Progress in prognosticating and treating patients with chronic lymphocytic leukemia (CLL) has led to deeper remissions, longer disease-free intervals, and better overall survival (OS) [1]. Many factors have led to these incremental improvements. First, understanding the different risk categories in CLL allowed better treatment refinement [2]. Second, incorporating anti-CD20 antibodies (specifically rituximab and then obinutuzumab) into optimized chemotherapy programs enhanced response rates and durations, leading to better OS [3,4]. Third, better supportive care and anti-infective prophylaxis led to minimizing morbidity and mortality [1]. Last but not least, understanding the role of B-cell receptor signaling pathways in the pathogenesis of CLL led to developing novel therapeutics that target the pathobiology of this disease [5,6].

These successes are tempered by challenges facing practicing oncologists, especially as we enter a reimbursement era that rewards value-based care, quality, and cost-effectiveness [7]. The cost of these new CLL therapies, their unique side effects, and the chronicity of the disease course, illustrate uncertainty to the optimal sequence of CLL therapies.

Expert opinions, guidelines, and consensus statements have generally been guiding tools on how to best diagnose and treat complex malignancies. These have largely been incorporated into clinical pathways governed by payers, oncologists, or both. These pathways are hypothesized to facilitate more consistent, more efficient, and more cost-effective care allowing better outcomes for patients while improving resource utilization for providers [8]. How to build and maintain these pathways continues to be challenging; CLL is an example of the complexity of such processes.

Core principles in designing clinical pathways argue that selecting the “most effective” therapy is always recommended. When two therapies have similar efficacy, the one with less toxicity is advised. If toxicity and efficacy are comparable, treatment with the lower cost is suggested [9]. In fact, the National Comprehensive Cancer Network (NCCN) utilized these principles as they developed the (“Evidence Blocks”) [10]. Whilst this approach appears straightforward, applying it to CLL is far from simple. First, efficacy results are lacking, as these novel targeted therapies have not been compared in randomized studies to each other, and their comparisons to commonly utilized standard chemoinmunotherapy regimens have not matured. Second, toxicity data are based on clinical trials that do not always represent post-marketing side effects encountered in community practice/commercial use of drug—the “real world.” Lastly, understanding the cost of these therapies is complicated. Cost to a patient as an out-of-pocket expense differs from cost to the overall health care system and to society. Further, defining cost from a payer perspective might not align with other stakeholders’ views and priorities. These factors pose significant challenges to building clinical pathways in CLL, a process that is urgently needed in a disease where expensive therapies are developed and patients are living longer.

We propose that building pathways for CLL must consider not only outcomes from clinical trials but also incorporate data from clinical practice (for both toxicity and efficacy) and patients’ reported outcomes. Patients enrolled on clinical trials do not generally represent those seen in the community especially in CLL, where the median age at diagnosis is >70 years and most newly diagnosed patients carry several co-morbidities, and are on several oral medications that might interact with CLL-directed therapies [11]. As an example, the top three side effects leading to ibritinib’s discontinuation in the landmark study that led to its’ approval differ with adverse events described in a real-world setting (Table I) [12]. Identifying newer toxicities observed in the post-marketing phase is critical to implement strategies to minimize side effects and optimize patients’ outcomes. To that end, we support the value of data obtained from ongoing observational studies for any approved CLL therapy where community patients are enrolled and data on adverse events and outcomes are captured. The questions about relative efficacy, the significant toxicities associated with treatment in this often frail and elderly population, and a prevailing dogma of “do no harm” is reflected in recent data demonstrating a complacency toward newer and more effective therapies earlier in the disease course [14]. Also, as managing CLL depends on risk stratification, incorporating risk categories into pathways is critical. It should be noted that several traditional poor risk features in CLL are overcome in part by B cell receptor signal transduction and BCL2 inhibitors underscoring the need to validate prognostic models in the modern era [15–18]. Additionally, refining these risk factors continues to evolve, especially as we enter an era of next generation sequencing, underscoring the importance of refining clinical pathways constantly to meet scientific advance [19].

When it comes to cost, involving patients in the decision-making is crucial [20]. Balancing costs with outcomes cannot be achieved without active patients’ engagement. The utility of a particular therapy vary amongst patients. While an improvement in overall survival with excessive out-of-pocket expense can be justified by one patient, they might not be perceived as advantageous by another. Clinical pathways, as they currently exist, rarely involve patients and their reported outcomes and values [21].

The urgent need for clinical pathways in managing CLL is accentuated by high costs of newer targeted oral agents and the lack of sequencing or comparative studies. Several timely action items are needed to move this process forward. First, engaging all stakeholders in the
TABLE I. Differences of Reported Adverse Events Between Clinical Trials and Real-World in Relapsed CLL Patients Receiving Ibrutinib

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trial (%) [13]</th>
<th>Real World (%) [12]</th>
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<tbody>
<tr>
<td>Toxicity</td>
<td>Diarrhea (49%)</td>
<td>Atrial Fibrillation (20%)</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infections (33%)</td>
<td>Infections (12%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Fatigue (32%)</td>
<td>Cytopenias (9%)</td>
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Beyond efficacy and toxicity is urgently needed. To properly design and refine this formula, clinical trials have to incorporate patients’ reported outcomes and should be designed to study and report subsequent therapies following study drug discontinuation beyond a censoring event [21]. Third, consideration for “real-world” registries is needed to better understand patterns of care and encountered toxicities that could vary from reported trial data. Lastly, updating these pathways is critical for sustainability and for evaluating whether this strategy truly and positively impact the delivery of care and the overall costs. Pathways have the potential to improve the quality and cost of care, decrease variance, increase clinical trial accrual, and optimize patients’ outcomes, but only if they are designed and maintained with scientific rigor that incorporates the needs of all stakeholders.

References