The NEW ENGLAND JOURNAL of MEDICINE

Perspective

NOVEMBER 28, 2024

The Duffy Null Phenotype — Addressing a Source of Discrimination in Cancer Care

Andrew Hantel, M.D., Stephen P. Hibbs, B.M., B.Ch., Lauren E. Merz, M.D., and Gregory A. Abel, M.D., M.P.H.

Structural racism describes the barriers to equity built into myriad societal domains. It operates in health care by means of policies, practices, and systems, "affecting health in ways often more difficult to recognize than explicit interpersonal racism."[1] Efforts are under way to dismantle these mutually reinforcing structures in oncology. Cancer research and care practices that adversely affect people with the Duffy null phenotype, however, are an underrecognized and widespread source of discrimination against people of African or Arab ancestry.

This erythrocytic phenotype, which is seen in approximately 67% of people who identify as African American, confers partial resistance to the malaria-causing parasite *Plasmodium vivax* by limiting its ability to enter red cells.[2] The Duffy null phenotype is also associated with a circulating absolute neutrophil count (ANC) that is approximately 40% lower than that in people without this phenotype, without conferring increased risks of infection or disease.[3] Although this variant is common and its effect on the ANC is predictable, cancer research and care practices continue to discriminate against people with Duffy null–associated neutrophil count (DANC). Areas of discrimination include clinical trial eligibility criteria, adverse-event grading, dose modification for systemic anticancer therapy, and remission criteria (see table).

Recently, we found that about 77% of phase 3 clinical trials for the five most prevalent cancers in the United States and the United Kingdom had eligibility criteria that explicitly or implicitly excluded some patients with DANC.[4] The ANC reference range for people with the Duffy null phenotype is approximately 1200 to 5400 cells per microliter,[3] and about 10% of healthy people with this phenotype have an ANC of less than 1500 cells per microliter. Clinical trials in oncology, however, frequently exclude patients with an ANC of less than 1500 cells per microliter, or an "abnormal blood count," on the basis of reference ranges that rely largely on populations of European ancestry.[4] These criteria are used not only in trials testing cytotoxic chemotherapy, in which neutropenia-related complications

Strategies for Addressing Discriminatory Practices That Affect People with Cancer and the Duffy Null Phenotype.*

Mechanism of Discrimination and Time Frame for Strategy	Strategy
Clinical trial eligibility criteria	
Short term	Eliminate use of ANC-based criteria when clinically significant myelosuppression is unlikely. Mandate Duffy testing during trial screening in people who would otherwise be excluded because of a low ANC. Reduce ANC cutoff in exclusion criteria to 1200 neutrophils per microliter or lower for people with DANC.
Adverse-event grading	
Short term	Modify grades 1 and 2 neutropenia definitions to specify that they do not apply to people with DANC.
Medium term	Establish expert consensus for DANC-specific adverse events.
Long term	Conduct real-world analyses to justify or modify the adverse-event grades initially established by means of expert consensus.
Therapy dose modifications	
Short term	Include DANC-specific dose modifications in new clinical trials. Consider including DANC-specific analyses for infection-related end points in new clinical trials.
Medium term	Conduct real-world studies of people with DANC, using proxy measures (e.g., studies of people who identify as African American and don't have other conditions that affect ANC) only when information on Duffy status cannot be obtained, to evaluate the rate of inappropriate dose modifications.
Long term	Conduct pragmatic trials in people with DANC to evaluate DANC-specific dose modifications for safety and effectiveness.
Remission criteria	
Short term	Modify remission criteria for chronic lymphocytic leukemia for people with DANC to include an ANC value at the lower threshold of the reference range for people with the Duffy null phenotype.
Medium and long term	Conduct analyses of hematologic cancers with ANC-based remission criteria to evaluate the need for adjustments for people with DANC.

* ANC denotes absolute neutrophil count and DANC Duffy null–associated neutrophil count.

are expected, but also in 50% of hormone therapy trials, in which they are not.[4]

It is inappropriate to continue using eligibility criteria that require an ANC of at least 1500 cells per microliter for people with DANC. Trials frequently allow exceptions to bilirubin-based exclusion criteria for patients with Gilbert's syndrome — a condition that is associated with high bilirubin levels, occurs predominantly in White people, and affects a proportion of the U.S. and United Kingdom populations similar to that affected by the Duffy null phenotype. We recommend that clinical trials minimize the use of ANC-based eligibility criteria, and when such criteria are required, mandate Duffy testing for participants who would potentially be excluded because of their ANC and reduce the ANC cutoff to 1200 cells per microliter or lower for people with DANC. Duffy testing is a routine, low-cost component of blood banking. Broad implementation of this approach would be facilitated by increased availability of Duffy-phenotype orders in electronic medical records and the establishment of clinical laboratory workflows for Duffy phenotyping that are separate from workflows for full red-cell typing.

Inappropriate eligibility criteria have been reinforced by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events classification of neutropenia. These criteria are the standard by which clinical trials are evaluated for safety. Currently, ANC levels used to define grades 1 and 2 neutropenia fall within the reference range for people with the Duffy null phenotype, meaning that some people

with DANC would be labeled as having an adverse event at their baseline value. Moreover, any further decrease in ANC during treatment could result in a grade 3 or 4 adverse event, which often leads to changes in therapy for the affected participant or even trialwide changes. In addition to discriminating against people with the Duffy null phenotype, these criteria negatively affect sponsors' promotion of inclusive trial participation.

Although the use of personalized thresholds based on each patient's baseline ANC would minimize false-positive and false-negative rates for adverse events, irrespective of Duffy status, establishing such a baseline is probably infeasible for many patients because of the fluctuating ANC effects of cancer, coexisting conditions, and medications. We recommend that trial sponsors, investigators, experts on the Duffy null phenotype, and representatives from the Food and Drug Administration (FDA) and the NCI convene to revise these criteria. At a minimum, grades 1 and 2 neutropenia could be omitted from adverse-event criteria for people with DANC. Ultimately, prospective trials and real-world evidence should be used to inform the delineation of each grade to ensure that these classifications reflect adverse-event severity for people with DANC.

Adverse-event criteria contribute to dose modifications for systemic anticancer therapies in clinical trials, which have also been agnostic to Duffy status. Together, adverse events and dose modifications occurring in trials guide clinical management after drug approval. People with DANC are therefore more likely than other patients to be subject to unnecessary dose delays and reductions or discontinuations of their standard therapies, which may affect their survival. Of the trials that form the evidence base for curative-intent regimens used to treat the most common cancers in the United States, as recommended by guidelines, more than half included dose modifications for ANC values within the reference range for people with the Duffy null phenotype.[4] In analyses that excluded trials of hormonal therapies, the prevalence of such modifications was nearly 70%. Similarly, the majority of FDA labels for these regimens recommended dose modifications.[4] Maintaining a relative dose intensity greater than 85% during cancer treatment is strongly associated with survival, and lower pretreatment ANC correlates with lower dose intensity.[5] Patients with DANC are therefore at increased risk for having an inappropriately lower relative dose intensity and poorer outcomes than other patients.

We believe changes should be incorporated in both existing treatment regimens and studies of new regimens. For new regimens, trial protocols should include dose modifications specific to people with DANC, and investigators could consider conducting DANC-specific analyses with infection-related end points to help develop an evidence base in this area. For existing regimens, investigators could conduct comparative-effectiveness analyses to evaluate the safety and effectiveness of DANC-specific dose modifications. In the interim, institutions in the United States and United Kingdom should partner with clinicians and researchers in regions where the Duffy null phenotype is common to gain insights on the safety and logistics of implementing DANC-specific dose modifications.

Finally, currently used remission criteria may be inappropriate for patients with DANC and hematologic cancers. Remission criteria for acute myeloid and lymphoblastic leukemias, myelodysplastic syndromes (MDS), and chronic lymphocytic leukemia (CLL) include reaching specific ANC thresholds and are agnostic to Duffy status. To our knowledge, only the International Workshop on CLL currently uses a definition of complete remission that includes an ANC of at least 1500 cells per microliter without growth-factor support, thereby excluding some people with an ANC within the reference range for people with the Duffy null phenotype. For people with DANC and other hematologic cancers, the use of ANC in remission criteria most likely increases the time to, and reduces the likelihood of, count recovery. Prognostic scoring systems that use such criteria (e.g., the Revised International Prognostic Scoring System for MDS) may also require reevaluation for people with the Duffy null phenotype. In addition, there are probably interactions between this phenotype and hematologic diseases that affect ANC variation and require further research. In the short term, remission criteria for CLL could be adjusted for people with DANC to an ANC value at the lower threshold of the reference range for people with the Duffy null phenotype. In the medium and long term, research involving people with DANC and hematologic cancers could evaluate

DANC-specific remission criteria, and such criteria could be adjusted, as appropriate.

Although the highest prevalence of the Duffy null phenotype is found among people with genetic ancestry from sub-Saharan Africa or the Arabian Peninsula, race or ethnic group alone is an inappropriate proxy for DANC. We therefore do not support simple "race based" modifications that have been previously proposed to address disparities associated with the Duffy null phenotype. Our suggested strategies for personalizing aspects of oncology care and ameliorating such disparities are broadly applicable and feasible. Uptake could help ensure that people with the Duffy null phenotype benefit from standards for research participation and clinical management as much as people without it. Investigators, clinicians, and regulators have the knowledge and ability to rectify these disparities and should work together to address them.

An audio interview with Andrew Hantel is available at NEJM.org

Disclosure forms provided by the authors are available at NEJM.org.

From the Dana–Farber Cancer Institute (A.H., L.E.M., G.A.A.), and the Center for Bioethics (A.H., G.A.A.), Harvard Medical School (A.H., L.E.M., G.A.A.) — both in Boston; and the Wolfson Institute of Population Health, Queen Mary University of London, London (S.P.H.).

This article was published on November 23, 2024, at NEJM.org.

1. Braveman PA, Arkin E, Proctor D, Kauh T, Holm N. Systemic and structural racism: definitions, examples, health damages, and approaches to dismantling. Health Aff (Millwood) 2022;41:171-8.
2. Legge SE, Christensen RH, Petersen L, et al. The Duffy-null genotype and risk of infection. Hum Mol Genet 2020;29:3341-9.
3. Merz LE, Osei MA, Story CM, et al. Development of Duffy null–specific absolute neutrophil count reference ranges. JAMA 2023;329:2088-9.
4. Hibbs SP, Aiken L, Vora K, et al. Cancer trial eligibility and therapy modifications for individuals with Duffy null-associated neutrophil count. JAMA Netw Open 2024;7(9):e2432475.
5. Hershman D, Weinberg M, Rosner Z, et al. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. J Natl Cancer Inst 2003;95:1545-8.

DOI: 10.1056/NEJMp2409329

Sickle Cell Trait, Inequity, and the Need for Change

Brian J. Carney, M.D., Maureen O. Achebe, M.D., M.P.H., and Richard L. Haspel, M.D., Ph.D.

Sickle cell trait (SCT) is a heterozygous carrier state defined by the inheritance of one sickle β-globin and one normal β-globin allele. It is usually benign. Manifestations of sickle cell disease (SCD), such as vaso-occlusive pain episodes, haven't been observed in people with SCT, although there is evidence of a small number of rare associated complications.[1] Nonetheless, because of misperceptions about risks, people with SCT in the United States may receive inequitable and potentially harmful treatment related to military service, participation in college athletics, and stem-cell transplantation.[2,3] SCT has also been used in troubling ways in forensic determinations of cause of death.[4]

Since in the United States, SCT is most common among people who identify as Black (occurring in 6 to 9% of Black Americans), such practices add to substantial inequities affecting this population. In the past several years, despite other efforts to reduce inequities in medicine, inequities related to SCT have been exacerbated.

SCT-related practices affecting members of the military and athletes generally stem from claims of a significant excess risk of rhabdomyolysis and death during physical exertion among people with SCT. A 2016 retrospective study that included nearly 50,000 Black U.S. Army soldiers, however, showed no increased risk of death associated with SCT. Although SCT was associated with an increased risk of rhabdomyolysis, this effect was similar in magnitude to that associated with tobacco use or having a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, as compared with a BMI of less than 25. It was smaller than the effect associated with recent use of a statin or an antipsychotic agent.[5]

Despite these data, U.S. military branches screen for SCT and single out people with the trait (but not those who smoke or use a statin). During basic training, to indicate that they have a medical condition, Air Force recruits with SCT are required to wear red dog tags, and Navy recruits wear a red belt.[2] We are unaware of an-