To the editor:

**The proposed diagnostic criteria change for chronic lymphocytic leukemia: unintended consequences?**

We read with interest the new consensus guidelines for the diagnosis of chronic lymphocytic leukemia (CLL).\(^1\) The new revisions have clarified the role of molecular prognostic markers, improved the classification of response, and defined the role of minimal residual disease monitoring, and we support these changes.

We are concerned, however, with the substantial changes in the CLL diagnostic criteria that have been suggested without clear supportive evidence. In particular, the new guidelines propose changing the diagnostic criteria for CLL from an absolute lymphocyte count (ALC) more than or equal to \(5.0 \times 10^9/L\) to a B-cell count more than or equal to \(5.0 \times 10^9/L\). Although we recognize this change was made to align with previously proposed monoclonal B-cell lymphocytosis (MBL) criteria,\(^3\) it will significantly change the diagnostic criteria for CLL, MBL,\(^3\) and small lymphocytic lymphoma (SLL).

This proposed change has several shortcomings.

(1) **Lack of established clinical relevance.** Although the shift from an ALC to a B-cell-based criterion may seem trivial, this modification will reclassify approximately 40% of Rai stage 0 patients from CLL to MBL.\(^4\) Such a change will dramatically alter the incidence rate and confound monitoring the epidemiology of CLL. The published data suggest that a cutoff of \(5.0 \times 10^9/L\) B cells does not have prognostic value, as there is no difference in time to treatment when current Rai stage 0 patients are reclassified.\(^4\) Indeed, recent data suggest that a numeric threshold for predicting overall survival in CLL and MBL patients may be as high as \(11.0 \times 10^9/L\) B cells.\(^5\) We hope that data like these can be used to support future classification changes.

With respect to epidemiologic studies, the change will also increase the number of patients classified as SLL, since those with lymphadenopathy and an ALC of \(5.0 \times 10^9/L\) or more, but a B-cell count less than \(5.0 \times 10^9/L\) (previously Rai stage I CLL), no longer fulfill the criteria to be classified as CLL.

(2) **Absence of a standardized way to measure B-cell counts.** Flow cytometric immunophenotyping for leukemia/lymphoma analysis is not a quantitative test, and no standardized approach for determining B-cell counts in CLL has been proffered.\(^5,6\) The determination of a B-cell count will vary based on the methodology used and the gating strategy used (Figure 1). Having a standard clinical laboratory approach for making quantitative measurements is critical if B-cell counts are to be included in any new diagnostic criteria. In addition, moving the monitoring of disease from an ALC via a complete blood count (CBC), an easily accessible and economically prudent assay, to a B-cell count using a flow cytometry–based procedure will also have unintended consequences affecting cost and access.

(3) **Artificial inflation of the risk of progression among MBL patients.** The proposed change will decrease the number of patients diagnosed with CLL, and will dramatically increase the number of patients labeled as having MBL and SLL. In the seminal paper by Rawstron et al,\(^3\) the clonal B-cell count among MBL patients identified through population screening ranged from 0.003 to 1.458 \(\times 10^9/L\) (median = 0.013 \(\times 10^9/L\)). The MBL label is now being expanded, and many of these new MBL patients will be identified after they undergo evaluation for a lymphocytosis (> \(3.0 \times 10^9/L\)) discovered in clinical practice, rather than via population screening as in the original observations of MBL.\(^3\) The risk of progression to requiring chemotherapy treatment among such clinically identified MBL cases is 1% to 2% per year.\(^7,10\) Profoundly different from that of patients with MBL diagnosed via population screening.\(^9\) Given the divergent progression risks, it may be confusing to group patients with a minuscule clone identified by population screening together with those that were previously labeled as CLL into a single category. Indeed this reclassification will likely worsen the prognosis for both Rai 0 CLL and MBL patients because the lowest risk patients from the previous Rai 0 CLL group will be moved to the MBL group and become their highest risk patients. Those patients remaining in the new Rai 0 CLL category will have higher ALCs and likely a greater risk of progression.

![Figure 1. Flow cytometric lymphocyte gating methodology influences B-cell counts.](Image)

BLOOD, 18 JUNE 2009 • VOLUME 113, NUMBER 25 6495
We commend the IWCLL for making much needed improvements to the guidelines, but we believe changing the diagnostic criteria for CLL to 5.0 × 10⁹/L B cells requires further study as the current recommendation will likely create more questions than answers. The real challenge is not to focus on numeric cutoffs, but to devise a classification system that recognizes a common clonal B-cell immunophenotype and reflects today’s genetic and biologic knowledge in a way that will best benefit our patients.

Curtis A. Hanson, Paul J. Kurtin, and Ahmet Dogan

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Curtis A. Hanson, MD, Division of Hematopathology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: cahanson@mayo.edu.

References
4. Shanafelt TD, Kay NE, Call TG, et al. MBL or CLL: which classification best categorizes the clinical course of patients with an absolute lymphocyte count >5x10⁹/L but a B-cell lymphocyte count <5x10⁹/L? Leuk Res. 2008;32:1458-1461.

To the editor:

Lymphocytes, B lymphocytes, and clonal CLL cells: observations on the impact of the new diagnostic criteria in the 2008 Guidelines for Chronic Lymphocytic Leukemia (CLL)

The diagnostic criteria for CLL have been constant for the past 20 years under the 1988 and 1996 Guidelines.¹² This has now changed with the 2008 Guidelines.³

(1) The effect of change in definition: Moving early CLL to MBL. The 1988 and 1996 Guidelines¹² established an absolute lymphocyte count (ALC) of 5.0 × 10⁹/L or more as the diagnostic criterion for CLL. Over the following decade, increasing numbers of patients with small clonal populations below this level were identified. In 2005, criteria for monoclonal B lymphocytosis (MBL) were proposed⁴ that suggested a cutoff of 5.0 × 10⁹/L B lymphocytes (not lymphocytes, ie, ALC). The converse of this criterion has now been recommended as the new definition for CLL. The impact of this change is noteworthy.

We analyzed in our laboratory a cohort of 322 patients who fulfilled the criteria for MBL with a typical CLL phenotype (Table 1). We found that only 156 (48%) did not fulfill 1988/1996 criteria for CLL with an ALC less than 5.0 × 10⁹/L. Hence, 52% previously classified as CLL are now redefined as MBL. Although the natural history of early CLL is well defined,⁵ evidence on clinical outcomes and rates of progression of MBL patients with ALC less than 5.0 × 10⁹/L is still emerging,⁶-⁸ based currently on small numbers identified from differently selected populations that are not easily comparable. Further data are needed on patients with low-level clones of uncertain significance.

(2) Practical observations with the change of definition. There is now significant variation in the ALC for a diagnosis of CLL. Using a B-lymphocyte definition means the ALC ranges from 5.0 × 10⁹/L to more than 10.0 × 10⁹/L (Table 1). This results in some additional complexity for patients, clinicians, and reporting laboratories, especially when patients have a prior diagnosis of CLL under earlier Guidelines. During follow-up of some MBL

Table 1. Absolute CD19, CD20, dual CD19/CD5, and total lymphocyte (ALC) counts in a cohort of patients (n = 322) with MBL with a typical “CLL phenotype”

<table>
<thead>
<tr>
<th>Absolute count × 10⁹/L</th>
<th>CD19</th>
<th>CD20</th>
<th>CD19/CD5</th>
<th>Lymphocytes (ALC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.99</td>
<td>44 (13.7%)</td>
<td>45 (14.0%)</td>
<td>62 (19.2%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>1.0-1.99</td>
<td>57 (17.7%)</td>
<td>64 (19.9%)</td>
<td>70 (21.7%)</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>2.0-2.99</td>
<td>69 (21.4%)</td>
<td>73 (22.6%)</td>
<td>71 (22.1%)</td>
<td>16 (5.0%)</td>
</tr>
<tr>
<td>3.0-3.99</td>
<td>84 (26.1%)</td>
<td>86 (26.7%)</td>
<td>82 (25.5%)</td>
<td>38 (11.8%)</td>
</tr>
<tr>
<td>4.0-4.99</td>
<td>68 (21.1%)</td>
<td>48 (14.9%)</td>
<td>35 (10.9%)</td>
<td>79 (24.5%)</td>
</tr>
<tr>
<td>5.0-5.99</td>
<td>6 (1.9%)</td>
<td>2 (0.6%)</td>
<td>70 (21.7%)</td>
<td></td>
</tr>
<tr>
<td>6.0-6.99</td>
<td>69 (21.4%)</td>
<td></td>
<td></td>
<td>70 (21.7%)</td>
</tr>
<tr>
<td>7.0-7.99</td>
<td>20 (6.2%)</td>
<td></td>
<td></td>
<td>70 (21.7%)</td>
</tr>
<tr>
<td>8.0-8.99</td>
<td>5 (1.6%)</td>
<td></td>
<td></td>
<td>70 (21.7%)</td>
</tr>
<tr>
<td>9.0-9.99</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td>70 (21.7%)</td>
</tr>
<tr>
<td>10+</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td>70 (21.7%)</td>
</tr>
</tbody>
</table>

Data show number of patients and percentage (in parentheses).
The proposed diagnostic criteria change for chronic lymphocytic leukemia: unintended consequences?

Curtis A. Hanson, Paul J. Kurtin and Ahmet Dogan