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Brief Overview about Diagnostic Modalities of Philadelphia-Like Acute Lymphoblastic Leukemia

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Abstract: morphologically and immunophenotypically resemble B-lineage and T-lineage precursor cells. These neoplasms may present predominantly as a leukemic process, with extensive involvement of the bone marrow and peripheral blood or may be limited to tissue infiltration, with absent or only limited (less than 25%) bone marrow involvement. Philadelphia-like (Ph-like) B-cell ALL is a high-risk subtype of B-cell ALL that shares a gene expression profile with Ph-positive ALL, but without a BCR::ABL1 fusion. A subgroup of these patients have fusions or rearrangements involving genes such as ABL1, ABL2, PDGFRβ, JAK2, and EPOR, some of which are potentially sensitive to tyrosine kinase inhibitors (TKIs). Prompt identification of these genetic aberrations are important for prognostication and treatment decisions. The presence of Ph-like defect in patients with ALL is a new marker of high risk subtype associated with poor outcome and frequent relapse. This review summarizes recent modalities of diagnosis of Ph-like ALL. **Conclusion:** The diagnosis of Ph-like ALL is challenging, however it carries predictive and prognostic implications that help to better define the patient's risk and to personalize the treatment approach based on the presence of targetable mutations. Gene expression profiling (GEP) is cumbersome to use in daily clinical practice. Other methods, relying on reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or combination of immune-phenotyping and DNA-sequencing have been used. Identifying sensitive and specific algorithms will be very helpful to identify and treat Ph-like ALL in daily clinical practice

Keywords: *Diagnostic Modalities, Philadelphia-Like Acute Lymphoblastic Leukemia*

Introduction

While 80% of ALL occurs in children, it represents a devastating disease when it occurs in adultsThe American Cancer Society's estimates for acute lymphocytic leukemia (ALL) in the United States for 2024 (including both children and adults) are: About 6,550 new cases of ALL (3,590 in males and 2,960 in females).About 1,330 deaths from ALL (640 in males and 690 in females) (American Cancer Society) ***(1).*** The incidence of ALL follows a bimodal distribution, with the first peak occurring in childhood and a second peak occurring around the age of 50. While dose intensification strategies have led to a significant improvement in outcomes for

pediatric patients, prognosis for the elderly remains very poor. Despite a high rate of response to induction chemotherapy, only 30–40% of adult patients with ALL will achieve long-term remission ***(2).***

Most ALL cases occur in children, with an incidence of 3 to 4/100,000 in patients from 0 to 14 years of age and ~1/100,000 in patients older than 15 years, in the United States. In children, ALLs represent 75% of all acute leukemias (which in turn represent 34% of all cancers in this age group), with a peak incidence at 2 to 5 years of age. This percentage is much lower in adults, in whom acute myeloid leukemias (AMLs) and chronic lymphocytic leukemias are more common.3,4 There is a slight male predominance in all age groups and a significant excess incidence among white children ***(3).***

There are several factors responsible for the poor outcome of ALL in adults, including comorbidities, poor performance status, poor compliance, and higher frequency of high-risk genomic subgroup ***(4).***

In one study, 264 of 1725 pre B-cell ALL cases (15.3%) among all age groups were labeled as Ph-like ALL. This same study showed that the prevalence of Ph-like ALL increases with age (from 10% among children to 27% among young adults). In another report Ph-like ALL accounted for 27.9% of young adults (age 21 to 39 years), 20.4% of adults (age 40 to 59 years), and 24.0% of older adults (age 60 to 86 years). The MD Anderson Cancer Center group reported that 49/148 (33.1%) adult patients who underwent gene expression profiling of leukemic cells had Ph-like ALL. On the other hand, a large European report showed that the incidence of Ph-like ALL was only 15% of pre B ALL cases. These differences are probably due to difference in the ethnicity of the patients and the diagnostic methods used by different groups. ***(10).***

The presence of Ph-like ALL in patients with ALL is a new marker of high risk subtype associated with poor outcome and frequent relapse. Across 15 different studies from different geographic regions that included 11,040 ALL patients with 1,546 Ph-like ALL, the pooled prevalence of Ph-like ALL of approximately 15%, which is approximately 2- 3 times more common comparable to the previously reported prevalence of Ph+ ALL with 6.3 %. The prevalence of Ph-like ALL was higher among adolescents (11-20 years) and young adults (21-39 years) with the lower prevalence observed among children and older adults, which is different from Ph+ ALL that is increasingly more prevalent with older age, with the prevalence less than 10% in age ≤ 20 years and more than 40% in age ≥ 40 years. *CRLF2* gene alterations were the most common genetic abnormalities among patients with Ph like ALL. IKZF1 gene deletion is a common co-genetic abnormality that was seen in almost 60% of these patients ***(4).***

Analysis also confirmed the similar aggressive nature of Ph-like ALL and Ph+ ALL as the odds of 5-year Over All Survival (OS), Disease Free Survival (DFS) and Event Free Survuval (EFS) were not significantly different between the two groups and were worse for Ph-like ALL compared with B-other ALL. Since several targeted therapies are currently under investigation for treatment of Ph-like ALL, the prognosis and survival outcome for these patients may improve in the future ***(4).***

Genetic characterization

In 1999 acute myeloid leukemia (AML) and ALL were shown to have a distinguished gene expression profile. In 2002 different gene expression profiles in ALL were linked to certain cytogenetic abnormalities that have impact on prognosis. In 2009, two papers described a new subtype of B cell ALL characterized by poor outcomes and by mutations, rearrangements, and copy number alterations involving cytokine receptor or kinase genes other than the BCR-ABL fusion, the investigators from the Children's Oncology Group (COG) and St. Jude Children's Research Hospital (SJCRH) called this subgroup " Ph – like ALL" while the Dutch group called it BCR-ABL1–like ALL. Later on the gene expression profile of this subgroup was shown to be similar to that of Ph-positive ALL ***(9).***

The COG/SJCRH group defined the Ph-like signature based on the prediction analysis of microarrays (PAM) classifier which consists of 255 gene probe sets. Using this method the investigators also showed frequent deletions of IKZF1 in this subgroup. However the Dutch group used a method that relies on hierarchical

clustering (HC) of 110 gene probes to classify pediatric ALL subtypes (high-hyperdiploidy, MLLrearranged, ETV6-RUNX1, TCF3, BCR-ABL, etc.). These two gene expression profiling (GEP) methods overlap by nine probe sets, and this explains the different definition and incidence of Ph-like/BCR-ABL1–like ALL between the two groups. The majority of cases are concordant, however some cases are discordantly defined as Ph-like by COG/SJCRH and BCR-ABL1–like by the Dutch group ***(10).***

Recently genome-wide association studies have also identified germline genetic variants of GATA3 (rs3824662) that confer susceptibility to developing Ph-like ALL, especially among older children and adults of Hispanic ancestry. Inherited polymorphisms of ARID5B, IKZF1, CEBPE, PIP4K2A and CDKN2A/CDKN2B genes have also been associated with the Ph-like subtype. Some of these variants have been shown to influence treatment outcomes; for example, single nucleotide polymorphisms in GATA3 have been associated with higher risk of relapse ***(11).***

In a study done by **Naglaa and her colleagues) ,** was significantly higher in Egyptian B-ALL pediatric patients compared to healthy subjects. CRLF2 overexpression was not an independent adverse prognostic parameter in pediatric B-ALL, but was associated with some bad prognostic parameters (high TLC, increased blast count in blood, intermediate risk**)(12).** CRLF2 encodes cytokine receptor-like factor 2 monomers, which in combination with IL7R-alpha subunit, form a heterodimeric receptor for thymic stromal lympho-poetin (TLSP) ***(38).***CRLF2, also known as TSLPR, encodes for a receptor protein that participates in activating STAT, possibly through JAK pathways. These pathways are important in immune system regulation**(39).**

In the landmark study led by **Roberts and his colleagues. a** cohort of 1725 B-ALL patients underwent microarray gene expression profiling, on the basis of which 154 patients were classified as Ph-like ALL. Detailed genomic profiling using next-generation sequencing technologies in these 154 Ph-like ALL patients unraveled the genomic landscape of Ph-like ALL across pediatric, adolescent and young adult age groups**(13)**. Despite its molecular heterogeneity, the unifying hallmark of Ph-like ALL is characterized by the diverse spectrum of genetic alterations activating tyrosine kinase and cytokine receptor genes, and frequent IKZF1 alterations ***(14).***

Philadelphia-like (Ph-like) B-cell ALL is a high-risk subtype of B-cell ALL that shares a gene expression profile with Ph-positive ALL, but without a *BCR::ABL1* fusion. A subgroup of these patients have fusions or rearrangements involving genes such as *ABL1*, *ABL2*, *PDGFRβ*, *JAK2*, and *EPOR*, some of which are potentially sensitive to tyrosine kinase inhibitors (TKIs). Prompt identification of these genetic aberrations are important for prognostication and treatment decisions. **(5)**

Philadelphia positive (Ph+) chromosome is a genetic translocation between chromosome 9 and 22 that causes the production of BCR-ABL1 fusion gene. This aberrant gene activates tyrosine kinase, leading to the increase in white blood cell proliferation. Ph+ chromosome is considered one of the worst prognostic factors when treated with chemotherapy alone although the availability of the combination therapy of tyrosine kinase inhibitors and intensive chemotherapy has drastically improved the outcome of these patients ***(6).***

den Boer and his colleagues reported a new genetic subtype of ALL called Philadelphia (Ph)-like or BCR-ABL1-like ALL that has disease phenotypes similar to Ph+ ALL. It is still unclear how common this genetic subtype of ALL is as the reported prevalence varied considerably across the studies**(7).** Studies have also suggested that the prognostic role for Ph-like ALL associated with elevated minimal residual disease at the end of induction therapy, high rate of treatment failure, and poor overall survival outcome similar to Ph+ chromosome ***(8).***

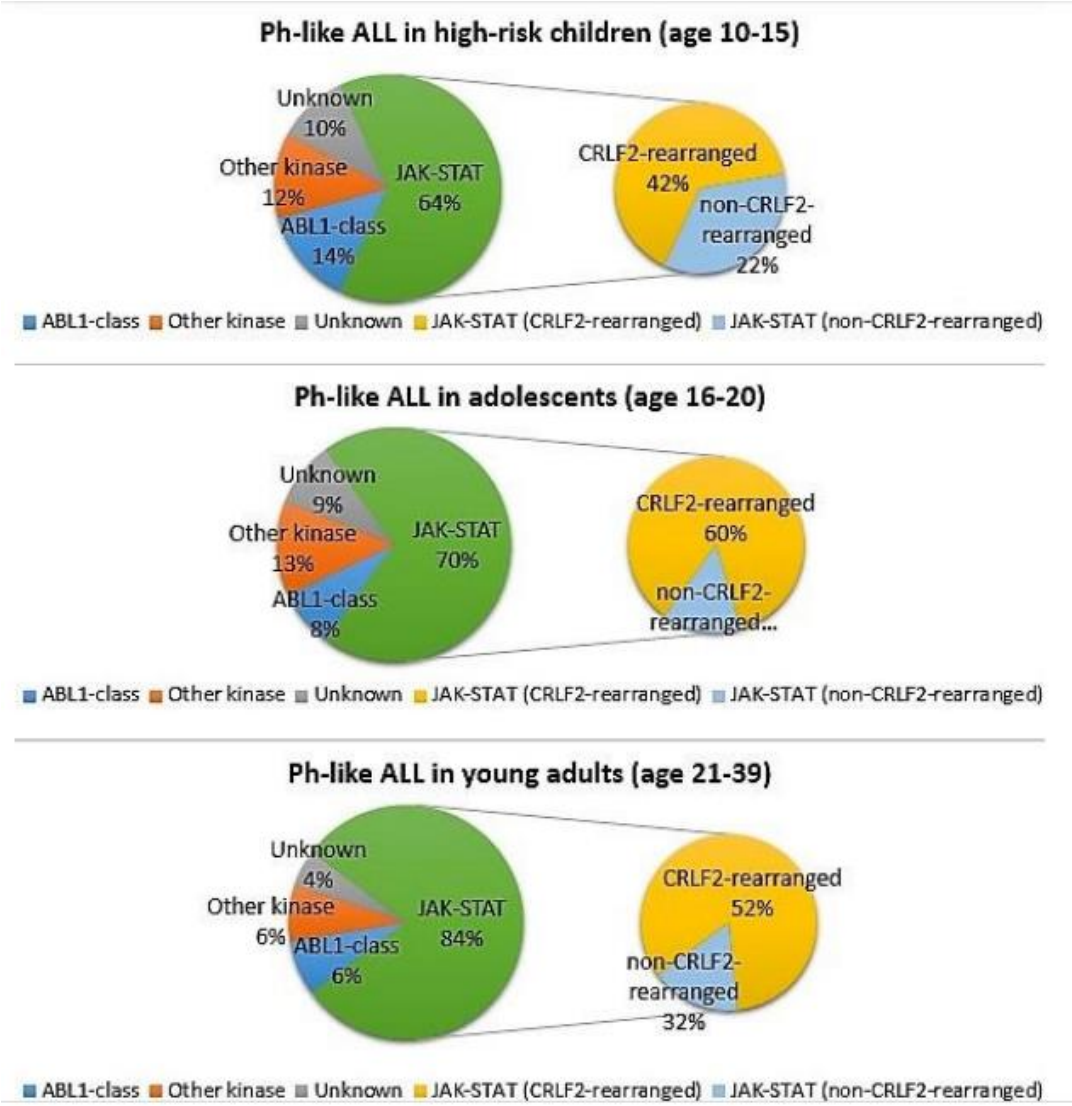

Figure 1: Genomic breakdown of Ph-like ALL by age group. Based on **Roberts et al. (13)** study supplementary data – the largest cohort of Ph-like ALL patients studied ***(14).***

Diagnosis of PH like ALL

The diagnosis of Ph-like ALL is challenging, however it carries predictive and prognostic implications that help to better define the patient's risk and to personalize the treatment approach based on the presence of targetable mutations. Gene expression profiling (GEP) is cumbersome to use in daily clinical practice. Other methods, relying on reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or combination of immune-phenotyping and DNA-sequencing have been used. Identifying sensitive and specific algorithms will be very helpful to identify and treat Ph-like ALL in daily clinical practice. As Ph-like ALL is only found in patients with B cell-ALL lacking translocation of BCR-ABL, ETV6-RUNX1, TCF3-PBX1, or KMT2A (MLL), Herold and his colleagues developed a flow chart to help identifying Ph-like ALL based on these facts ***(34).***

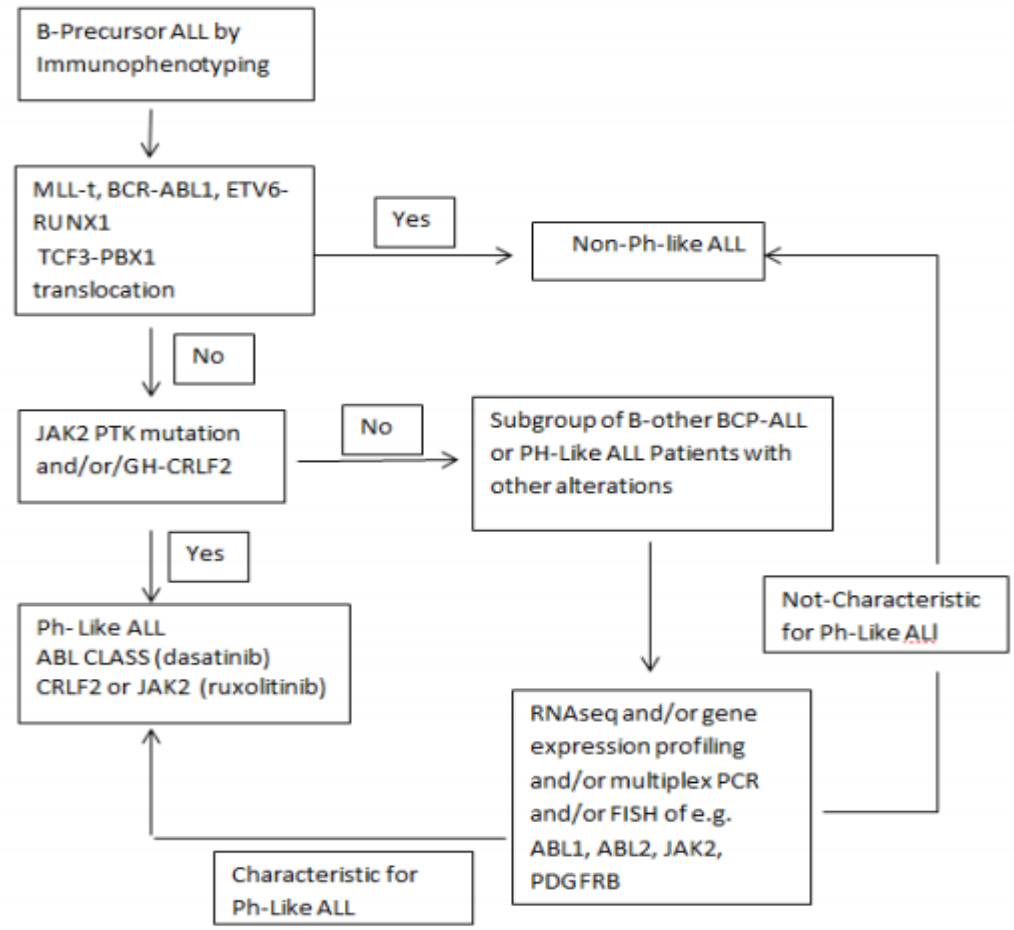

Figure 2: Algorithm for the identification of Ph-like ALL according to Herold et al.(34) PTK, protein tyrosine kinase; RNAseq, RNA sequencing; PCR, polymerase chain reaction; FISH, fluorescence in situ hybridization ***(10).***

It was developed a different diagnostic algorithm based on:

1) Analysis of cytokine receptor like factor 2 CRLF2 expression,
2) FISH targeting ABL and Janus Activated Kinase (JAK) pathway activating fusions involving the genes ABL1, ABL2, CSF1R, PDGFRB and JAK,
3) Fusion specific RT-PCR for the identification of the respective ABL and JAK fusion partner. Another method used by St. Jude uses a 15 gene classifier that could be analyzed on Low Density Microarray (LDA) cards and can identify Ph-like ALL with targetable mutations that may respond to tyrosine kinase–therapy ***(10).***

Ideally having a quick, user friendly, sensitive and specific diagnostic test or approach (e.g like PCR or FISH in Ph-positive ALL), will help standardize the diagnostic approach and thus accurately identifies these patients to enroll them on clinical trials to better define this group and to identify the best therapeutic approach. Eventually, like it is suggested by some investigators, ALL can be broadly divided into 3 categories with clearly defined prognosis and therapeutic modality: Ph-positive, Ph-like and other B ALL ***(15)***

In summary, using delicate genomic methods the Ph-like ALL can be subdivided into different subgroups. Currently at least 7 subgroups have been described depending on the altered pathway: ***(15)***

1) Patients with CRLF2 rearrangements (49.7%);
2) ABL fusions (ABL1, ABL2, CSF1R, PDGFRB) (12.6%);

3) JAK2 (7.4%) or EPOR (3.9%) rearrangements;
4) Genetic alterations of IL7R, FLT3, TYK2, SH2B3, IL2RB, JAK1, JAK3 and other JAK–STAT" (12.6%);
5) Ras mutations (4.3%);
6) Uncommon fusions (DGKH, NTRK3);
7) Others with no kinase activating alterations (4.8%).

(15).

Cytogenetics and fluorescence in situ hybridization

Conventional cytogenetics analysis and fluorescence in situ hybridization (FISH) studies are routinely performed in the diagnostic evaluation of patients with newly diagnosed ALL; results are usually available in 7 to 10 days. Although karyotypic analysis can identify major structural alterations [eg, t(9;22) resulting in *BCR-ABL1* rearrangement in Ph⁺ ALL], the majority of Ph-like ALL–associated alterations are cytogenetically cryptic. However, clinical break-apart FISH probes have been developed for many of the 3′ genes commonly involved in Ph-like ALL translocations, including *ABL1*, *ABL2*, *CRLF2*, *EPOR*, *JAK2*, and *PDGFRB* (this probe often also detects *CSF1R*), with rapid result return often within 3 or 4 days. Although FISH analysis often cannot identify the specific 5′ fusion gene partner, abnormal 3′ gene results can provide the first clinical suspicion for ABL class or *CRLF2*-R/JAK pathway-mutant Ph-like ALL and allocate patients efficiently who require further molecular characterization. Ostensibly, clinical FISH testing with results return within 7 to 10 days of leukemia diagnosis could facilitate earlier therapeutic intervention with JAK inhibitor or ABL/PDGFR inhibitor addition early in induction chemotherapy (as is done for patients with Ph⁺ ALL(20,21) .

RT-PCR and polymerase chain reaction analyses

Molecular characterization of specific Ph-like ALL kinase fusions can be rapidly accomplished using RNA/complementary DNA–based reverse-transcriptase polymerase chain reaction (RT-PCR) analyses. These targeted assays have a turn-around time of as little as 2 to 3 days and can be "multiplexed" with capabilities for simultaneous testing of multiple kinase fusions. Multiplexed RT-PCR of 39 known Ph-like fusions was an initial approach used by the COG and other consortia for molecular characterization of Ph-like alterations in LDA⁺ ALL specimens. **(22)** However, these RT-PCR assays had significant "false-negative" potential because 5′ and 3′ genes and breakpoints must be known a priori; thus, these assays were often unable to identify kinase fusions with promiscuous breakpoints or previously unknown 5′ partners. DNA-based polymerase chain reaction (PCR) assays have been very useful in the detection of common Ph-like ALL–associated mutations, including *JAK2* and *JAK1* point mutations **(23,24)** and *IL7R* indels.**(25)** Rarely, *CRLF2* F232C point mutations occur in *CRLF2*-overexpressing ALL cases **(26,27)** ; these mutations seem to be largely independent of the *IGH-CRLF2* and *P2RY8-CRLF2* rearrangements and can be easily discovered by PCR. Confirmatory clinical Sanger sequencing of all PCR-detected fusions, point mutations, and indels is recommended**.(27).**

Flow cytometric immunophenotyping

Increased surface thymic stromal lymphopoietin receptor (TSLPR; encoded by *CRLF2*) staining of ALL blasts, which is readily detectable by flow cytometry, has proven to be highly predictive of *IGH-CRLF2* and *P2RY8-CRLF2* rearrangements and *CRLF2* F232 point mutations in primary Ph-like ALL cells. **(28)** Clinical TSLPR immunophenotyping (now performed as part of routine diagnostic flow cytometry panels is highly cost effective and can identify patients with probable *CRLF2*-R B-ALL within 24 hours of specimen acquisition. Several institutions are now routinely incorporating TSLPR flow cytometry into their diagnostic ALL evaluations and/or using it for potential clinical trial screening , and/or RT-PCR should be performed to characterize the specific *CRLF2* alterations as well as potential JAK and *IL7R* mutations by PCR analysis, if desired.

(29).

Molecular genetics perspectives and future directions

Advances in molecular technologies over the past decades helped to characterize the genetic basis of several disorders. Starting with the Karyotype analysis, which enable scientists to rearrange chromosomes and detect copy number changes, followed by the technology of using the loss of heterozygosity analysis, technologies keep moving forward and recently the DNA/RNA sequencing resolved lot of mysterious genomic mutations including small insertions/deletions, base substitutions, rearrangements and copy number alterations. In molecular testing, Sanger sequencing technique is one of the most widely used analysis platform for mutation detection. The innovation of the gene expression profiling along with next-generation sequencing (NGS) lead to advanced molecular subtyping with a promising future in regards to earlier diagnosis, accurate prognosis, identification of targeted therapies and eventually disease prevention. Using NGS a panel of multiple genes could be screened for mutations in a single quick analysis with a considerably low cost, through the application of massive parallel sequencing technology ***(36).***

Currently, scientist are able to use high-throughput technologies including genomics, transcriptomics, proteomics and metabolomics to reveal several diseases' enigmatic secrets including Ph like ALL. Characterizing the molecular genetic basis of Ph-like ALL at diagnosis by NGS, will facilitate rapid, accurate and cost-effective diagnosis, along with identification or predictive and prognostic tools, which will translate into better management of such patients **(10) .**

Table 1 summarizes the currently available diagnostic methods of Ph like ALL ***(10).***

Method	Advantage	Limitations
FISH	Easily available	Limited to the specific probes and algorithm to follow May miss many subtypes
Gene sequencing	Can detect all mutations and fusion genes	Expensive and time consuming Not commercial available
Low Density Microarray (LDA) cards	quick, user friendly, sensitive and specific diagnostic test	identify only targeted mutations Requires frozen tissue

Clinical implementation of Ph-like ALL screening: an example of the current COG approach

Linear Discrimnant Analysis(LDA) screening of all pediatric and adolescent and young adult (AYA) patients with HR B-ALL has been broadly implemented by the COG and used by other consortia to efficiently identify patients with Ph-like ALL who merit additional detailed genetic testing and may be eligible for clinical trials testing relevant TKIs with chemotherapy. **(22)** In practice, LDA results have been returned within 48 to 72 hours, allowing rapid "ruling out" of the 70% to 80% of non-Ph–like ALL patients ("LDA⁻") and triggering further genetic testing recommendations for patients with LDA positivity. Of note, the LDA assay also detects specimens with *BCR-ABL1* and *ETV6-RUNX1* rearrangements due to similarities in expression signatures; accordingly, such patients are not allocated for further testing. In the COG workflow, specimens identified as Ph-like are initially triaged based upon the level of *CRLF2* expression (high or low) assessed by LDA, including direct identification of potential *P2RY8-CRLF2* fusions in *CRLF2*-overexpressing specimens. Ph-like specimens with high *CRLF2* expression that test negative for the *P2RY8-CRLF2* fusion by LDA are then assessed for *IGH-CRLF2* translocations by FISH assays, with results returned in 1 week. All *CRLF2*-R samples are further

subjected to *JAK1*, *JAK2*, and *IL7R* PCR mutation analysis that usually also requires 1 week for resulting. LDA+ specimens with normal *CRLF2* expression are sent for customized Archer-based kinase fusion testing to assess for *JAK2*, *EPOR*, and ABL class rearrangements and other rare Ph-like–associated alterations, with a current turnaround time ~ 3 weeks. **(22)** As above, clinical RNAseq analysis can be performed for specimens with the Ph-like expression signature in which no kinase fusion or other oncogenic mutation is identified, but this testing often requires 4 to 8 weeks to result and is generally too slow to allow allocation of relevant patients to TKI-based clinical trials that begin at the consolidation phase of therapy **(35).**

Clinical characteristics and outcomes

Clinical characteristics: Ph-like ALL is more common in males with a peak incidence among young adults. Furthermore, patients with Ph-like ALL generally have higher leukocyte counts at presentation compared to patients with non–Ph-like ALL (106,000 vs. 59,000 percubic millimeter, P<0.001). Two adult studies have confirmed that the incidence of Ph-like ALL was higher (42%) in patients younger than 40 years of age, compared with 24% in those 40 years or older (P= 0.02)**(29).** However Herold and his colleagues found no significant differences in baseline characteristics, including age, sex, white-cell count, hemoglobin, platelet count between the Ph-like and remaining pre B-ALL subgroups. This can potentially be explained by differences in the comparative group between the studies and the differences of criteria used to define Ph-like ALL. Within the Ph-like ALL subgroups the baseline characteristics seem to be different based on the altered pathway ***(10).***

Outcomes: ALL is a chemosensitive disease and complete remission (CR) rates above 90% are universally achieved in all subgroups including Ph-like ALL, however maintaining remissions is less likely in Ph-like ALL. Increasing age is known to correlate with poor tolerance to chemotherapy and inferior outcomes in all subgroups of ALL and this holds true for Ph-like ALL as well. Several studies from different groups comparing adult and pediatric patients with Ph-like ALL to non Ph-like ALL patients from the same age group showed lower continuous remission rates, higher relapses and thus lower survival in the Ph-like group ***(37).***

Conclusion: Ph-like ALL is a common leukemia subtype in children and adults that is associated with high rates of chemotherapy resistance and relapse. Historically, clinical diagnosis of patients with Ph-like ALL has proven quite challenging **.**Given the last-known significant genetic heterogeneity of associated kinase fusions that are often cytogenetically cryptic and that previously required lengthy step-wise and costly testing that, nonetheless, failed to identify many lesions. Sophisticated RNA-based testing platforms (many of which are far more capable of new fusion partner discovery) that are now widely clinically available have appreciably facilitated identification of patients with Ph-like ALL and their specific leukemia-associated fusions, but these approaches require several weeks for data resulting. Instead, routine clinical FISH testing with the use of new *ABL1*, *ABL2*, *CRLF2*, *JAK2*, and *PDGFRB* probes and flow cytometric immunophenotyping for increased TSLPR surface expression may provide early suspicion for Ph-like ALL in relevant patients. Such approaches could be used for early intervention with appropriate TKI addition to chemotherapy while awaiting specific Ph-like ALL molecular analysis by more detailed testing. The diagnosis of Ph-like ALL is challenging, however it carries predictive and prognostic implications that help to better define the patient's risk and to personalize the treatment approach based on the presence of targetable mutations. Gene expression profiling (GEP) is cumbersome to use in daily clinical practice. Other methods, relying on reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or combination of immune-phenotyping and DNA-sequencing have been used. Identifying sensitive and specific algorithms will be very helpful to identify and treat Ph-like ALL in daily clinical practice.

No Conflict of interest.

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