latent covariates, not captured in registries or clinical trials, contribute to imperfect prediction. However, by the law of diminishing returns, adding more features to the model will only marginally increase accuracy.[8] Another consideration is the ratio between the effect and sample size. Mathematical simulations show that 5000 to 10 000 patients are needed to detect an association between a gene that has a moderate-size prognostic effect on outcome and is present in 1% of the population.[1] Therefore, in the era of next-generation sequencing, huge collaborative registries should be formed to capitalize on the wealth of data available. Furthermore, methods such as shrinkage techniques and machine learning algorithms capable of dealing with high-dimensional data (ie, the number of features is high relative to the number of patients) are needed.[9] Finally, with all humility, physicians must acknowledge that there is inherent uncertainty to prediction. It is unrealistic to expect that features at the beginning of a patient's journey or even at the time of transplantation will unambiguously determine his fate. Instead, prediction should be dynamic, recalculating probabilities throughout the course based on previous events. This sort of Bayesian approach was recently applied in diffuse large B-cell lymphoma, yielding sequential individualized estimation of disease-free survival following diagnosis, interim, and end-of-treatment response evaluation.[10]

These caveats notwithstanding, the work presented in this manuscript gives us a glimpse of what the future can hold. Some physicians might be wary of black box computer-generated algorithms, fearful that they might threaten the contribution of clinical judgment to decision making. But indeed, these models use many more variables than any clinician could likely juggle in his or her head. Tools such as these complement our clinical experience and can only enhance our ability to make what very well could be lifesaving recommendations to our patients (see figure). When the stakes are as high as they are for HSCT, we must embrace every opportunity to steer our patients to safe harbor.

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TRANSPLANTATION

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Eliminating disparities improves outcomes

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In this issue of *Blood*, Bona and colleagues report an analysis utilizing the Center for International Blood and Marrow Transplant Research (CIBMTR) database to evaluate neighborhood poverty exposure as a predictor of poor outcome for pediatric patients undergoing allogeneic hematopoietic stem cell transplant (HSCT).[1] This report is a first of its kind describing the influence of social determinants on children undergoing HSCT; however, similar analyses have been conducted in children with asthma, cancer, acute appendicitis, sickle cell disease, as well as those requiring solid organ transplant, peritoneal dialysis, or utilization of intensive care.[2,3] In any situation assessing success of HSCT, there are biologic variables, such as underlying disease, condition of the patient, donor availability and degree of match, access issues such as proximity to an HSCT center and facility capacity, and treatment outcome factors such as disease response and remission status, and acute and chronic treatment-related complications. The study presented in this issue evaluates many patients suffering from both malignant (n = 2053) and nonmalignant (n = 1696) conditions, describing a variety of discrete variables that are validated by the CIBMTR. This report identifies several issues that deserve attention. Specifically, the study reports differences in outcome for patients with malignant and nonmalignant indications for HSCT based on social determinants of health (SDOH).

This and many other reports from health care, educational, environmental, and other domains continue to demonstrate worse outcomes for persons living in poverty. The topic of SDOH is receiving well-deserved and overdue attention. The World Health Organization defines SDOH as "the conditions in which

people are born, grow, live, work and age."[4]

Many pediatric medical centers routinely include assessments of SDOH. These include such factors as household poverty, material hardships such as food availability or insecurity, and housing access and condition. The data currently available have identified several SDOH factors that have been shown to influence outcomes for adult and pediatric hematology, oncology, and HSCT patients. For example, patients with SCD presenting to an emergency department for care experience longer wait times than other groups, even after accounting for assigned triage level. The authors conclude that race and a diagnosis of SCD each may contribute to biases that lead to longer wait times for these patients.[5] In a comprehensive literature review by Majhail and colleagues, Black patients had disparate access to autologous or allogeneic HSCT compared with White patients. The racial disparities in HSCT outcomes are more significant for allogeneic than autologous HSCT recipients.[6] For adult patients with acute myeloid leukemia (AML), Black patients and patients from poorer communities experienced significantly poorer survival. When outcomes were adjusted by multivariate Cox regression analysis for patients under age 60, sex, Black, and a history of smoking had a significant impact on outcomes. Interestingly, Byrne and colleagues noted that younger adults with AML and those with government insurance had longer median survival times compared with those who were older and those with a combination of Medicare and Medicaid insurance.[7] More recently, Roeland and colleagues have shown that adolescent and young adult patients with cancer experience low rates of hospice referral and high rates of in-hospital death regardless of socioeconomic status.[8] The retrospective manner in which such information is collected and reported is subject to well-described limitations; however, many centers do not routinely collect this information in an organized prospective manner or correlate these data with outcomes.

Better and more comprehensive prospective assessments of these risk factors during the intake and diagnostic workup period with members of the medical and intake team should be considered a new standard of care. These factors must be considered when determining how best to support a patient and family during care, particularly for complex and chronic illnesses.

In high-poverty communities, all-cause mortality from violence and other diseases may be covariates or confounding variables. In addition, confounding/ concomitant illnesses and medical comorbidities, such as obesity, diabetes, asthma, and cardiovascular diseases, are known to have higher prevalence in resource poor populations. Understanding the influence of these factors needs to be evaluated in a more formal way in future studies.

For an HSCT population, both infection and graft-versus-host disease may be surrogates for compliance. However, access to medications and follow-up care, frequency of care, or even transportation issues may prevent access to care and impact compliance. This is supported by the findings from a single institution in a large urban center that show that of 133 children undergoing hematopoietic cell transplantation (HCT) for nonmalignant conditions, half of whom lived in high-poverty neighborhoods and two-thirds of whom had public insurance, treatment at a tertiary care center with a multidisciplinary approach where all patients undergo consistent psychosocial and sociodemographic assessment including barriers to care could mitigate drivers of disparities shown to be significant in other settings.[9]

Bona et al report here that in children transplanted for nonmalignant conditions there was no relationship between neighborhood poverty and outcome for any HCT variable, while in patients with malignant diseases, higher neighborhood poverty predicted higher transplant-related mortality, but there was no impact on overall survival or other adverse transplant outcomes. This was striking, as this difference was despite similar median duration of follow-up, percent of patients living in high-poverty neighborhoods, percent insured by Medicaid, and similar percentage of patient who were Black or Hispanic. Nevertheless, analyses based on patient-reported ZIP code have limitations. Patients with complex medical conditions requiring allogeneic transplant, as Bona et al mention, often receive substantial amounts of care in the outpatient setting, often far from their primary residence both before and after HSCT.

Therefore, ZIP code at the time of HSCT may not accurately reflect the patient's true home and environment. Many pediatric HSCT centers are geographically located in large urban areas with significantly larger populations who live in high poverty. Studies like that of Harney et al may identify mitigation strategies to help level these barriers.[9]

Utilizing reported insurance coverage as a surrogate for poverty exposure is a particularly challenging metric. Families with prolonged or chronic illnesses may have recently lost employment or insurance coverage, or, because of being underinsured for serious conditions, may have even dropped coverage to opt for public plans. Patients classified as "foreign nationals" are a very mixed group of patients, ranging from undocumented with limited resources to wealthy individuals seeking international care. A challenge in the Bona paper is that CIBMTR data do not include detailed insurance information, socioeconomic status, or measures of household material hardship, and therefore, correlations and specific insurance data are not available for this very large group. In addition, this study only evaluates patients who were able to successfully get to transplant. Thus, factors that may prevent patients from obtaining a transplant are not presented. Based on these data, it remains unclear why the current CIBMTR data reveal a difference between patients with malignant and nonmalignant conditions. Several factors may contribute to the apparent differences this study reveals. The only true way to address SDOH's impact on outcomes is to collect complete information prospectively.[10,11] Eliminating disparities in the SDOH is a critical and readily addressable factor for improved outcomes for patients.

The finding by Bona and colleagues of the different impact of SDOH in patients with malignant disease vs nonmalignant disease and selection bias toward transplanting only those with higher resources if they have nonmalignant conditions has enormous implications. Now more than ever, as a society, we must be more conscious of systemic racism and preconceived notions about patients, which can be unfounded and/or inappropriate. We must address the social and potentially discriminating implications of systemic racism at the society level now and

in the future and pay special attention to ensuring balanced and equal consideration of opportunities, risks, and benefits for all patients. The authors suggest this, and paying close attention to these issues could be a start toward correcting what is already a disturbing dynamic and one in which the health care field must not be complicit.

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