



Social determinants of health. Reprinted from the US Department of Health and Human Services.¹⁰

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provide valuable insight on the potential impact of poverty on ALL outcomes and support the comprehensive, longitudinal collection and analysis of social determinants of health data in childhood cancer clinical trials in the context of well-established prognostic indicators, with the hope of informing future intervention strategies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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CLINICAL TRIALS AND OBSERVATIONS

Comment on *Kanapuru et al*, page 235

Equality: trial and error?

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In this issue of *Blood*, Kanapuru and colleagues¹ describe that specific eligibility criteria in trials in multiple myeloma (MM) may lead to underrepresentation of Black patients due to failure to meet hematology laboratory- and treatment-specific requirements.

The authors reviewed clinical trials in MM submitted to the US Food and Drug Administration (FDA) for drug approval, including ethnicity and reasons for screen failure. Similar to a recent systematic review analyzing all randomized clinical MM trials conducted over the past 15 years, they found a low representation of non-White patients (17%), with only 4% being Black.² The present study, which comprised nearly 9500 patients, is unique for its focus on identifying the reasons behind ineligibility for study participation. Its objective was to identify opportunities for narrowing racial disparities that exist in clinical trials. The study found that Black patients had the highest overall ineligibility rate at 24%,

compared with 17% in White patients and 11% in Asian patients. The primary reason for this disparity was that fewer Black patients met hematology laboratory criteria, potentially due to an inherent lower hemoglobin level and neutrophil count. Additionally, the authors suggest that limited access to standard care led to a higher percentage of Black patients who failed to meet treatment-specific eligibility criteria. This lack of access would disqualify them from participating in trials that increasingly require patients to have undergone a certain number of prior therapies, with different mechanisms of action and demonstrated refractoriness to multiple drugs.

This and previous analyses show an underrepresentation of minorities and support the continued efforts of the US FDA to enhance the participation of individuals from underrepresented racial and ethnic populations in clinical trials.^{2,3} The rationale behind this endeavor is multifaceted, with the generalizability of findings frequently cited as the primary objective. However, in the scientific context, it is generally not assumed that the study population of a randomized trial is representative of all patients when extrapolating the results to real-world practice, but rather that the relative effects of the experimental treatment are comparable across various subgroups. Therefore, it is crucial to investigate whether there are any reasons to anticipate divergent outcomes based on race and ethnicity before embarking on the design of trials that aim to represent these groups. If so, the study population must not only be representative for the general population but also possess adequate statistical power to allow solid conclusions regarding the treatment's impact on the specific racial and ethnic subgroups.⁴ Indeed, differences exist between Black patients with MM and White patients with MM. Black patients have a higher incidence of MM and tend to develop it at a younger age compared with White patients. Moreover, studies have reported a lower response rate but higher overall survival rates in Black patients.^{5,6} Biologically, race and ethnicity are associated with specific molecular landscapes: non-Hispanic Black patients often exhibit mutations in *SP140*, *AUTS2*, and *SETD2*, whereas *IRF4* mutations are most frequently observed in Hispanic patients. Considering the prognostic significance of somatic mutations in cancer, the clinical outcome might be affected.⁷ This reinforces the need for improving equality in clinical trial access for patients with MM. To attain that objective, gaining a comprehensive understanding of the factors contributing to a limited participation rate in clinical trials is essential.

The findings of Kanapuru and colleagues suggest that the use of race-specific eligibility criteria may improve inclusion of Black patients. However, less than 5% of Black and Hispanic patients were screened for trial participation. This low figure means that it is not possible to determine statistically significant reasons for screen failures across racial and ethnic

subgroups. In addition, specific data on hematology parameters and data that led to ineligibility in trials were unavailable. Furthermore, data to validate the claim that patients did not receive the required previous lines and types of therapy to qualify for enrollment in studies were lacking. Importantly, 88% of patients were screened at sites outside the United States, raising the possibility that cultural differences between countries may have affected the results of Kanapuru and colleagues, but this possibility cannot be tested in the current analysis.

It is likely that factors other than screen failures are primarily responsible for the underrepresentation of minorities in clinical trials, given that the difference in screen failures between Black and White patients was only 8%, whereas the difference in total number of screened patients was 80%. There are many hypothesized reasons for the unequal representation of minorities in clinical trials—such as distrust in the health care system, health illiteracy, poor understanding of clinical trials, increased cost to the patient from participation, and transportation difficulty accessing trial centers—but few data on specific trial designs that effectively address this issue.^{2,8} Race and ethnicity are frequently underreported, with a recent cohort study of more than 20 000 US-based trials revealing that only 43% reported such data.⁸ This is partly due to barriers in registering race or ethnicity in clinical trials, such as, for example, France's legal prohibition against collecting data on race, ethnicity, or religion.⁹ Furthermore, data availability varies across trials initiated by academia, industry, and government.⁸ As a result of this complex knowledge gap, proposing and implementing measures to improve equal enrollment of minorities remains challenging and emphasizes the need for data collection on race and ethnicity in future clinical trials.

To support data collection on race and ethnicity in clinical trials, the 4 R's (require, report, recruitment, royal) should be employed. The FDA and European Medicines Agency should implement a "require" and "report" strategy concerning the incidence of race and ethnicity. When it is reasonable to expect differences in relative effects of treatment among subgroups, they should require separate

analyses of these subgroups. The "recruitment" of racial minorities should be facilitated by evidence-based intervention strategies taking not only patients but also providers, institutions, and communities into account.¹⁰ Finally, inclusion criteria should be "royal," allowing patients to be included irrespective of race and ethnicity, which could be facilitated by either race-specific inclusion criteria or a high level of liberty.

We strongly support the ethical obligation to ensure equitable access to investigational medicine for all racial and ethnic groups. Kanapuru and colleagues made a compelling appeal for inclusive entry criteria in future trials to prevent errors that stem from exclusion.

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

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HEMATOPOIESIS AND STEM CELLS

Comment on [Gutierrez-Rodrigues et al](#), page 244

VEXAS: walking on the edge of malignancy

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In this issue of *Blood*, [Gutierrez-Rodrigues et al](#) analyze a large cohort of 80 patients with VEXAS syndrome for additional somatic mutations. Based on these findings, they reconstruct major patterns of clonal hierarchy and correlate the findings with clinical outcomes.¹

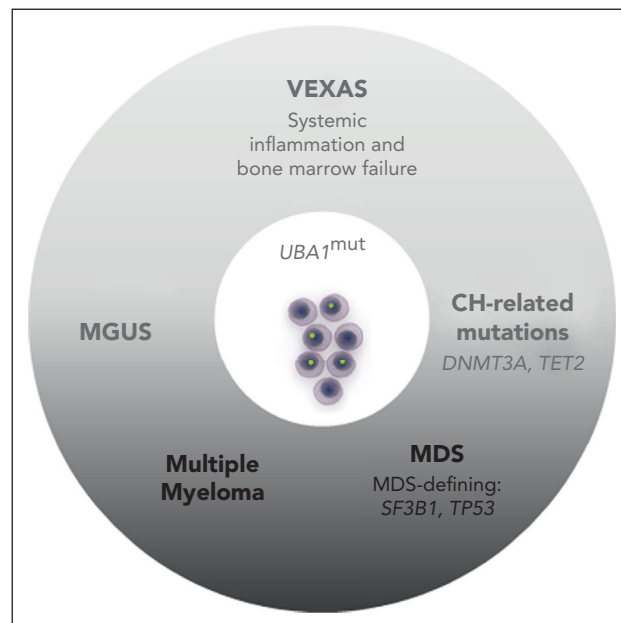
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a systemic autoinflammatory disease associated with acquired somatic mutations arising in hematopoietic stem/progenitor cells in the gene *UBA1*, an X-linked gene encoding an enzyme involved in ubiquitylation.² *UBA1* mutations are propagated in the myeloid lineage and trigger the activation of inflammatory pathways, resulting in severe systemic inflammatory symptoms.³ Patients with the VEXAS syndrome have a predisposition for hematologic malignancies, including myelodysplastic syndrome (MDS) and plasma cell dyscrasias (see [figure](#)). Notably, although MDS has been reported at a high frequency in VEXAS syndrome, most cases are classified as relatively low-risk MDS, while increased blasts and progression to acute myeloid leukemia (AML) has been reported occasionally.

Concomitant somatic mutations in genes within the spectrum of myeloid drivers have been reported occurring with *UBA1* mutation in VEXAS syndrome. However, the true prevalence and the biological and clinical implications of these comutations have not been so far fully elucidated. The study by Gutierrez-Rodrigues et al found typical myeloid mutations cooccurring with *UBA1* mutations in 60% of patients. Notably, approximately half of these patients showed somatic mutations in 2

or more myeloid genes, consistent with an increased propensity to the emergence and expansion of mutant clones. The observed mutations largely involved *DNMT3A* and *TET2*, detectable in approximately 50% of patients, although somatic mutations in classical MDS-associated genes, including *TP53*, *KRAS* and *NRAS*, *SF3B1*, *STAG2*, and *IDH2*, were also observed.

Although the variant allele frequency (VAF) of *UBA1* mutations was almost invariably consistent with being the dominant hematopoietic clone, the VAF of other mutated myeloid genes ranged from 27% for *DNMT3A* to <10%, for *TET2* clearly delimiting divergent clonal hierarchies. Accordingly, single-cell DNA analysis revealed distinct patterns of clonality. *DNMT3A* mutations mainly preceded *UBA1* mutation, consistent with the occurrence of the latter on the background of a *DNMT3A*-driven clonal hematopoiesis. Conversely, *TET2* and other genes mainly occurred as *UBA1* mutation subclones or independent clones. Although hematologic phenotype apparently did not differ between patients with or without additional myeloid mutations, survival was significantly affected by co-occurring mutations and clone metrics. Surprisingly, whereas severe cytopenias (transfusion-dependent anemia and thrombocytopenia) strongly associated with a diagnosis of MDS, additional somatic mutations apparently did not.

The study by Gutierrez-Rodrigues et al sheds light on the spectrum of mutations and their clonal trajectories in patients with VEXAS syndrome. The results further corroborate the association



Spectrum of clonal trajectories of *UBA1* mutant clones. Patients with the VEXAS syndrome have increased risk of MDS and plasma cell dyscrasias (monoclonal gammopathy of undetermined significance [MGUS] and multiple myeloma). Additional somatic mutations in typical drivers of clonal hematopoiesis (*DNMT3A* and *TET2*) and/or other genes enriched/specific for MDS contribute to clonal progression toward overt malignancy. A staging based on conventional clinical parameters (cytopenia and bone marrow dysplasia) is complicated by the inflammatory environment. CH, clonal hematopoiesis.