treatment PET-CT results. In concert with the pretreatment study, they demonstrated that patients with no risk factors (MTV <510 cm^3, negative end of induction PET-CT) had a 5-year PFS of 67% vs 33% with 1 factor, and only 23% with both high MTV and a positive end of induction scan. These values for low- or high-risk patients do not appear dissimilar from the prior publication using pretreatment TMTV alone[8]; nonetheless, they identify a markedly worse outcome in the intermediate risk group. It would have been interesting to see how the FLIPI-2, which was integral to their former study, affects the current analysis.

Whereas the additive value of the restaging PET-CT may predict outcome better than either study alone, it falls short of our goal. The Holy Grail for FL patients remains the accurate prediction of patient outcome before treatment. Rather than waiting to retreat with residual disease or upon recurrence, the primary focus should be on improving predictability before initial therapy by incorporating other correlative studies including the M7 FLIPI. Sarkozy et al[9] suggested that a quantitative clonotypic assay (Clonoseq) or other next-generation sequencing performed pretreatment predicts outcome. Studies are under way assessing the additive value of such assays with TMTV.

Risk-adapted trials using appropriate biomarkers need to distinguish those patients likely to do well with standard treatments who might require less therapy. Those unlikely to do so would be spared the time delay and toxicity of unsuccessful treatments and instead would be referred for novel therapeutic strategies, hopefully leading to improved patient outcome. It will be our greatest challenge to figure out what those therapies are.

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REFERENCES

1. Cottereau AS, Versari A, Luminari S, et al. Prognostic model for high-tumor-burden follicular lymphoma integrating baseline and end-induction PET: a LYSA/FIL study. *Blood*. 2018;131(22):2449-2453.
2. Shadman M, Li H, Rimsza L, et al. Continued excellent outcomes in previously untreated patients with follicular lymphoma after treatment with CHOP plus rituximab or CHOP plus ^{131}I-tositumomab: long-term follow-up of phase III randomized study SWOG-S0016. *J Clin Oncol*. 2018;36(7):697-703.
3. Luminari S, Ferrari A, Manni M, et al. Long-term results of the FOLL05 trial comparing R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage symptomatic follicular lymphoma. *J Clin Oncol*. 2018;36(7):689-696.
4. Salles GA, Seymour JF, Feugier P, et al. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years [abstract]. *Blood*. 2017;130(suppl 1). Abstract 486.
5. Shi Q, Flowers CR, Hiddemann W, et al. Thirty-month complete response as a surrogate end point in first-line follicular lymphoma therapy: an individual patient-level analysis of multiple randomized trials. *J Clin Oncol*. 2017;35(5):552-560.
6. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol*. 2015;33(23):2516-2522.
7. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol*. 2015;16(9):1111-1122.
8. Meignan M, Cottereau AS, Versari A, et al. Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. *J Clin Oncol*. 2016;34(30):3618-3626.
9. Sarkozy C, Huet S, Carlton V, et al. Quantitative assessment of circulating clonal IG-VDJ sequences in plasma of follicular lymphoma at diagnosis is highly predictive of progression free survival (PFS) [abstract]. *Blood*. 2015;126(23). Abstract 2675.

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TRANSPLANTATION

Comment on Zhu et al, page 2490

Non-HLA genetic mismatches and BMT outcome

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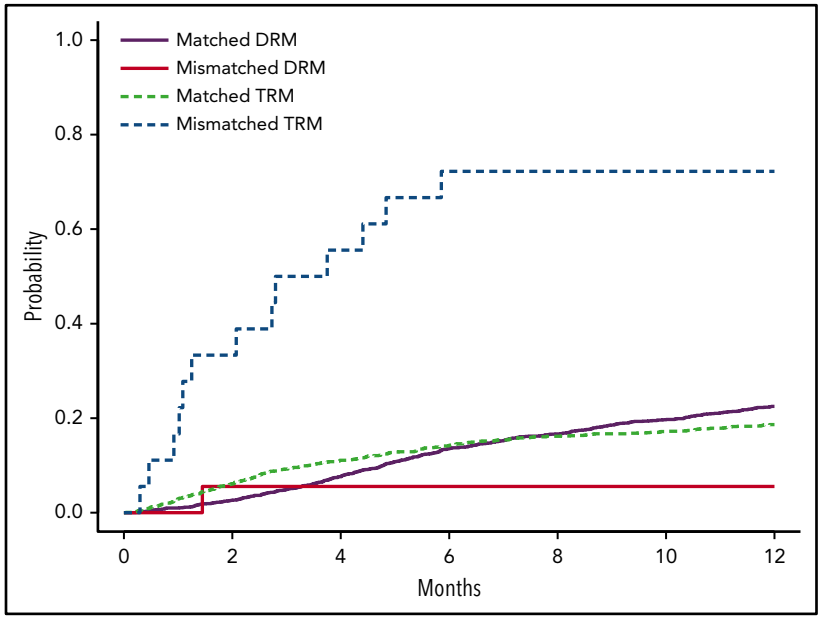
In this issue of *Blood*, Zhu et al identify a novel rare genotype mismatch in the testis-expressed gene *TEX38* that is prognostic of blood and marrow transplant (BMT) mortality (see figure).[1] The single-nucleotide polymorphism (SNP) that was identified (rs200092801) in this first of its kind exome-wide association study (EXWAS) is a nonsynonymous variant, suggesting a functional consequence underlying this association. The hunt for prognostic and predictive biomarkers is a key component to precision medicine efforts, and the assessment by Zhu et al is an important step in that direction for those who receive BMT.

Notably, BMT remains a primary treatment option for those with malignant hematologic diseases, including acute lymphoblastic leukemia, acute myeloid leukemia, and myelodysplastic syndrome. Because of better donor selection, supportive care, and infection control, outcomes for individuals receiving BMT have improved in recent years. However, 1-year mortality is still ~40%.[2] An important predictor of outcome in BMT is matching patients with unrelated donors based on 4 human leukocyte antigen (HLA) genetic loci: *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*.[2] In spite of the predictive power of these HLA genetic loci, there still remains significant interindividual variation in survival after BMT, suggesting there is more to learn in terms of predicting BMT outcome. Therefore, several studies have explored the role of non-HLA genetic loci on BMT survival.

There are multiple strategies available when identifying genetic variants associated with outcomes, and the "best" strategy depends on the research question. Zhu et al employed an EXWAS to identify variants and genes associated with overall survival (OS), transplant-related mortality (TRM), and disease-related mortality (DRM). In this scenario, a genotyping array (often called a chip) was used rather than whole-exome sequencing (WES). While WES provides greater coverage of the exome, the cost



Estimated cumulative incidence curves with TRM and DRM as competing events for recipients with donor genotypes having 1 allele mismatch and no mismatch of rs200092801 in cohort 1. Two allele mismatches of this variant between recipients and donors were not observed. See Figure 1 in the article by Zhu et al that begins on page 2490.

is still higher than using a genotyping array. This is particularly important when evaluating outcomes in the >4000 individuals included in the DISCOVeRY-BMT (Determining the Influence of Susceptibility COnveying Variants Related to one-Year mortality after BMT) study.[3] The number of SNPs on the particular chip used in this analysis numbered >200 000. When conducting an EXWAS, the appropriate research question would be "what is the role of rare (eg, minor allele frequency [MAF] <0.5%) coding variants on a particular outcome?"[4] This is in contrast to a genome-wide association study, where one would be evaluating the role of common genetic variants (eg, MAF >5%) across the entire genome (regardless of coding status), or a whole-genome sequencing study, where one typically evaluates the role of rare variants across the entire genome.[4,5] Another approach would be a so-called candidate gene study. However, as the authors noted, candidate gene studies of BMT outcome have yield mixed results,[6] which is true for multiple outcomes.[5]

This study contributes importantly to our understanding of the role of non-HLA genetic variants on BMT outcomes. As noted, the authors leveraged the DISCOVeRY-BMT study to conduct the first reported EXWAS of outcomes in individuals treated with BMT. An important methodologic aspect of this particular assessment was the evaluation of genetic variants in 2 independent cohorts: cohort 1 included 1970 recipients and 1741 donors, and cohort 2 included 503 recipients and 480 donors. Specifically, the authors found that donor–recipient mismatches for *TEX38* rs200092801 were significantly ($P = 3.51 \times 10^{-7}$) associated with TRM. The effect was stronger when either the donor or recipient was female. Specifically, the median survival time for donor–recipient pairs mismatched at *TEX38* rs200092801 was 1.1 months for female donor to female recipient, 0.9 months for female donor to male recipient, and 4.4 months for male donor to female recipient. These are dismal outcomes for these individuals. Unfortunately, as *TEX38* rs200092801 is rare variant (MAF 0.3%), the minor allele was not observed in cohort 2, which is one potential limitation of the current study. However, the authors presented additional functional evidence in support of this their finding.

Aside from the single-variant association analyses, the authors also conducted gene-level association analyses, which aggregate information on multiple SNPs within a gene to make gene-level inferences. While not as useful for identifying single prognostic biomarkers, these gene-level approaches could provide insights to the underlying biology of poor outcomes among those who receive BMT. Genes identified in these analyses that were associated with OS, TRM, or DRM include *OR51D1* (recipient), *ALPP* (donor), *EMID1* (donor), *SLC44A5* (donor), *LRP1* (donor), *HHAT* (donor), *LYZL4* (donor), and *NT5E* (donor).

What is next on the horizon for predicting poor outcomes for those who receive BMT? Of course there are several directions to move from the study by Zhu et al, but 4 important strategies would be: (1) Replicating the *TEX38* rs200092801 finding in an independent population. This is particularly important as the effect of this variant could not be evaluated in cohort 2 of the present study. (2) Functionally validating *TEX38* rs200092801. While the authors did provide some biological plausibility for their finding, much work is needed to understand why this variant is associated with TRM. (3) Applying genome-wide approaches for identifying variants that are prognostic of OS, TRM, and DRM. Common variants and/or variants in noncoding regions have been identified in relation to several treatment-related outcomes and diseases.[5,7] It is important to assess the role of these variants to identify novel prognostic biomarkers of outcome in populations receiving BMT. (4) Evaluating genetic variants and BMT outcomes in non-European populations. While it is important to account for population stratification bias in genetic association studies,[5] it is also vital to evaluate the role of these and other variants in other populations, which often have different responses to treatment.[8] Ultimately, it is clear from this study that evaluating non-HLA genetic mismatches is an important strategy for predicting outcomes among those who receive BMT.

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REFERENCES

1. Zhu Q, Yan L, Liu Q, et al. Exome chip analyses identify genes affecting mortality after HLA-matched unrelated-donor blood and marrow transplantation. *Blood*. 2018;131(22):2490-2499.

2. Hahn T, McCarthy PL Jr, Hassebroek A, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *J Clin Oncol*. 2013;31(19):2437-2449.

3. Hahn T, Sucheston-Campbell LE, Preus L, et al. Establishment of definitions and review process for consistent adjudication of cause-specific

mortality after allogeneic unrelated-donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2015;21(9):1679-1686.

4. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009;461(7265):747-753.

5. Manolio TA. Bringing genome-wide association findings into clinical use. *Nat Rev Genet*. 2013; 14(8):549-558.

6. Sucheston-Campbell LE, Clay A, McCarthy PL, et al. Identification and utilization of donor and recipient genetic variants to predict survival after HCT: are we ready for prime-time? *Curr Hematol Malig Rep*. 2015;10(1): 45-58.

7. Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. *J Clin Oncol*. 2015;33(11):1235-1242.

8. Bustamante CD, Burchard EG, De la Vega FM. Genomics for the world. *Nature*. 2011; 475(7355):163-165.

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