Precursor Lymphoid Neoplasms

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Neoplastic Hematopathology Update 2017

- I have no disclosures.

Precursor lymphoid neoplasms

- Abnormal proliferations of immature lymphoid cells.
- Biologically and clinically heterogenous but most present as acute leukemia.
- Majority (75%) occur in children, adolescents and young adults.
- Median age at diagnosis = 15 years

The evolving classification

- French-American-British (FAB) Classification (1976)
  - Based on morphologic features of blasts on aspirate smears and cytochemistry
  - Did not include lymphoblastic lymphoma
- Flow cytometric immunophenotyping => Immunological classification of ALL
  - Pro-, Pre-pre-, pre- , mature B-cell ALL
  - Pro- , Pre-, cortical, mature T-cell ALL

2001 WHO Classification

- Divided blastic lymphoid proliferations by lineage:
  - Precursor B-cell Precursor T-cell
- Defined lymphoblastic ***leukemia*** and ***lymphoma*** as different manifestations of the same disease.
- Incorporated clinical features.
- Provided guidelines for the diagnosis of mixed lineage acute leukemia.

2001-2008: Genetic abnormalities in precursor lymphoid neoplasms

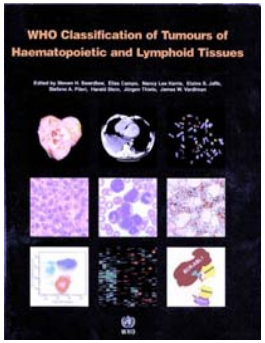
Numerical abnormalities
(additions, deletions, amplifications)

Reciprocal translocations leading to formation of fusion genes and expression of chimeric proteins

Translocations resulting in juxtaposition of a proto-oncogene next to TCR or Ig promoter gene => over-expression of normal or truncated protein

Mutations

2008 WHO Classification



B lymphoblastic leukemia/lymphoma *with recurrent genetic abnormalities*

Hyperdiploidy
Hypodiploidy
t(9;22)(q34;q11.2); *BCR-ABL1*
t(v;11q23); *MLL* rearranged
t(12;21)(p13;q22); *TEL-AML1*
t(1;19)(q23;p13.3); *E2A-PBX1*
t(5;14)(q31;q32); *IL3-IGH*

B lymphoblastic leukemia/lymphoma, *not otherwise specified*

T lymphoblastic leukemia/lymphoma

Case 1

- 26 year old Hispanic woman who presented with worsening fatigue of several months' duration, dyspnea on exertion, and easy bruising.
- CBC
  - WBC 900/uL: Hbn 8.2g/dL; platelets 44,000/uL
  - Differential: Blasts 5%, Neut 42.0%, Lymphs 53%
- Bone marrow examination
  - Hypercellular marrow (95%) with 81% blasts
- Flow cytometry:
  - CD10 (strong), CD19, CD22, CD24, CD34, CD38, CD45 (dim to negative), Tdt, and HLA-DR

Case 1

- FISH Cytogenetics: Negative for *BCR/ABL1, KMT2A (MLL)*
- Molecular: Negative for BCR-ABL1 p210 and p190 fusion products
- Cytogenetics: 47, XX, inv(9)(p13q34.1), +10 [11/23]
- Diagnosis: B- lymphoblastic leukemia, not otherwise specified.
- Treated with modified augmented Berlin-Frankfurt-Munster (BFM) regimen, induction cycle 1

Translocations in precursor B neoplasms

- Common: Reciprocal translocations resulting in chimeric protein expression
  - t(9;22)(q34;q11) => *BCR/ABL1*
  - t(1;19)(q23;p13) => *TCF3-PBX1* (*PBX/ETA)*
  - t(4;11)(q21;q23) => *KMT2A (MLL/AF)*
  - t(12;21)(p13;q22) => *ETV6/RUNX1 (TEL/AML1)*
- Rare: Juxtaposition of a proto-oncogene to Ig promoter => over-expression
  - t(5;14)(q31;q32) => *IL3/IGH*

"Ph-Like B-ALL"

- Gene expression profiling studies identified a group of B-ALL lacking *BCR-ABL1* but with a pattern of gene expression very similar to that seen in ALL with *BCR-ABL1*.
- Relatively common: 15% childhood, 30% adult B-ALL
  - 10% children with standard risk ALL
  - 13% children with high risk ALL
  - 21% adolescents
  - 27% young adults (< 40yrs)
  - 30% adults (> 40 yrs)
- Males > Females
- More frequent in Hispanic and Native American populations
- Associated with a high WBC at presentation, MRD+ at end of induction, and poor outcome

Roberts KG et al. N Engl J Med 2014;371:1005-1015
Jain N et al. Blood 2017;129: 572-581

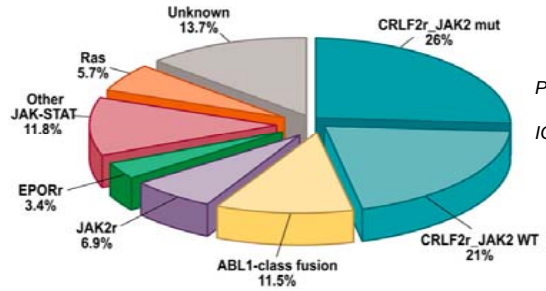
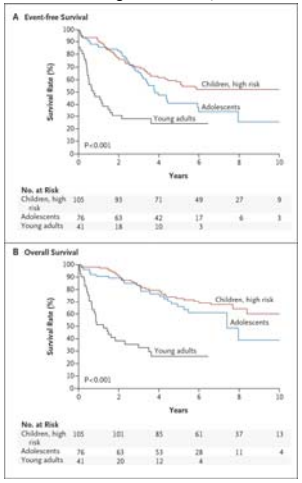


Figure 3. Frequency of subtypes of Ph-like ALL. Combined prevalence of Ph-like ALL subtypes in children, adolescents, and young adults including *CRFL2*-rearranged *JAK2* mutant (CRLF2r_JAK2 mut) and *CRFL2*-rearranged *JAK2* wild-type (CRFL2r_JAK2 WT), ABL1-class rearrangements (*ABL1*, *ABL2*, *CSF1R*, and *PDGFRB*), *JAK2* and *EPOR* rearrangements and other mutations in JAK-STAT signaling (*FLT3*, *IL7R*, *SH2B3*, *JAK1/3*, *TYK2*, *IL2RB*, and *TSLP*), Ras mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*, and *BRAF*), and unknown alterations. Data from Roberts et al.[22] HR, high-risk.

The number of pathways is limited, and all may be amenable to treatment with tyrosine kinase inhibitors.

Kaplan–Meier Estimates of Event-free and Overall Survival among Patients with Philadelphia Chromosome–like Acute Lymphoblastic Leukemia (Ph-like ALL).

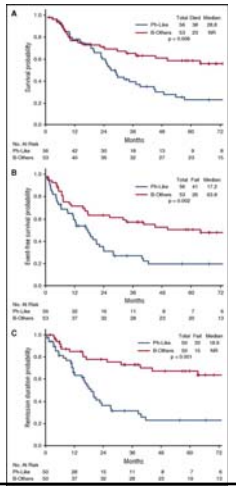
Roberts KG et al. N Engl J Med 2014;371:1005-1015



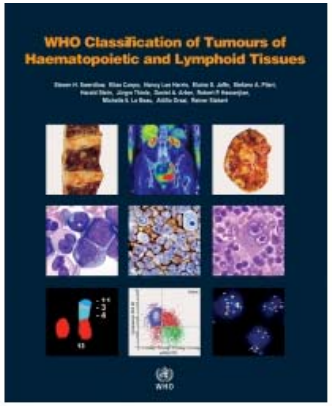
The presence of Ph-like genetic abnormality was an independent predictor of poor prognosis across all ages.

Clinical outcomes of patients with Ph-like ALL and B-other ALL. (A) OS, (B) EFS, and (C) remission duration of Ph-like ALL and B-other ALL.

Nitin Jain et al. Blood 2017;129:572-581



2016 Classification



- B lymphoblastic leukemia/lymphoma, *not otherwise specified*
- B lymphoblastic leukemia/lymphoma with
  - t(9;22)(q34;q11.2); *BCR-ABL1*
  - t(v;11q23); *KMT2A (MLL) rearrang.*
  - t(12;21)(p13;q22); *ETV6-RUNX1*
  - Hyperdiploidy
  - Hypodiploidy
  - t(1;19)(q23;p13.3); *TCF3-PBX1*
  - t(5;14)(q31;q32); *IGH/IL3*
  - ***BCR-ABL1-like (provisional)***
  - ***iAMP21 (provisional)***
- T lymphoblastic leukemia/lymphoma

Kinase Fusions Identified in Ph-like Acute Lymphoblastic Leukemia.

Roberts KG et al. N Engl J Med 2014;371:1005-1015

Table 1. Kinase Fusions Identified in Ph-like Acute Lymphoblastic Leukemia.

Kinase Gene	Tyrosine Kinase Inhibitor	Fusion Partners	Patients	5′ Genes
		number		
ABL1	Dasatinib	6	14	*ETV6,[11] NUP214,[11] RCSD1,[11] RANBP2,[11] SNX2,[19] ZMIZ1[20]*
ABL2	Dasatinib	3	7	*PAG1,* * *RCSD1,* * *ZC3HAV1* *
CSF1R	Dasatinib	1	4	*SSBP2* *
PDGFRB	Dasatinib	4	11	*EBF1,[13-15] SSBP2,* * *TNIP1,* * *ZEB2* *
CRLF2	JAK2 inhibitor	2	30	*IGH,[21] P2RY8[22]*
JAK2	JAK2 inhibitor	10	19	*ATF7IP,* * *BCR,[11] EBF1,* * *ETV6,[23] PAX5,[11] PPFIBP1,* * *SSBP2,[24] STRN3,[11] TERF2,* * *TPR* *
EPOR	JAK2 inhibitor	2	9	*IGH,[11] IGK* *
DGKH	Unknown	1	1	*ZFAND3* *
IL2RB	JAK1 inhibitor, JAK3 inhibitor, or both	1	1	*MYH9* *
NTRK3	Crizotinib	1	1	*ETV6*[25-27]†
PTK2B	FAK inhibitor	2	1	*KDM6A,* * *STAG2* *
TSLP	JAK2 inhibitor	1	1	*IQGAP2* *
TYK2	TYK2 inhibitor	1	1	*MYB* *

* The gene is a previously unreported fusion partner.
† *ETV6–NTRK3* has been reported in multiple cancers, including congenital fibrosarcoma[25,26] and secretory breast carcinoma,[27] but it has not previously been described in acute lymphoblastic leukemia.[26,27]

The majority of patients with Ph-like ALL have genetic alterations that respond to tyrosine kinase inhibitors that are already FDA-approved.

Case 1

- Comprehensive molecular profiling by next generation sequencing: ***NUP214-ABL1* fusion**

- Previously reported primarily in T-LBL (~6-8%)
- *NUP214* (Nucleoporin 214): Located on 9q34.13
  - Nucleocytoplasmic transporter
- *ABL1*- Located on 9q34.12
  - Tyrosine kinase
- *NUP214-ABL1*: Results from amplification with formation of episomal elements

2008 Classification	**2016 Classification**
B Lymphoblastic leukemia/lymphoma, *not otherwise specified*	B lymphoblastic leukemia/lymphoma, *not otherwise specified*
B lymphoblastic leukemia/lymphoma with	B lymphoblastic leukemia/lymphoma with
t(9;22)(q34;q11.2); *BCR-ABL1*	t(9;22)(q34;q11.2); *BCR-ABL1*
t(v;11q23); *MLL* ***rearranged***	t(v;11q23); *KMT2A (MLL) rearrang.*
t(12;21)(p13;q22); *TEL-AML1*	t(12;21)(p13;q22); *ETV6-RUNX1*
Hyperdiploidy	Hyperdiploidy
Hypodiploidy	Hypodiploidy
t(1;19)(q23;p13.3); *E2A-PBX1*	t(1;19)(q23;p13.3); *TCF3-PBX1*
t(5;14)(q31;q32); *IL3-IGH*	t(5;14)(q31;q32); *IGH/IL3*
	BCR-ABL1-like (provisional)
	iAMP21 (provisional)
T lymphoblastic leukemia/lymphoma	T lymphoblastic leukemia/lymphoma

Case 1 Follow-up

- Day 28 marrow showed persistent blasts (25%)
- Treated with induction cycle 2 and **dasatinib**
- Persistent blasts (3%)
- Allogeneic stem cell transplantation
- Fully engrafted but minimal residual disease + post-HCT
- Treated with dasatinib maintenance

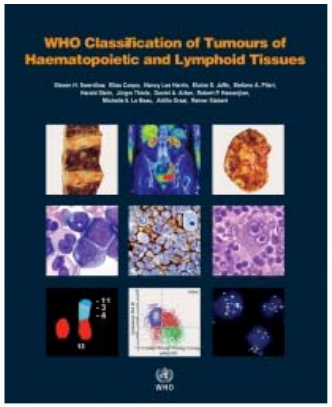
Case 2

- 23 year old man who presented with shortness of breath and was found to have a mediastinal mass and a large pleural effusion.
- CT-guided needle core biopsies: T lymphoblastic lymphoma
  - IHC: CD2, CD3, CD5, CD7, CD10, CD99, TdT
- Right pleural effusion: T lymphoblastic lymphoma
  - Flow Cytometry: CD1a, CD2, cytoplasmic CD3, CD4, CD5, CD7, CD8, CD10, CD34 (weak/partial), CD38, CD45, TdT
- Bone marrow: Negative

Case 2

- On admission:
  - Thoracentesis=> 1900 cc of bloody fluid.
  - Cytology: T lymphoblastic lymphoma
  - Flow cytometry: 79% blasts expressing CD1a, CD2, cytoplasmic and partial surface CD3, CD4, CD5, CD7, CD8, CD38, HLA-DR, Tdt (79% of cells)
- Treated on Phase III trial with bortezomib on a modified augmented BFM backbone

2016 Classification



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  - t(5;14)(q31;q32); *IGH/IL3*
  - ***BCR-ABL1-like***
  - ***iAMP21***
- T lymphoblastic leukemia/lymphoma

Genetic abnormalities in precursor T neoplasms

- 50% of patients have normal karyotype at diagnosis
- Mutations are present in 60% of cases
- Translocations are present in 30% of cases
- Deletions are frequent if detected by FISH
  - Del(9)(p21) resulting in loss of the tumor suppressor gene *CDKN2A* in 70% => loss of G1 control in the cell cycle

Translocations in precursor T neoplasms

- Common: Juxtaposition of a proto-oncogene to TCR promoter => over-expression
  - t(10;14)(q24;q11) => *HOX11*
  - t(1;14)(p32-34;q11) => *TAL1*
  - t(7;9)(q34;q34.3) => *NOTCH1*
- Rare: Reciprocal translocations resulting in chimeric protein expression
  - t(11;19)(q23;p13.3) => MLL/ENL
  - ABL1 rearrangements (*NUP214/ABL1*)

Mutations in precursor T neoplasms

	Frequency
Activating mutations *NOTCH1*	**58%**
Missense mutations *FBXW7*	**30%**
PHF6	**20%**
OTHERS….	

Spinella et al. Oncotarget 2016: 7:

Case 2: Comprehensive mutational profiling by NGS

- Mutations:

Gene	Nucleotide	Amino Acid	Allele Frequency (%)	COSMIC ID
CCND3	c.753_754ins12	p.R252*	24.87	N/A
FBXW7	c.2065C>T	p.R689W	34.56	27083
NOTCH1	c.4778T>C	p.L1593P	57.91	13042
PHF6	c.820C>T	p.R274*	75.43	144567

Case 2

- ***NOTCH1* c4778T>C; p.L1593P**
  - Encodes NOTCH1 transmembrane protein
  - Functions in multiple developmental processes, cell-cell interactions, receptor
  - Regulates T-cell development, with a direct downstream target of *MYC*
  - Mutations present ~60% of T lymphoblastic leukemia/lymphoma
  - L1593P mutation is in the HD domain and is an activating mutation.
- ***FBXW7* c.2065C>T; p.R689W**
  - Tumor suppressor gene encoding ubiquitin E3 ligase which targets for degradation several proto-oncogenes including NOTCH1
  - Negative regulator of NOTCH1
  - Missense mutation results loss of function => decreased proteosomal degradation of NOTCH1= > increased half-life of NOTCH1 protein
  - R689W previously described in in T-ALL

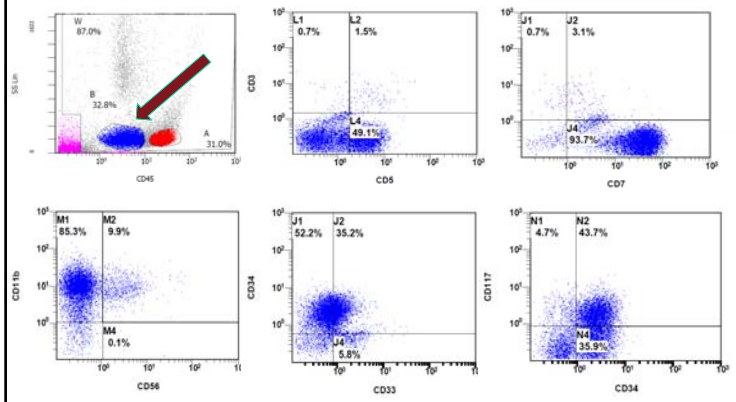
LY3039478 is a NOTCH1 inhibitor under study for relapsed/refractory disease with *NOTCH1* or *FBXW7* mutations.

Case 2

- ***PHF6* c.820C>T; p.R274***
  - Encodes transcriptional co-repressor
  - Mutations present in ~20% T lymphoblastic leukemia/lymphoma
  - R274* occurs in the ePHD2 domain and is a common hotspot
  - Nonsense alteration => loss of function
- ***CCND3* c.753_754 ins12; p.R252***
  - Encodes a protein that regulates CDK kinases in the cell cycle
    - Normal protein is critical for lymphocyte development, cell cycle control, and is a downstream target of activated **NOTCH-1** in T lymphoblastic leukemia/lymphoma
  - In-frame 12 base pair insertion => nonsense alteration at codon 252=> loss of function of the gene.
  - Not previously reported

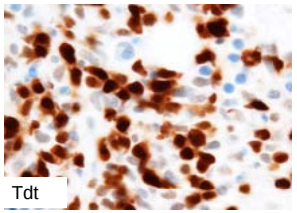
Case 3

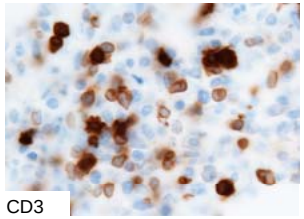
- 66 year old woman with leukopenia and extensive lymphadenopathy.
- CBC:
  - Hbn 13.8 g/dL with normal RBC indices
  - Platelets 152,000/uL
  - WBC = 1,440/uL with 6% neutrophils, 3% bands, 69% lymphocytes, 4% monocytes, 18% blasts
- Bone Marrow:
  - Hypercellular marrow (95%) with 80% blasts
  - Negative for myeloperoxidase, Sudan black B and dual esterase by cytochemistry



Negative for CD2, CD4, CD8, CD11c, CD13, CD14, CD15, CD16, HLA-DR , MPO

Case 3


Tdt


CD3

Case 3

- Del (7)(q22q34) in 1/20 metaphases
- FISH: Del 7q31 in 15% nuclei
- Molecular studies for TCR gamma chain gene rearrangements demonstrated a clonal rearrangement.

Diagnosis?

Early T-cell precursor lymphoblastic leukemia

- New subtype first identified in series of childhood T- ALL
  - Coustan-Smith et al. Lancet Oncol 2009;10:147-56
- ~12% pediatric, 5-10% adults T-ALL
- Associated with poor clinical outcome
  - 10 year OS and EFS ~20%
- Increased genomic instability
  - Complex karyotypes
  - More genomic gains and losses
- Distinctive phenotype

Early T-cell precursor lymphoblastic leukemia

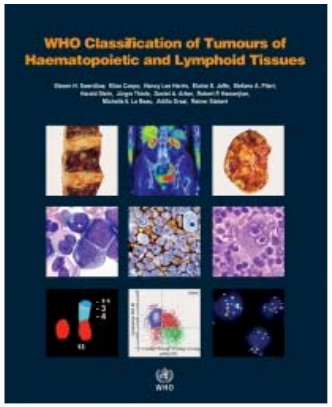
Coustan-Smith et al. Lancet Oncol 2009;10:147-56

- CD3+ (cyto >> surface)
- CD5 **weak**, and <75% of blasts
- CD7+
- ≥1 Myeloid or stem cell markers in ≥25% of blasts
  - CD11b, CD13, CD33, CD34, CD65, CD117, HLA-DR
- CD1a -
- CD8 –
- MPO –
- CD2, CD4, Tdt: + / -

Early T-cell precursor lymphoblastic leukemia

- Distinctive gene expression profile similar to normal early T-cell precursors
  - Recent immigrants from bone marrow to thymus
  - Retain multi-lineage differentiation potential
- Activating mutations in cytokine receptor and *RAS* signaling pathways
  - *NRAS, KRAS, BRAF, FLT3, IL7R, JAK3, JAK1, SH2B3*
- Inactivating mutations of genes encoding hematopoietic development transcription factors
  - *GATA3, ETV6, RUNX1, IKZF1, EP300*
- Mutations in histone modifying genes
  - EZ*H2, EP300*

Zhang et al. Nature 2012; 481:157-163



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  - t(12;21)(p13;q22); *ETV6-RUNX1*
  - Hyperdiploidy
  - Hypodiploidy
  - t(1;19)(q23;p13.3); *TCF3-PBX1*
  - t(5;14)(q31;q32); *IGH/IL3*
  - ***BCR-ABL1-like (provisional)***
  - ***iAMP21 (provisional)***
- B lymphoblastic leukemia/lymphoma, *not otherwise specified*
- T lymphoblastic leukemia/lymphoma
- ***Early T-cell precursor lymphoblastic leukemia***
- ***NK-lymphoblastic leukemia/lymphoma (provisional)***

Initial Diagnostic Workup of Acute Leukemia

Guideline From the College of American Pathologists and the American Society of Hematology

Daniel A. Arber, MD; Michael J. Borowitz, MD, PhD; Melissa Cessna, MD; Joan Etzell, MD; Kathryn Foucar, MD; Robert P. Hasserjian, MD; J. Douglas Rizzo, MD; Karl Theil, MD; Sa A. Wang, MD; Anthony T. Smith, MLS; R. Bryan Rumble, MSc; Nicole E. Thomas, MPH, CT(ASCP)^{cm}; James W. Vardiman, MD

• *Context.*—A complete diagnosis of acute leukemia requires knowledge of clinical information combined with morphologic evaluation, immunophenotyping and karyotype analysis, and often, molecular genetic testing. Although many aspects of the workup for acute leukemia are well accepted, few guidelines have addressed the different aspects of the diagnostic evaluation of samples from patients suspected to have acute leukemia.

Objective.—To develop a guideline for treating physicians and pathologists involved in the diagnostic and prognostic evaluation of new acute leukemia samples, including acute lymphoblastic leukemia, acute myeloid leukemia, and acute leukemias of ambiguous lineage.

Design.—The College of American Pathologists and the American Society of Hematology convened a panel of experts in hematology and hematopathology to develop recommendations. A systematic evidence review was conducted to address 6 key questions. Recommendations were derived from strength of evidence, feedback received during the public comment period, and expert panel consensus.

Results.—Twenty-seven guideline statements were established, which ranged from recommendations on what clinical and laboratory information should be available as part of the diagnostic and prognostic evaluation of acute leukemia samples to what types of testing should be performed routinely, with recommendations on where such testing should be performed and how the results should be reported.

Conclusions.—The guideline provides a framework for the multiple steps, including laboratory testing, in the evaluation of acute leukemia samples. Some aspects of the guideline, especially molecular genetic testing in acute leukemia, are rapidly changing with new supportive literature, which will require on-going updates for the guideline to remain relevant.

(*Arch Pathol Lab Med.* 2017;141:1342–1393; doi: 10.5858/arpa.2016-0504-CP)

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From the Department of Pathology, University of Chicago, Chicago, Illinois (Dr Arber); the Department of Pathology, Johns

October 2017 Archives of Pathology and Laboratory Medicine

CAP/ASH Guideline: Key Question #1

Arch Pathol Lab Med 2017;141:1342-1393

- What clinical and laboratory information should be available during the initial diagnostic evaluation of a patient with acute leukemia?
  - Age, sex, ethnicity
  - History of any hematological disorder, prior malignancy, or other predisposing conditions, including family history.
  - Exposure to cytotoxic therapy, radiation, immunotherapy, toxins, etc.
  - Confounding factors: recent growth therapy, transfusions, etc.
  - Relevant physical examination and imaging findings.

CAP/ASH Guideline: Key Question #2

Arch Pathol Lab Med 2017;141:1342-1393

- What specimens and sample types should be evaluated during the initial work-up?
  - CBC with differential, peripheral blood smear
  - Bone marrow aspirate for
    - Morphological examination
    - Cytogenetics/FISH
    - Comprehensive flow cytometry immunophenotyping
    - Molecular testing
  - Core biopsy, touch imprints, clot sections if obtained.
  - If receiving intra-thecal therapy, cerebrospinal fluid for cell count and differential, and morphological examination by pathologist.
  - If extramedullary disease without marrow or blood involvement, tissue biopsy with sufficient tissue to perform the above.

CAP/ASH Guideline: Key Question #3

Arch Pathol Lab Med 2017;141:1342-1393

- At the time of diagnosis, what tests are *required* for *all* patients?

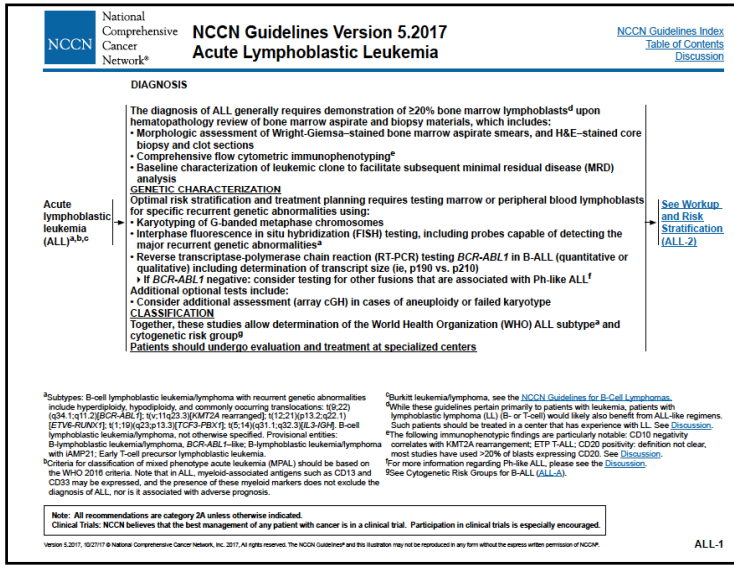
- Everything on the previous slide plus
  - Cytochemical studies if needed for lineage assignment
  - Flow cytometric studies sufficiently comprehensive to allow subsequent detection of minimal residual disease (MRD)

CAP/ASH Guideline: Key Question #4

Arch Pathol Lab Med 2017;141:1342-1393

- Which tests should be performed on only *a subset* of patients, including in response to results from initial tests and morphology?

- Pediatric patients with B-LBL
  - t(12;21) *ETV6-RUNX1*
  - t(9;22) *BCR-ABL1*
  - *KMT2A (MLL)* rearrangement
  - iAMP21
  - Trisomy 4, trisomy 10
- Adults with B-LBL
  - t(9;22) *BCR-ABL1*
  - *KMT2A (MLL)* rearrangement
- Additional mutational analysis including
  - B-LBL: *PAX5, JAK1, JAK2, IKZF1*
  - T-LBL: *NOTCH1, FBXW7*



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2017
Acute Lymphoblastic Leukemia

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSIS

Acute lymphoblastic leukemia (ALL)[a,b,c] →

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts[d] upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:
- Morphologic assessment of Wright-Giemsa–stained bone marrow aspirate smears, and H&E–stained core biopsy and clot sections
- Comprehensive flow cytometric immunophenotyping[e]
- Baseline characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysis

GENETIC CHARACTERIZATION

Optimal risk stratification and treatment planning requires testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:
- Karyotyping of G-banded metaphase chromosomes
- Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities[a]
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing *BCR-ABL1* in B-ALL (quantitative or qualitative) including determination of transcript size (ie, p190 vs. p210)
  - If *BCR-ABL1* negative: consider testing for other fusions that are associated with Ph-like ALL[f]

Additional optional tests include:
- Consider additional assessment (array cGH) in cases of aneuploidy or failed karyotype

CLASSIFICATION

Together, these studies allow determination of the World Health Organization (WHO) ALL subtype[a] and cytogenetic risk group[g]

Patients should undergo evaluation and treatment at specialized centers

→ See Workup and Risk Stratification (ALL-2)

[a]Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities include hyperdiploidy, hypodiploidy, and commonly occurring translocations: t(9;22) (q34.1;q11.2)[*BCR-ABL1*]; t(v;11q23.3)[*KMT2A* rearranged]; t(12;21)(p13.2;q22.1) [*ETV6-RUNX1*]; t(1;19)(q23;p13.3)[*TCF3-PBX1*]; t(5;14)(q31.1;q32.3)[*IL3-IGH*]. B-cell lymphoblastic leukemia/lymphoma, not otherwise specified. Provisional entities: B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*–like; B-lymphoblastic leukemia/lymphoma with iAMP21; Early T-cell precursor lymphoblastic leukemia.

[b]Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2016 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis.

[c]Burkitt leukemia/lymphoma, see the NCCN Guidelines for B-Cell Lymphomas.

[d]While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) would likely also benefit from ALL-like regimens. Such patients should be treated in a center that has experience with LL. See Discussion.

[e]The following immunophenotypic findings are particularly notable: CD10 negativity correlates with KMT2A rearrangement; ETP T-ALL: CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20. See Discussion.

[f]For more information regarding Ph-like ALL, please see the Discussion.

[g]See Cytogenetic Risk Groups for B-ALL (ALL-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ALL-1

CAP/ASH Guideline: Key Question #5

Arch Pathol Lab Med 2017;141:1342-1393

- Where should laboratory testing be performed?

- Laboratories in compliance with regulatory and/or accreditation requirements

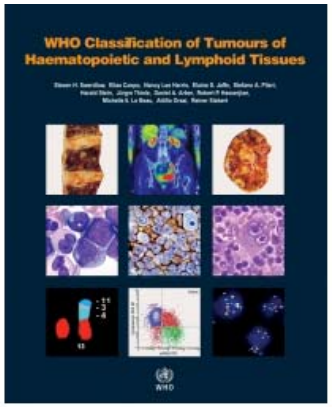
For any given assay, find the lab that:

- **Has expertise in the specific disorder.**
- **Understands the technology and uses it appropriately.**
- **Provides clinically useful results.**
- **Is cost-effective.**

CAP/ASH Guideline: Key Question #6

Arch Pathol Lab Med 2017;141:1342-1393

- How should test results and the diagnosis be correlated and reported?
  - Initial report: all laboratory, morphological, immunophenotypic, cytochemical data on which diagnosis is based, AND a list of any tests pending at the time of initial signout.
  - Results of pending tests for classification, management, prognosis, and disease monitory should be added to the pathology report as these become available.
  - ***Diagnosis and classification using the current WHO terminology.***



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