Introduction

Chronic lymphocytic leukemia (CLL), a leukemia of small, mature B cells, mostly affects adults over 65 years of age. It is the most common form of lymphoid malignancies in adults, accounting for approximately 11% of all hematologic neoplasms and 24% of all leukemias. The annual age-adjusted incidence rate from 2004 to 2008 was 4.2 per 100,000 individuals, and the age-adjusted death rate from 2003 to 2007 was 1.5 per 100,000 individuals. Peripheral blood, bone marrow, spleen, and lymph nodes are typically involved. An evaluation of prognostic factors at the time of diagnosis can guide the timing and strategy of treatment. Several prognostic factors have been studied over the years. This article explores current clinical and pathologic prognostic factors in CLL.

Diagnosis of CLL

CLL is characterized by the accumulation of CD5-positive monoclonal B cells in peripheral blood, bone marrow, and primary and secondary lymphoid tissues. An accurate diagnosis of CLL is necessary before evaluating prognostic markers. In the absence of extramedullary tissue involvement, more than 5 × 10^9/L monoclonal New biological and cytogenetic features help predict both treatment-free and overall survival of patients with chronic lymphocytic leukemia.
CD5-positive B lymphocytes must be present in the peripheral blood for a diagnosis of CLL. According to the 2008 guidelines from the World Health Organization and the International Workshop on Chronic lymphocytic leukemia (IWCLL), the clonal lymphocytosis must last at least 3 months. This specification allows for lower lymphocyte counts in patients with cytopenias or disease-related symptoms. The term small lymphocytic lymphoma (SLL) refers to non-leukemic cases with the tissue morphology and immunophenotype of CLL. The IWCLL defines SLL as lymphadenopathy with no cytopenias due to bone marrow infiltration and fewer than 5 $\times$ 10^9/L clonal B lymphocytes in the peripheral blood.

Monoclonal B-cell lymphocytosis (MBL) is an asymptomatic hematologic condition characterized by low levels of clonal B cells ($<5 \times 10^9$/L) with a surface immunophenotype similar to that in CLL clonal B cells. General lymphadenopathy and diffuse bone marrow infiltration should not be present in MBL. MBL is commonly seen in adults (mostly > 50 years of age), with an estimated prevalence of more than 3%. MBL represents the vast majority of unexplainable clonal B-cell expansions observed in the peripheral blood of otherwise healthy people. While it is not well understood, the ability of MBL to evolve into a frank leukemic state could depend on biological and molecular features in the patient population and on the presence of additional genetic abnormalities. Because the age and gender profile of the MBL population parallels that of CLL patients, it would seem that the conditions share a similar inherited risk. Recent studies suggest that the distinction between CLL and MBL has clinical implications with respect to risk of progression and also suggest that this classification system should be used in routine practice.

CLL must be distinguished from other chronic lymphoproliferative disorders such as prolymphocytic leukemia and hairy cell leukemia, as well as the leukemic phases of mantle cell lymphoma, follicular lymphoma, and splenic lymphoma with villous lymphocytes. This usually can be accomplished by evaluating the morphology and immunophenotype. Additional ancillary studies such as cytogenetics by conventional karyotyping, fluorescence in situ hybridization (FISH) analysis, and immunohistochemical staining can be helpful in atypical cases.

**Clinical Parameters Associated With a Prognosis of CLL**

For patients diagnosed with CLL, it is necessary to clinically stage the disease by both the Rai and Binet systems. Although both staging systems are related to systemic spread, disease severity, and prognosis, concurrent genomic and molecular aberrations could alter the clinical course and outcome and could influence treatment strategy and clinical trial selection. Clinical factors that influence survival for patients with CLL include stage, tumor burden, performance level, cell types, extranodal involvement, peripheral hemoglobin level, response to initial treatment, and duration of response. The MD Anderson Cancer Center group proposed a CLL prognostic index that includes the following independent characteristics as predictors for survival: patient age, $\beta_2$-microglobulin level ($\beta_2$M), absolute lymphocyte count, sex, Rai stage, and number of involved lymph node groups. The total score is determined by adding up the scores of these six components. A score of 1 to 3 is identified as low risk; 4 to 7 is considered intermediate risk; and 8 or higher is considered high risk. This prognostic index has been widely accepted.

**Stage**

The Rai and Binet staging systems are correlated with survival of CLL patients. The Rai classification system for CLL has been widely applied in practice, mainly in North America. It includes five stages (0, I, II, III, and IV) according to three major parameters: lymphocytosis $>15 \times 10^9$/L for 4 weeks, anemia with hemoglobin level of $<110$ g/L, and thrombocytopenia of $<100 \times 10^9$/L platelets. This is in addition to the presence or absence of lymphadenopathy or splenomegaly. The Rai system has been simplified into low risk (stage 0), intermediate risk (stages I and II), and high risk (stages III and IV). The Binet staging system for CLL, more commonly used in Europe, is divided into three stages: A, B, and C. Peripheral blood hemoglobin level and platelet count are two critical parameters, in conjunction with number of areas involved by CLL, which includes head and neck, axilla, groin, palpable spleen, and clinically enlarged liver. Patients in stage A have fewer than three sites of involvement by CLL, the hemoglobin level is $\geq 100$ g/L, and the platelet count is $\geq 100 \times 10^9$/L. Those in stage B have three or more sites of involvement, the hemoglobin level is $\geq 100$ g/L, and the platelet count is $\geq 100 \times 10^9$/L. In stage C, any number of sites may be involved, with a hemoglobin level of $<100$ g/L, and/or a platelet count of $<100 \times 10^9$/L. In general, early-stage or low-risk patients (Rai stage 0 and Binet stage A) have a median survival of more than 10 years, and they are not usually treated. This group comprises approximately 80% of the newly diagnosed patients. Patients in the intermediate-risk category (Rai stage I/II and Binet stage B) have generalized lymphadenopathy, splenomegaly, or both. These patients have a median overall survival of 7 to 9 years. Treatment is necessary for patients in the high-risk group (Rai stage III/IV and Binet stage C) who have anemia, thrombocytopenia, or both, and these patients have a median survival of 1.5 to 5 years.

Recent studies have pointed out some of the shortcomings in these traditional staging systems. Not all early-stage patients fall into the same prognostic category. A 2009 study from Vroblová et al showed that the classic staging systems by Rai and Binet are not able to determine an individual patient’s ongoing clinical course.
at the time of diagnosis, particularly in early stages. In 2010, Letestu et al identified four critical factors for predicting the clinical course in Binet stage A CLL: serum thymidine kinase (sTK) level, lymphocytosis, β₂M level, and CD38 expression. Bulian et al recently conducted a retrospective analysis based on complete records from 1,037 CLL patients, and they argued against absolute lymphocyte count and Rai stage as being independent predictors of survival. In contrast, they concluded that the Binet staging system — which incorporates the number of involved lymph node regions as a variable — has independent predictive power.

**Bulky Disease**

Bulky lymph nodes and a markedly enlarged spleen have intermediate to high risk, according to Rai staging. Careful assessment for underlying large B cells is important because transformation of CLL/SLL to diffuse large B-cell lymphoma (DLBCL), or Richter’s syndrome, carries a poor prognosis with a median survival of less than 1 year. Survival in patients with Richter’s syndrome has improved: 20% of patients may live longer than 5 years after aggressive combination chemotherapy.

**Performance Status**

Performance status is used to describe a person’s ability to follow a typical lifestyle. The Eastern Cooperative Oncology Group (ECOG) Performance Status is a useful measurement of a patient’s condition. Using a scale of 0 to 5, a higher score has a poorer performance status measurement of a patient’s condition. A score of 0 indicates a fully active individual with no symptoms, while a score of 5 indicates death.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
<th>Description</th>
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<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease performance without restriction.</td>
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<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.</td>
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<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
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<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.</td>
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<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
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</tr>
<tr>
<td>5</td>
<td>Dead.</td>
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**Atypical Lymphocytes in Blood**

Increased circulating atypical lymphocytes, mainly prolymphocytes and large atypical lymphocytes, are associated with the progression of CLL to prolymphocytic leukemia (PL) or transformation to DLBCL. The clinical outcome in these atypical cases is worse than that of typical CLL. Atypical lymphocytes can also show cleaved or lobated nuclei, irregular nuclear contours, or enlarged size, without having prolymphocytic or large-cell components. The significance of atypical morphologic features in CLL has been a source of controversy for many years. Que et al noted that patients meeting FAB criteria for CLL/PL had a greater likelihood of having atypical lymphocyte morphology and trisomy 12 compared with patients with typical CLL. Matutes et al and Oscier et al noted an increased incidence of trisomy 12 and an adverse clinical course among CLL patients having more than 15% lymphocytes with irregular nuclei or lymphoplasmacytoid cells.

**Bone Marrow Lymphocytic Infiltrate**

Although a bone marrow examination is rarely required to make the diagnosis of CLL in general practice, it may provide valuable information prior to the start of treatment. Bone marrow infiltration by CLL/SLL can be divided into four common patterns: interstitial, nodular, mixed interstitial and nodular, and diffuse (packed marrow). Whether the pattern and the degree of lymphocyte infiltration are independent factors is controversial. Early studies suggested that a diffuse infiltrative pattern was associated with advanced stage of disease. For nodular and interstitial patterns, the median survival times were 90 and 46 months, respectively, while a diffuse pattern was associated with a median survival time of 28 months.

**Clinical Laboratory Parameters Associated With Prognosis in CLL**

Multiple factors, measured in standard clinical laboratory tests, affect the clinical course of CLL. These factors include lymphocyte count, lymphocyte doubling time, β₂M level, sTK level, angiopoietin-2 (Ang-2) level, and soluble cluster designation markers (CD14, CD23, and CD49d).

**Lymphocyte Count and Lymphocyte Doubling Time**

There is still debate over the cutoff lymphocyte count (eg, 40–50 × 10⁹/L) that is a reliable prognostic factor. Early studies demonstrated a median survival time of 8.6 years for patients with a lymphocyte count of < 20 × 10⁹/L and 3.7 years for those with a count of > 40 × 10⁹/L. Apart from the absolute lymphocyte count, the lymphocyte doubling time (LDT) is a useful indication of disease progression. Taking longer to double the lymphocyte count (> 12 months) implies a favorable prognosis, while aggressive cases show a shorter doubling time (< 12 months). A recent study by Bergmann et al...
revealed a shorter median progression-free survival (PFS) for Binet stage A patients with LDT < 12 months than for those with LDT > 12 months (median PFS = 20 months vs 75 months; \( P < .001 \)). In the same study, patients with an absolute lymphocyte count of > 30 \( \times 10^9/L \) had a median PFS of 17 months compared with an 88-month median PFS for those with an absolute lymphocyte count of < 30 \( \times 10^9/L \). Clinically, since there are many factors affecting the growth rate of lymphoma cells, relying on a single prognostic parameter is not recommended; LDT needs to be evaluated in context.

\( \beta_2M \) Level
\( \beta_2M \) is an extracellular protein component of the HLA class I complex and has been established as a marker of disease activity in malignancies, autoimmune conditions, and infections. \( \beta_2M \) is present in small amounts in the serum and urine of normal individuals. The normal range varies among laboratories. Viral infections, particularly Epstein-Barr virus and cytomegalovirus infections, can cause an elevation of serum \( \beta_2M \) levels. In CLL, \( \beta_2M \) measures (1) the amount of CLL present and (2) the turnover rate of CLL cells. Elevated \( \beta_2M \) has been observed in patients with high tumor burden and extensive bone marrow infiltration. An MD Anderson study\(^{35} \) concluded that a high serum level of \( \beta_2M \) is an independent adverse prognostic factor for complete remission, overall survival, and treatment-free survival among CLL patients, following first-line treatment with fludarabine, cyclophosphamide, and rituximab regardless of age or creatinine clearance.

sTK Level
The enzyme sTK is involved in the salvage pathway of DNA synthesis, and it correlates with proliferative activity. A prior study in CLL showed that sTK adds independent prognostic information to the definitions of smoldering and nonsmoldering CLL in Binet stage A. Hallek et al\(^{34} \) reported that untreated patients with nonsmoldering stage A CLL could be separated into two subgroups on the basis of sTK levels: patients with sTK values > 7.1 U/L had a median PFS of 8 months, whereas those with sTK values ≤ 7.1 U/L could expect a PFS of 49 months (\( P < .001 \)), which is similar to that for smoldering CLL (42 months). Levels of sTK can be determined by radioenzyme assays and chemiluminescence.\(^{34,35} \)

Ang-2 Level
Several studies have demonstrated the potential prognostic importance of angiogenesis in CLL. Ang-2, the blood vessel-destabilizing Tie2 ligand, is a molecule that plays a role in modulating angiogenesis during tumor growth.\(^{36} \) Maffei et al\(^{37} \) measured the Ang-2 plasma level, an angiogenic cytokine, in 316 patients with CLL and found that a high Ang-2 level predicted a shorter time to first treatment and shorter overall survival. Also, significant associations were found between high levels of Ang-2 and advanced clinical stage, high \( \beta_2M \), unmutated status of the immunoglobulin heavy chain variable (IgVH) gene segments, and adverse cytogenetics. A similar result was reported for 33 untreated CLL patients, indicating that Ang-2 mRNA was differentially expressed in patients with CLL and that increased expression appears to be associated with poor prognostic features.\(^{38} \)

Soluble CD Antigens
The survival of CLL cells depends on microenvironmental factors. Multiple soluble cluster designation (CD) antigens play a role in the prognosis of CLL.

Soluble CD14, a novel monocyte-derived cell survival factor, is present at abnormally high levels in CLL cells in vitro and in vivo.\(^{39} \) Seiffert et al\(^{39} \) reported that the addition of recombinant soluble CD14 to primary CLL cells resulted in significantly increased cell survival rates, which were associated with higher activity of the transcription factor NFκB.

Soluble CD23 (sCD23) is a protein derived from the B-cell membrane CD23 antigen and is selectively elevated in the serum of CLL patients compared with those from other B-lymphoproliferative disorders.\(^{40} \) A study demonstrated that a selective increase of CD23 provoked B-CLL lymphocytes into the S phase of the cell cycle.\(^{41} \) Elevated sCD23 levels above the median value (> 574 U/\( \muL \)) has been shown to predict a significantly shorter time to disease progression and a shorter overall survival.\(^{42} \)

CD49d is a 150 kDa protein that belongs to the integrin family, specifically the \( \alpha_4 \) integrin chain.\(^{32} \) It is directly involved in mononuclear leukocyte trafficking by acting as an adhesion molecule for cell-to-cell and cell-to-extracellular-matrix interactions. CD49d has been found on the surface of CLL cells. Recent studies have shown that low levels of CD49d expression, along with long telomere length, are associated with a favorable outcome for CLL patients.\(^{43} \)

Pathology Evaluation of CLL
The pathology laboratory can offer a great deal of useful information in CLL evaluation. Flow cytometry, FISH analysis, cytogenetics, and molecular studies have important roles in determining the stage and prognosis of a patient’s disease. A typical initial workup in our laboratory consists of a B-cell flow cytometry panel, a CLL FISH panel, and an evaluation of zeta-chain-associated protein of 70 kDa (ZAP70) expression and IgVH mutation status conducted on a peripheral blood specimen. Bone marrow biopsies are useful for patients with cytopenias and can be used to evaluate overall marrow involvement.

Flow Cytometry: CD38 and ZAP70
Flow cytometry can provide a basic phenotype in addition to useful prognostic information. Both CD38 and ZAP70 expressions are traditionally evaluated by flow
CD38 is an ectoenzyme, an enzyme present on the cell surface. It participates in cell adhesion, signal transduction, and calcium regulation. CD38 is able to metabolize extracellular nucleotides, e.g., ATP and NAD, into nucleosides that can be taken up by cells. By metabolizing NAD+ and cyclic adenosine diphosphate (ADP) ribose, CD38 plays a role in increasing cytoplasmic calcium concentrations. The endothelial cell antigen CD31 interacts with CD38 on CLL cells. This interaction has been demonstrated in vivo with immunohistochemical techniques. Increased CD38 expression, along with increased vascular density in lymph nodes, correlates with increased lymphocyte proliferation and disease progression.

Expression of CD38 on CLL cells has been shown to be increased in more proliferative clones. There is a close association between CD38 expression and increased Ki67 proliferation index along with increased ZAP70 positivity. This suggests that CD38-positive clones enter the cell cycle more frequently than do CD38-negative clones. CD38-positive clones also appear to over-express vascular endothelial growth factor (VEGF), which is associated with increased expression of Mcl-1, an antiapoptotic protein.

CD38 is measured by flow cytometry and plotted against B-cell marker CD19 expression. A recent report from Letestu et al indicates that CD38 is an independent predictor of PFS in Binet stage A patients. A cutoff value for positivity in CD38 has been a source of discussion. Traditionally, surface expression of CD38 in >30% of B-CLL cells was thought to be associated with more progressive disease. Damle et al showed that high levels of CD38 (>30%) identified those with unmutated IgVH genes in 100% of cases. Conversely, 82% of those patients with <30% CD38-positive cells were identified with mutated IgVH genes. A large study by Kröber et al reported that a cutoff value of 7% was most effective in separating the different prognostic groups. Letestu et al also utilized a CD38 expression level of >7% in their recent analysis. This finding is also supported by Hock et al, who reported on their study of 130 untreated CLL patients. They found that overall survival significantly improved in truly negative CD38 cases, while there was no clinically significant difference between those with high (>95%) CD38 expression and those with only >5% CD38 expression.

ZAP70, a tyrosine kinase, is associated with T-cell signaling. It is most commonly evaluated by flow cytometry. A ZAP70 analysis by reverse transcriptase-polymerase chain reaction (RT-PCR) has been developed that utilizes sorted leukemic cells. A rapid and accessible PCR test is not yet present in mainstream clinical laboratories. Currently, the two main techniques for measuring ZAP70 by flow cytometry involve comparing ZAP70 expression in B cells either against an isotype control or against ZAP70 expression in T cells within the sample. Crespo et al found that, at a cutoff of 20%, ZAP70 positivity clearly separated CLL patients into two groups; those with <20% ZAP70 had increased survival time and decreased chance of disease progression. Therefore, in most laboratories, ZAP70 is considered positive when at least 20% of the CLL cells have a signal that is greater than the background control signal.

Subjectivity in these methods can lead to variable results among research laboratories. To overcome this subjectivity, it has been suggested that mean fluorescence intensity (MFI) values from CLL cells and background T lymphocytes be measured rather than percentage of positive cells. Rossi et al reported that when using MFI values and calculating the ratio of T cells to B cells, those patients with a ratio lower than 3 had a shorter time-to-treatment than ZAP70-negative CLL patients and those estimated to be ZAP70-positive by the T-cell percentage method only. PCR-based methods to evaluate ZAP70 appear to have a high correlation with IgVH mutation analysis, with 94% of patients with unmutated IgVH being ZAP70-positive by PCR and 92% of patients with mutated IgVH being ZAP70-negative.

There are discordant cases in which ZAP70 and IgVH mutation status do not agree (i.e., ZAP70-positive and mutated IgVH). Orchard et al examined 6 patients with these findings and found that the ZAP70-positive patients had a 96% to 97% homology with the germline sequence. Patients with less than 96% homology did not express ZAP70. The converse situation also has been identified (i.e., ZAP70-negative and unmutated IgVH). Both Crespo et al and Orchard et al observed patients with this situation in their studies, with the latter report suggesting that longer follow-up of these patients is necessary to determine whether ZAP70 or IgVH will emerge as the better prognostic indicator.

**IgVH Mutation Analysis**

IgVH mutation analysis is a PCR-based study that compares IgVH DNA sequences from the CLL B cells to germline sequences. When the DNA sequence varies by more than 2% from the germline sequence, it is considered mutated. Mutated IgVH is associated with a longer treatment-free interval for CLL patients and, as such, a better prognosis than unmutated forms. One exception
to this rule is patients with the VH3-21 gene segment, which belongs to the mutated group but behaves like an unmutated clone with a higher frequency of p53 dysfunction and poorer survival.\textsuperscript{64,65} Unmutated IgVH is associated with elevated levels of CD38 expression, ZAP70 positivity, and unfavorable cytogenetic changes such as del(17p) and del(11q23).\textsuperscript{66} IgVH mutation analysis has the inherent limitations of PCR tests: the specimen must be fresh when evaluated (when intact RNA is still viable for RTPCR), and there must be a sufficient amount of CLL cells present for accurate analysis (> 10% of lymphocytes). An analysis of ZAP70, CD38, and IgVH mutation status, combined, showed an increased median survival in patients who were ZAP70 negative/CD38 negative/IgVH mutated (13+ years, median not yet reached) vs those who were ZAP70 positive/CD38 positive/IgVH unmutated (5 years 5 months).\textsuperscript{63}

The correlation between B-cell activation and IgVH mutation status has also been investigated. Some subtype distinction genes are thought to be induced by protein kinase C (PKC) signaling. One mechanism for PKC activation is through B-cell antigen receptor signaling. Rosenwald et al\textsuperscript{67} found that genes with higher expression in unmutated IgVH CLL (such as cell cycle control genes and cell metabolism genes) were induced during B-cell activation. The converse was also true: genes that were expressed at lower levels in unmutated cases were downregulated during B-cell activation.

**Cytogenetics/FISH**

While cytogenetics can be performed on peripheral blood specimens, CLL clones do not always divide in culture and thus cytogenetics is not always successful. FISH studies have increased the detection of common abnormalities. Most CLL FISH panels performed today evaluate for common cytogenetic aberrations including del(17p13) [p53], del(11q23) [ATM], trisomy 12, and del(13q14). Some panels also evaluate for t(11;14) to rule out mantle cell lymphoma, another CD5-positive B-cell malignancy.

Del(17p13) results in the deletion of TP53, a tumor suppressor gene that is lost or mutated in a variety of malignancies. Normal p53, the protein product of TP53, binds to the gene for p21 and stimulates production of that protein. The p21, in turn, binds to cdk, the cell division-stimulating protein, preventing cdk from signaling progression of the cell cycle.\textsuperscript{68} Loss of p53 leads to deregulated cell division. CLL patients with deletion of TP53 are associated with poor prognosis and shortest survival.\textsuperscript{50} BCLL clones with unmutated IgVH have a high frequency of poor-risk genetic abnormalities such as del(17p13).\textsuperscript{59}

Deletion of 11q23 involves the loss of the ATM gene. ATM represents ataxia telangiectasia mutated. The protein product of this gene is also involved in cell cycle regulation. It typically regulates tumor suppressors such as p53 and is involved in DNA repair.\textsuperscript{50} When the gene is mutated, it is associated with ataxia telangiectasia. As with del(17p13), CLL patients with del(11q23) typically have a poor prognosis, with an earlier onset of therapy. Del(11q23) is the second most common genetic abnormality in CLL.\textsuperscript{5}

The most common genetic abnormality in CLL, 13q14, is also the one with the best prognosis, when it is the sole abnormality. The overall survival rate associated with this genetic abnormality is even better than that associated with “normal” cytogenetics. Recent studies have shown that two micro-RNA (miRNA) genes, miR-15a and miR-16-1, are coded for at 13q14.\textsuperscript{71} Deletion of this region decreases production of these two miRNA genes that have been shown to negatively regulate Bcl-2 expression.\textsuperscript{71} This deletion allows the CLL cells to survive.

Trisomy 12 has a typical morphologic picture in that it is atypical. Most cases with trisomy 12 have atypical lymphocytes with irregular nuclear contours. This cytogenetic abnormality results in the classic “atypical” CLL; patients with the “atypical” CLL frequently have an atypical phenotype, with loss of CD5 or expression of FMC7, a marker usually absent in CLL. While the overall survival of patients with trisomy 12 is better than that of patients with del(17p) or del(11q23), it is worse than that of patients with del(13q14).\textsuperscript{50}

**Conclusions**

CLL is a heterogeneous disease, and accurate staging and prognosis studies are necessary to assist in treatment planning and clinical outcome. Full clinical and pathology evaluations are needed. Establishing a universal algorithm will likely improve prognostic accuracy. Further studies into new genomic testing options such as miRNAs and single nucleotide polymorphism arrays may provide additional parameters.

**References**

9. Shanafelt TD, Kay NE, Rabe KG, et al. Brief report: natural history of...


