some patients with *GATA2* mutation lack a phenotype, corroborating that cellular deficiency may evolve over time. However, even before problems emerge, there is, in some cases, an elevation of Flt3 ligand, which can be a marker of stress hematopoiesis. They point out that the DCML immunophenotype resembles a pattern of terminal differentiation seen with aging and chronic viral infection. Indeed, they demonstrate a tendency toward clonal myelopoiesis, consistent with GATA2s role in maintaining stem cell longevity.

Both papers provide important insights into the pathophysiology and clinical features of this disorder and are packed with practical recommendations aimed at a multidisciplinary approach to patient care, involving screening and diagnosis, as well as treatment, including prophylaxis for infectious complications and hematopoietic stem cell transplantation. That so many patients with a seemingly rare disorder could be identified and evaluated in such a relatively short period of time would indicate that heritable *GATA2* mutations might not be uncommon.

As with all good studies, there are more questions than answers. Without robust genotype-phenotype correlation, how much of the varied clinical manifestations, including differences among individuals within the same family sharing a common germ-line mutation, are due to environment—particularly infectious exposures—vs modifier genes and acquired mutations either as a second hit to *GATA2* or other genes? What is cause and what is effect? In other words, an orthodox interpretation might suggest that cytopenias are contributing to infections, yet the possibility that an overtaxed response may be helping to drive malignant transformation remains intriguing, though untested.

GATA2 joins the ranks of other transcription factors,[9] namely RUNX1, CEBPA, and PAX5,[10] central to development and hematopoiesis, where germ-line mutations confer Mendelian predisposition to leukemia. In addition to MDS and AML, *RUNX1* mutation is also associated with thrombocytopenia and platelet functional defects and *CEBPA* mutation with eosinophilia. Thus far, there are no extramedullary complications known to occur with *PAX5* mutations associating with familial acute lymphoblastic leukemia, although, perhaps, greater scrutiny is warranted.

The categorical unity of leukemia predisposition genes may support the concept that, fundamentally, leukemia derives from loss of transcriptional control of the hierarchic differentiation program during blood cell development and may augur well for therapies directed toward promoting cellular differentiation. Further definition of the consequences of heritable deficiency of GATA2 and its cohort of other transcription factors should continue to enlighten understanding of benign and malignant hematopoiesis, as well as flesh out associated clinical features extending beyond blood.

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● ● ● **CLINICAL TRIALS & OBSERVATIONS**

Old variables, new value: a refined IPI for DLBCL

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In this issue of *Blood*, Zhou and colleagues present a refined prognostic index for patients with de novo diffuse large B-cell lymphoma (DLBCL), addressing the need for a tool that can better separate risk groups in the rituximab era.[1]

The International Prognostic Index (IPI) was originally devised in the era before rituximab and before DLBCL was consistently separated from other large cell lymphoma entities.[2] The use of rituximab has improved survival in DLBCL, but has also narrowed the outcome differences between the IPI risk groups. With current first-line therapies, even the highest risk group identified by the original IPI has a 5-year overall survival of 50%.[3,4] Many have sought to identify new prognostic tools using molecular markers, gene expression signatures, or interim positron emission tomography response assessment, but all of these approaches have limitations and none are ready to be broadly adopted into clinical practice in the immediate future. At present, prognostic models that rely on widely available clinical parameters are more easily applied than models that include variables requiring highly specialized or nonstandardized measures. Thus, revisiting the IPI among patients with DLBCL who were treated with rituximab-containing regimens using well-standardized clinical variables is timely and appropriate.

Zhou and colleagues have devised a new prognostic model: the National Comprehensive Cancer Network–IPI

	IPI	NCCN-IPI
Patient 1		
Age, 50 y	0	1
Stage IV	1	1
Normalized LDH 1.5	1	1
ECOG performance status 0	0	0
Extranodal sites: kidney, bone	1	0
Score	3	3
Risk group	High-intermediate	Low-intermediate
5-y OS estimate	62%	82%
Patient 2		
Age, 76 y	1	3
Stage IV	1	1
Normalized LDH 3.5	1	2
ECOG performance status 1	0	0
Extranodal sites: bone marrow	0	1
Score	3	7
Risk group	High-intermediate	High
5-y OS estimate	62%	33%

Illustrative example of how 2 patients with the same prognostic score using the IPI would have very different prognostic scores and survival estimates using the NCCN-IPI.

ECOG, Eastern Cooperative Oncology Group.

(NCNN-IPI). The model is straightforward and looks similar in many ways to the original IPI. The authors initially constructed the index using data from an NCCN cohort of patients with DLBCL and then externally validated the approach using an independent cohort from the British Columbia Cancer Agency registry. Statistical efforts gleaned additional information from familiar prognostic variables, including age, serum lactate dehydrogenase (LDH), and extranodal sites of disease. The authors demonstrate that the effect of age on survival is linear, while the effect of LDH on survival plateaus when normalized LDH is more than threefold the upper institutional limit of normal. The continuous nature of these data are taken into consideration in the NCCN-IPI and it is not surprising that additional prognostic information was gained by moving away from dichotomizing these variables. The authors also refined extranodal disease as a prognostic variable, finding that specific sites of involvement (bone marrow, liver/gastrointestinal, central nervous system, or lung) performed better in the model than a variable based solely on the number of extranodal sites of disease.

This enhanced NCCN-IPI compares favorably with the original IPI insofar as it better differentiates those with the best and worst prognoses. Using the NCCN-IPI, the outcomes among risk groups spans a larger range, with the low-risk group having an estimated 5-year overall survival (OS) of 96% and the high-risk group having an estimated

5-year OS of 33%. This is in contrast to 90% and 54% for low- and high-risk groups, respectively, using the IPI. The ability of the NCCN-IPI to better discriminate risk groups can be illustrated by examining the prognostic scores and associated outcome predictions for 2 hypothetical patients with DLBCL (see table). Although both patients have the same 5-year OS estimate by the IPI (62%), the NCCN-IPI indicates that patient 1 has a much better chance of a good outcome with a 5-year OS estimate of 82% compared with patient 2 with a 5-year OS estimate of 33%. Taken together, it seems likely that this report will set a new standard for prognostication in DLBCL. From a practical standpoint, the NCCN-IPI can be easily applied in academic and community-based practice settings alike. In the age of web-based calculators and smartphone apps, incorporating the NCCN-IPI into daily practice can be simply achieved with a software update.

DLBCL remains a heterogeneous disease with biologic mediators of treatment response and outcome that are not fully elucidated, much less incorporated into a prognostic model. In Hodgkin lymphoma, the International Prognostic Score similarly relies on routine clinical and laboratory parameters amid growing appreciation that more specific biologic characteristics in these tumors appear to carry prognostic significance. Analogous situations exist for most other hematologic malignancies as well. More complex prognostic markers such as gene-expression–based signatures and molecular biomarkers should be evaluated for their ability to improve upon the NCCN-IPI and contribute additional risk prediction on an individual level.[5] The NCCN-IPI can serve as the new framework upon which to evaluate the clinical utility of these novel prognostic markers.

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

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● ● ● **CLINICAL TRIALS & OBSERVATIONS**

Ph+ ALL: imatinib grows older with patients

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In this issue of *Blood*, Fielding et al demonstrate a significant enhancement of long-term outcomes for a large series of adult patients with Philadelphia-positive