study is in-line with other major surgical procedures.

One must be cautious and consider the exclusion criteria of the study, such as increased risk of bleeding, cerebral metastases, or other risks of intracerebral bleeding, or renal or liver dysfunction. The study also excluded patients with an underlying indication for anticoagulation, as prophylactic doses of anticoagulation may not be sufficient for the other indication. Individual patients may also have other comorbidities precluding safe and effective use of prophylactic rivaroxaban.

The field of anticoagulation has certainly become more nuanced since the introduction of heparin and warfarin, well over 60 years ago. When there was 1 choice available, the choice was simple. With the expanding number of indications, therapeutic options, and dosing regimens, we have the ability and opportunity to be more selective and optimize safety and efficacy.

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TRANSPLANTATION

Comment on McReynolds et al, page 909

Playing with fire: unrecognized AA genetic predisposition

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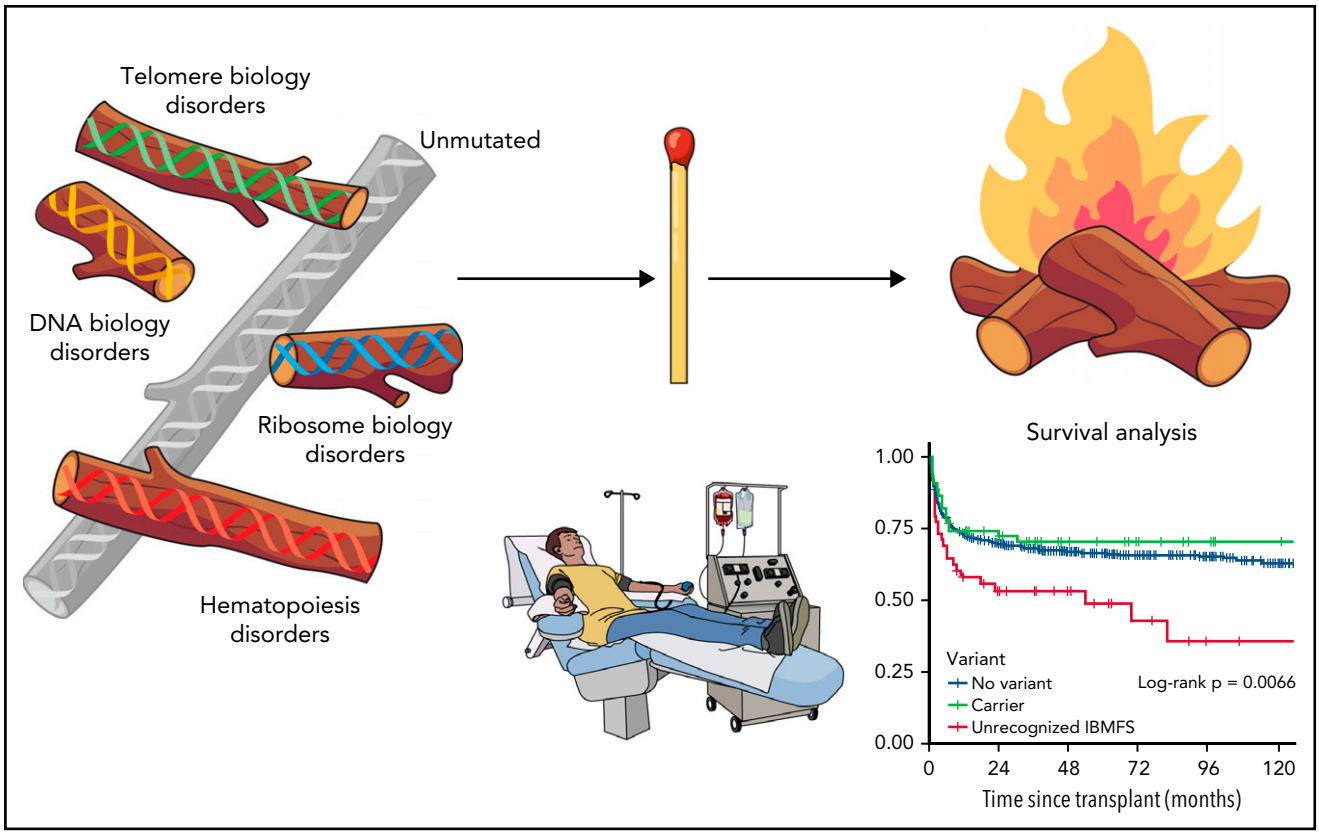
In this issue of *Blood*, McReynolds et al[1] report a study of extended genetic testing that revealed clinically unrecognized forms of germline aplastic anemia (AA) or inherited bone marrow failure disorder (IBMFD) in patients undergoing hemopoietic cell therapy (HCT). Their cohort of 732 patients with AA underwent either a related or unrelated HCT over nearly 30 years in centers affiliated with the Center for International Blood and Marrow Transplant Research. All patients had a blood sample available for whole-exome analysis.

AA, the quintessential disorder of bone marrow failure, can be acquired or inherited (inherited bone marrow failure disorder [IBMFD]). Acquired forms are usually immune-mediated, whereas inherited forms may be caused by DNA repair defects (Fanconi anemia), short telomere syndromes (dyskeratosis congenita), ribosomopathies (Shwachman-Diamond and Diamond-Blackfan anemia), or other germline mutations (*GATA2*, *RUNX1*). Acquired severe AA (SAA) is preferentially treatedwith allogeneic HCT (vs immunosuppressive therapy [IST]) in patients with a suitable donor. Immunosuppression is not a rational therapeutic option in inherited AA, and HCT, when appropriate, requires optimization for the underlying disorder. Thus, knowledge of any germline etiology of the patient's AA has therapeutic relevance.

McReynolds et al used a curated list of 104 genes relevant to hematopoietic differentiation, DNA damage response, telomere, and ribosome biology. After variant selection, they studied the correlation between potential germline mutations and specific post-transplant outcomes. With a rigorous statistical approach, they identified single-nucleotide variants and copy-number variants in 48 patients (6.6%). One-third were adult patients; however, only 3 patients with identified mutations were >40 years of age.

Patients with AA who had genetic evidence of previously unrecognized IBMFD present in the pre-HCT sample experienced worse survival, irrespective of the transplant platform (myeloablative or reduced intensity [RIC] conditioning) or donor relationship. The increased mortality was attributed to organ failure, with the highest rates in those patients with



Transpant outcomes for aplastic anemia affected by inherited predisposition. Professional illustration by Patrick Lane, ScEYEnce Studios.

mutations identified in DNA damage response genes followed by telomere biology genes (see figure). These patients unfortunately seem to "melt" with HCT. Patients who were only noted to be carriers of pathogenic variants experienced outcomes similar to presumed acquired cases. In the no-variant group, graft-versus-host disease (GVHD) was the most common cause of death.

With ever-evolving diagnostic techniques[2,3] and increasing recognition of genetic etiologies of AA,[4] the standard diagnostic algorithm for AA has become multifaceted. The combination of etiologic heterogeneity with increasingly earlier use of HCT[5,6] emphasizes the need for an appropriate diagnostic work to guide the therapeutic paths pursued for all patients with AA.

Over the course of this study, there were lower percentages of unrecognized IBMFD in each subsequent time interval (12 of 236 from 2011 through 2015, compared with 36 of 496 from 1989 through 2010) suggesting increasing awareness of the need to properly diagnose inherited predisposition. This result also coincides with improved use of functional testing, such as peripheral blood lymphocyte telomere length measurement by flow-fluorescence in situ hybridization[7] and chromosome breakage with diepoxybutane to rule out short telomere syndromes and Fanconi anemia. McReynolds et al did not have access to fresh plasma to do these tests specifically but were able to confirm the telomere lengths in those mutation-bearing patients by polymerase chain reaction. This series confirms that baseline assessment for these disorders is the minimum mandatory workup before HCT for AA. Furthermore, the study strengthens the case for more comprehensive germline testing such as whole-exome sequencing in all patients with SAA <40 years of age, as 45 of the 48 identified lesions were in this age range.

However, it must be noted that McReynolds et al did not have the ability to do paroxysmal nocturnal hemoglobinuria (PNH) testing on these samples. It is known that the presence of a PNH clone represents a marker of acquired AA disease and can be identified by flow cytometry.[8] Genetic testing is costly and not readily accessible in many parts of the world, so the use of PNH clones with the aforementioned functional testing is a cost-conscious initial step. This cohort study would also suggest that adults >40 years of age with negative function testing and a PNH clone may not require additional genetic work-up, especially in resource-limited areas.

It is widely recognized that patients with short telomere syndromes and Fanconi anemia must undergo a less intensive HCT conditioning regimen to avoid morbidity and mortality. McReynolds et al nicely illustrate the lengths required to document these mutations accurately to avoid the "firestorm" of organ toxicity and mortality from HCT. Indeed, even RIC regimens had similarly bad outcomes in this study. Given that 31% of the patients with new mutations documented had variants in telomere biology genes, preparatory regimens that even further attenuate conditioning for these patients are important for future clinical investigations. Lastly, the cause of death in the patients without any identified variants was GVHD, not organ toxicity. There is currently an increased focus on the use of

very intensive GVHD regimens in nonmalignant diseases, such as AA,[9] to address these potential GVHD complications.

There has been a marked improvement in outcomes of HCT with unrelated donors[10] and even those with mismatched donors[5] in recent years. In a young patient with a concern for unrecognized IBMFD, there is often concern about higher rates of GVHD with the use of an unrelated donor competing with the worry about the use of a related donor with same mutational issues. Reassuringly, there was not a difference by donor relationship in this cohort, suggesting it is the patient and the conditioning that are critical in HCT optimization for SAA. Interestingly, 5 of 7 patients with unrecognized IBMFD had DNA available from their related donor, and only 1 donor was a carrier. It is more likely that prompt recognition of IBMFD will prompt testing of at-risk relatives who are being considered as a potential donor for related HCT.

The relevance of the data from McReynolds et al to the current rationale for screening to differentiate acquired and inherited AA is very clear. Thorough and comprehensive germline genetic testing for younger patients with AA (outside of those with PNH and 6pCNLOH clones) will inform the patient's care and allow optimized outcomes. The future of the marrow failure field will be additional demonstration of the potential harm from the use of immunosuppressive therapy in patients with correctly diagnosed IBMFD as well as lack of benefit. Thus, a more personalized and tailored HCT approach will increase survival in all patients with AA and avoid outcomes that go "up in flames."

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MYELOID NEOPLASIA

Comment on Heiblig et al, page 927

Ruxolitinib takes center stage for VEXAS syndrome

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In this issue of *Blood*, Heiblig et al[1] report on the efficacy of Janus kinase (JAK) inhibition in treating patients who have VEXAS (vacuoles in myeloid progenitors, E1 ubiquitin–activating enzyme, X-linked, autoinflammatory manifestations, somatic) syndrome. VEXAS syndrome is a recently described disorder consequent to somatic mutation in the *UBA1* gene.[2]

Patients with VEXAS syndrome present with various combinations of inflammatory symptoms that mimic different rheumatic diseases and hematologic conditions (myelodysplastic syndrome or monoclonal gammopathy). Resistance to treatment is one of the characteristics that a patient who is initially suspected of having a rheumatic disease may have VEXAS syndrome instead. Although sporadic cases are identified among this population of patients with treatment-resistant rheumatic disease, screening studies have demonstrated a high diagnostic yield in undiagnosed cytopenic males, with VEXAS syndrome identified in 1% of such cases.[3] To date, only high-dose glucocorticoids have demonstrated significant efficacy in treating VEXAS syndrome, but symptoms frequently relapse when any dose reduction is attempted, and sustained high-dose glucocorticoids have an unacceptable safety profile.[2]

It is noteworthy that in the study by Heiblig et al, the authors describe evidence of significant treatment efficacy with the preferential JAK1/2 inhibitor ruxolitinib. Other JAK inhibitors also seem to have some, albeit lesser, efficacy in treating VEXAS syndrome. The authors describe 30 patients treated with JAK inhibitors. At months 1, 3, and 6 after beginning treatment with a JAK inhibitor, a clinical response was seen in 50%, 57%, and 82%, respectively, of those remaining on treatment. These overall results masked the marked discrepancies between individual JAK inhibitors; rates of clinical remission favored ruxolitinib over other JAK inhibitors at 67% vs 38% at month 1, 83% vs 18% at month 3, and 87% vs 11% at month 6. There was also a marked steroid dose reduction of 83.6% with ruxolitinib and 75% with other JAK inhibitors; 3 patients stopped glucocorticoid treatment entirely. The significant reductions in glucocorticoid dose suggests that the benefit of JAK inhibitors other than ruxolitinib is possibly greater than would be suggested by the headline numbers, because patients with