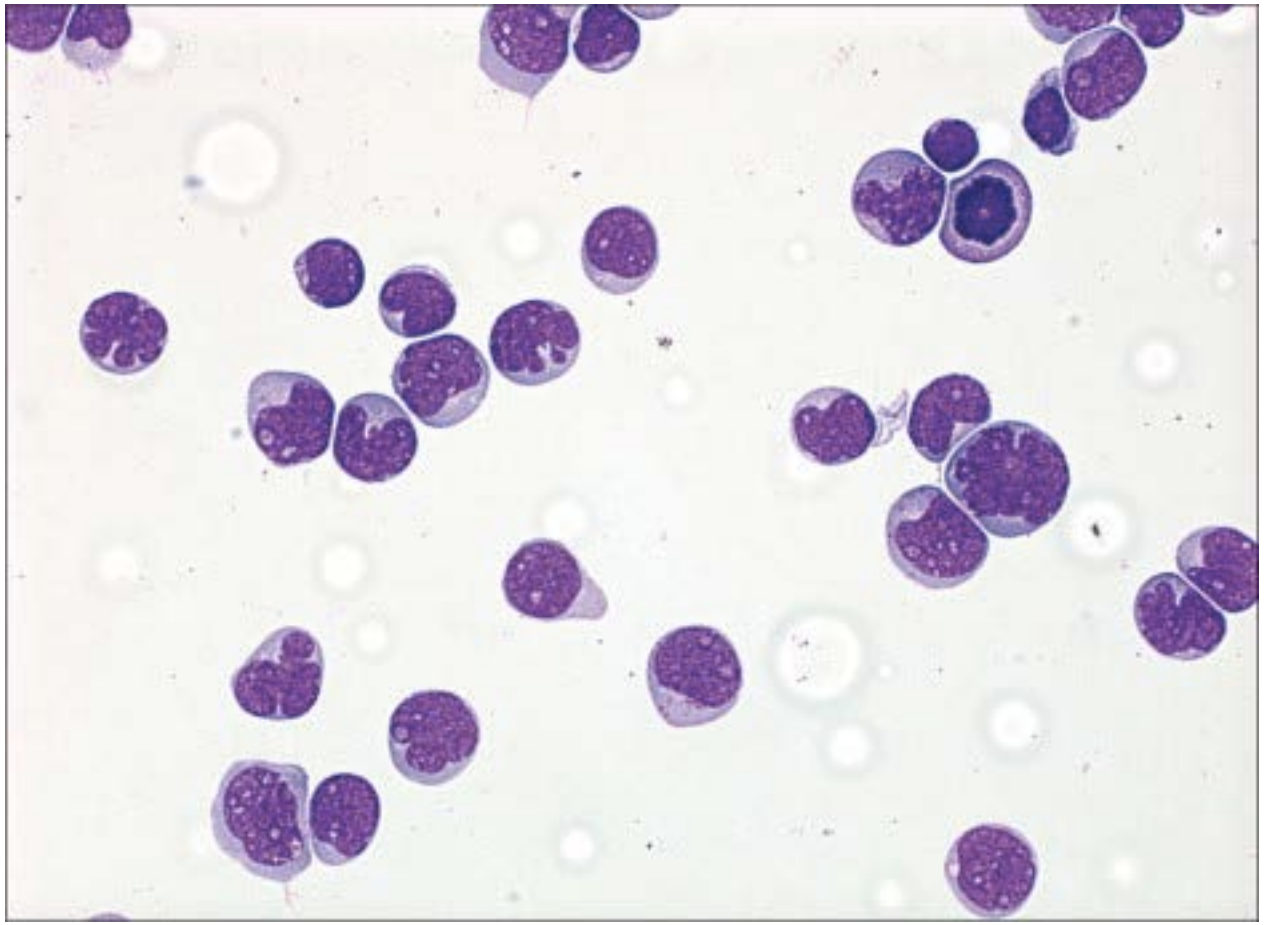




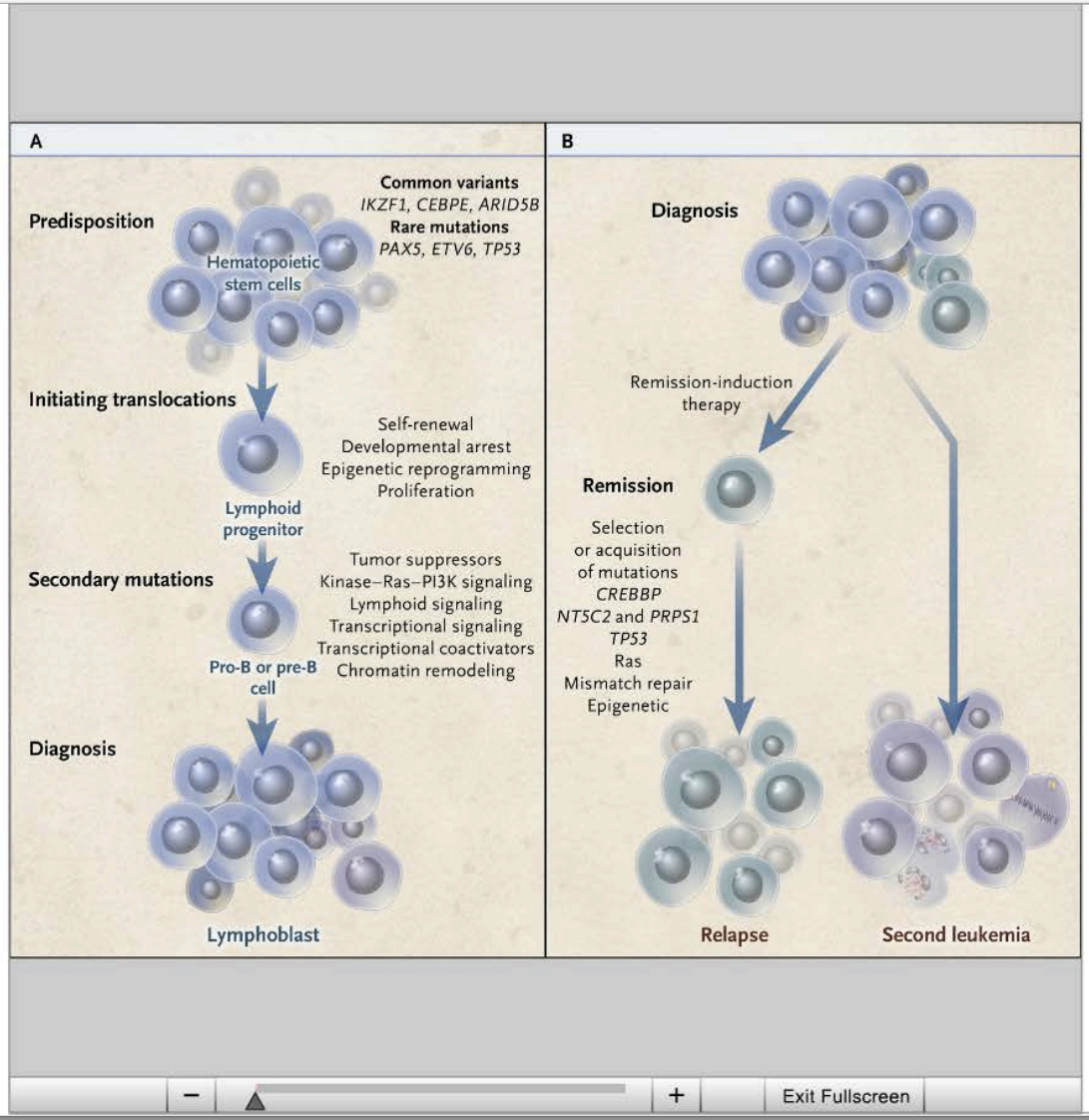


Figure 2. Proposed Sequential Acquisition of Genetic Alterations Contributing to the Pathogenesis an Relapse of ALL.

As shown in Panel A, either common inherited variants or, rarely, deleterious germline mutations confer a predisposition to ALL. Initiating lesions, commonly translocations, are acquired in a lymphoid progenitor. Secondary sequence mutations and structural genetic alterations contribute to an arrest in lymphoid development and perturbation of multiple cellular pathways, resulting in clinically manifest leukemia. PI3K denotes phosphatidylinositol 3-kinase. As shown in Panel B, ALL is commonly genetically polyclonal at diagnosis. Initial therapy suppresses or eliminates more proliferative predominant clones, leaving subclones that harbor or acquire mutations that confer resistance to specific chemotherapeutic agents. Less commonly, relapse clones share no genetic alterations with diagnosis clones and probably are a second leukemia in persons with a genetic predisposition.

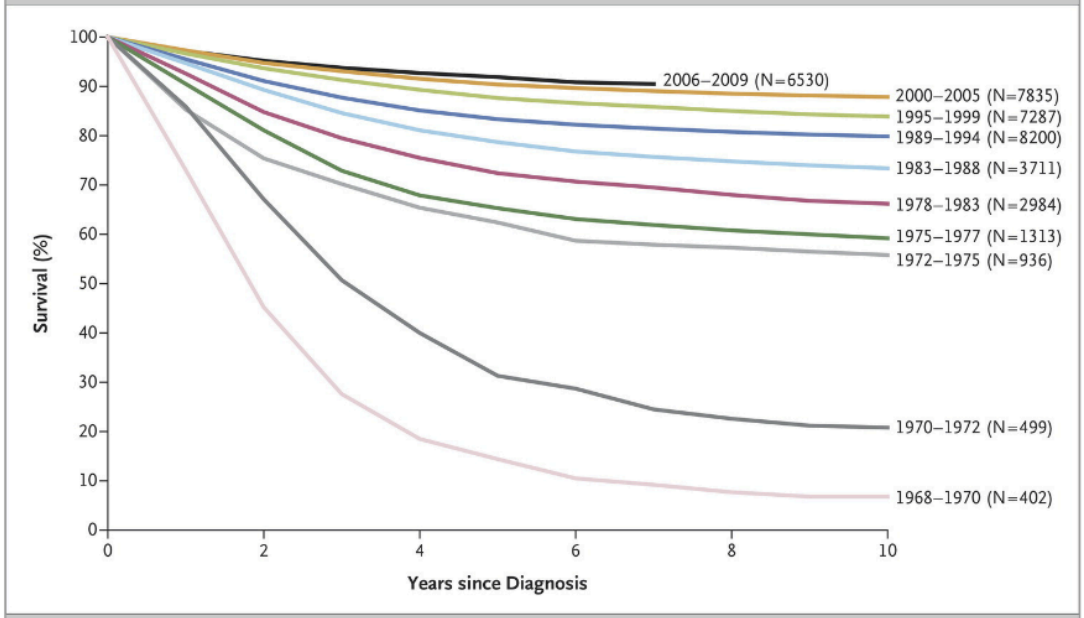


Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Table 1. Important Prognostic Factors in Acute Lymphoblastic Leukemia (ALL) in Children.

Table 1. **Important Prognostic Factors in Acute Lymphoblastic Leukemia (ALL) in Children.***

Variable	Favorable Factor	Adverse Factor	Use in Risk Stratification
Demographic and clinical features			
Age	1 to <10 yr	<1 yr or ≥10 yr	This feature is a part of NCI risk group definition
Sex	Female	Male	No
Race or ethnic group	White, Asian	Black, Native American, Hispanic	No
Initial white-cell count	Lower (<50,000/mm^3)	Higher (≥50,000/mm^3)	Part of NCI risk group definition
Biologic or genetic features of leukemia cells			
Immunophenotype	B-cell lineage	T-cell lineage	Often used to select therapy backbone
Cytogenetic features	*ETV6-RUNX1*, hyperdiploidy, favorable chromosome trisomies	*BCR-ABL1*, *MLL* rearrangements, hypodiploidy	Often used to select treatment intensity, assign the patient to HSCT, or both; some features (e.g., *BCR-ABL1*) can be used to select targeted therapy
Genomic features	*ERG* deletions	*IKZF1* deletions or mutations; Philadelphia chromosome–like ALL with kinase gene alterations	Some research groups use *IKZF1* deletions to assign patients to more intensive therapy; kinase gene mutations may be used to assign patients to targeted therapy, but this is not yet part of routine care
Early response to treatment			
Response to 1 wk of glucocorticoid therapy	Good response to prednisone (<1000 blasts/mm^3)	Poor response to prednisone (≥1000 blasts/mm^3)	Easy to measure and used by many groups; may be supplanted by MRD
Marrow blasts after 1–2 wk of multiagent therapy	M1 marrow (<5% blasts) by day 8 or 15	No M1 marrow (≥5% blasts) by day 8 or 15	Easy to measure and used previously by many groups; now being supplanted by MRD
MRD quantitation during or at end of induction	Reaching low (<0.01%) or undetectable MRD by specific time points	Persistence of MRD ≥0.01% at specific time points; the higher it is, the worse the prognosis	Most important single prognostic factor for contemporary therapy; critical for modern risk stratification
MRD at 3–4 mo	Low (<0.01%), preferably undetectable	Persistence of MRD ≥0.01%	May help select patients for HSCT or new therapies in first remission

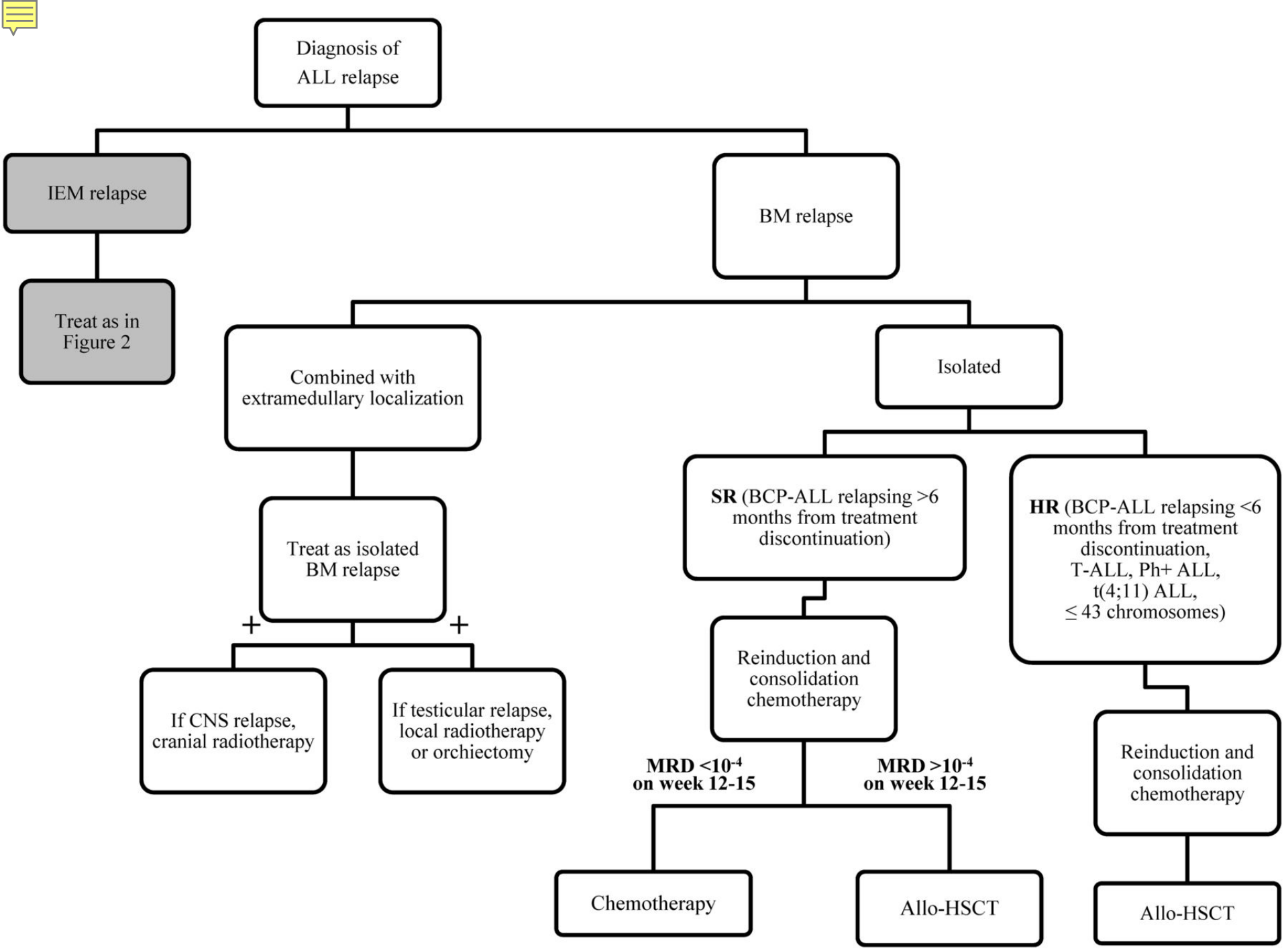
* HSCT denotes hematopoietic stem-cell transplantation, MRD minimal residual disease, and NCI National Cancer Institute.

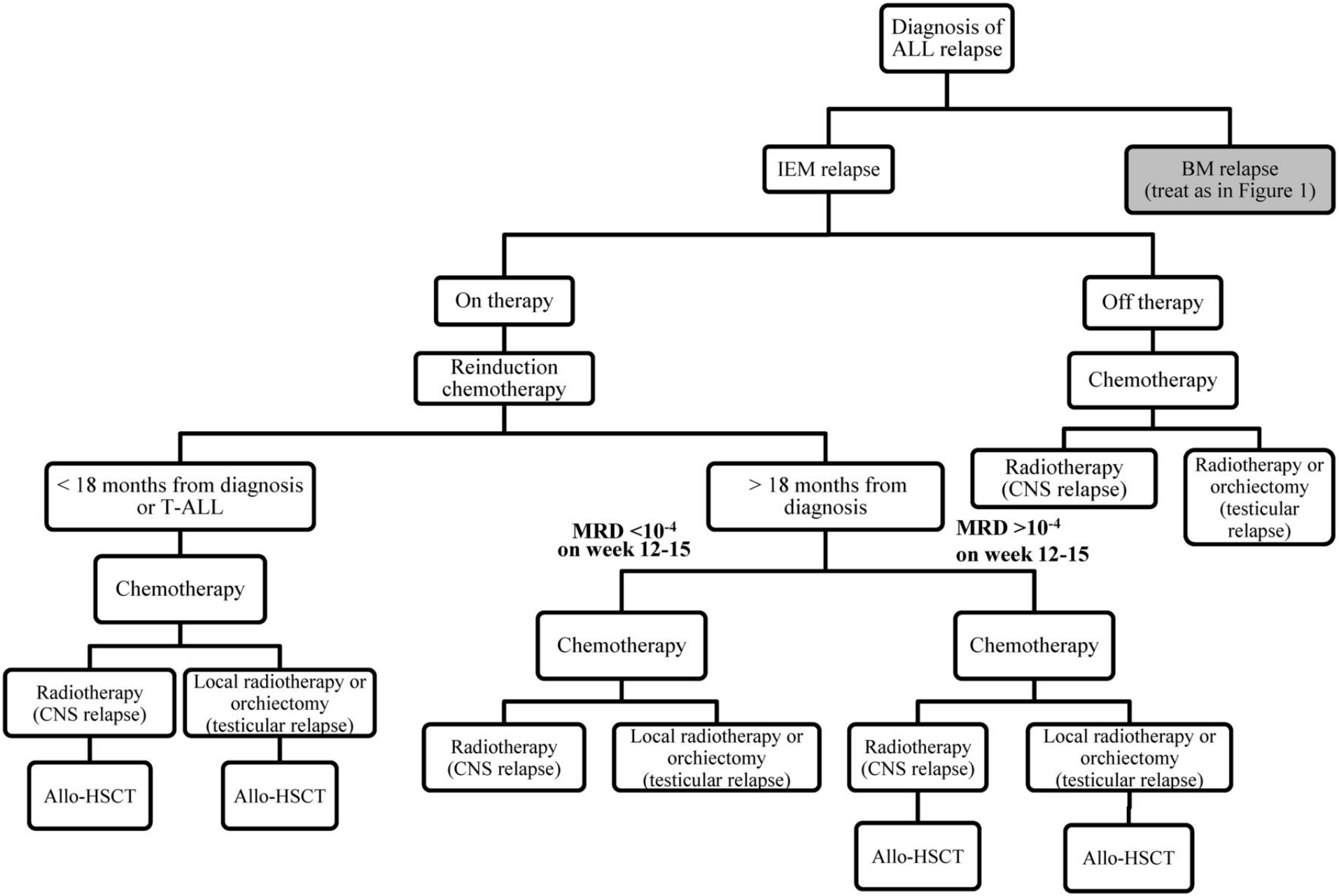
Table 1

BFM classification of relapsed childhood ALL

Group (% of relapsed cases)	Definition of relapse	% of patients reaching CR, %	OS at 5 y with chemotherapy, %	OS at 5 y with HSCT, %
S1 (5%)	1. Late extramedullary relapses	99	60-70	Not used
S2 (55%)	1. Early extramedullary relapses	97	40	60
	2. Very early extramedullary relapses			
	3. Non-T late BM relapses			
	4. Non-T combined early/late relapses			
S3 (15%)	1. Non-T early BM relapses	80-85	< 5	30
S4 (25%)	1. Very early BM relapses	70-75	< 5	25
	2. Very early combined relapses			
	3. T-phenotype bone marrow relapses			

Very early relapse indicates < 18 months from diagnosis; early relapse, > 18 months from diagnosis but < 6 months from treatment discontinuation; and late relapse, > 6 months from treatment discontinuation.


Diagnosis of ALL relapse
IEM relapse
Treat as in Figure 2
BM relapse
Combined with extramedullary localization
Treat as isolated BM relapse
+
+
If CNS relapse, cranial radiotherapy
If testicular relapse, local radiotherapy or orchiectomy
Isolated
SR (BCP-ALL relapsing >6 months from treatment discontinuation)
Reinduction and consolidation chemotherapy
MRD <10-4 on week 12-15
MRD >10-4 on week 12-15
Chemotherapy
Allo-HSCT
HR (BCP-ALL relapsing <6 months from treatment discontinuation, T-ALL, Ph+ ALL, t(4;11) ALL, ≤ 43 chromosomes)
Reinduction and consolidation chemotherapy
Allo-HSCT


Diagnosis of ALL relapse
IEM relapse
BM relapse (treat as in Figure 1)
On therapy
Off therapy
Reinduction chemotherapy
Chemotherapy
< 18 months from diagnosis or T-ALL
> 18 months from diagnosis
Radiotherapy (CNS relapse)
Radiotherapy or orchiectomy (testicular relapse)
MRD <10-4 on week 12-15
MRD >10-4 on week 12-15
Chemotherapy
Chemotherapy
Chemotherapy
Radiotherapy (CNS relapse)
Local radiotherapy or orchiectomy (testicular relapse)
Radiotherapy (CNS relapse)
Local radiotherapy or orchiectomy (testicular relapse)
Allo-HSCT
Allo-HSCT
Allo-HSCT
Allo-HSCT