Duffy Status Assessment
In Clinical Trials

The American Society of Hematology strongly recommends requiring assessment of Duffy

There are differences in normal absolute neutrophil counts (ANC) by Duffy status. Duffy testing should be obtained for all patients in clinical trials that use ANC eligibility criteria or dose-modification parameters, or record neutropenia or febrile neutropenia adverse events. Duffy testing may allow for personalization of ANC eligibility criteria and dose-modification parameters as well as assessment of important endpoints like differences in dose-modifications, adverse events, and disease response by Duffy status. Testing for the Duffy antigen is low-cost and low-risk, and will allow for critical data analyses that may be practice-changing for clinical trial standards and personalization of treatment recommendations.

What is the Duffy null variant?

The Duffy antigen is found on erythrocytes and form a minor blood group ***(1)***. A single nucleotide polymorphism (SNP) causing a T to C substitution at rs2814778 in the gene ACKR1 results in the lack of expression of the Duffy protein on erythrocytes ***(2)***. This is called the Duffy null phenotype (Fy[a-b-]). This variant was likely a selective advantage as it is partially protective against infection with Plasmodium vivax ***(3)***. Accordingly, the Duffy null variant prevalence is highest in people with genetic ancestry from the African continent or Arabian Peninsula ***(4)***. Approximately 80-100% of people from West Africa and >50% of people from the Arabian Peninsula have the Duffy null phenotype ***(4)***. In the United States, 66% of people who self-identify of Black of African American are estimated to have the Duffy null phenotype as opposed to <1% of people with genetic ancestry from Europe or Asia ***(4,5)***.

How do you obtain Duffy testing?

Duffy status can be obtained by serology or genotyping. Serological testing is reimbursed at $12.70 by the Centers for Medicare & Medicaid Services (CMS). Any laboratory that can report a type and screen likely has the resources and technical skill to obtain Duffy serologies. However, significant improvements in Duffy testing (i.e. ability to electronically order testing and reporting of results in the electronic medical record) as well as provider education is needed at many centers. Genotyping can also be used but is often more costly and may be a send-out test in many laboratories. Genotyping is useful when samples can be batched or when analyzing biobank samples.

How does the Duffy null variant impact absolute neutrophil counts?

The Duffy null variant is closely associated with lower absolute neutrophil counts (ANC) as measured from the peripheral blood, but there is no excess risk of infection ***(6-8)***. One study reported healthy adults with the Duffy null variant have a median ANC of 2820/uL (IQR: 2088-3490) vs 5005/uL (IQR: 3675-5828) ***(5)***. A UK biobank study reports a mean ANC of 2820/uL (SD=1020) in Duffy null adults vs 4430/uL (SD=1410) in Duffy non-null adults ***(7)***. In these studies, approximately 20% of those with the Duffy null phenotype had an ANC<2000/uL ***(5,7)***. A Duffy null-specific ANC reference interval of 1210-1540/uL for adults has been published and is in use for clinical care ***(9)***. Efforts through the American Society of Hematology and the Doris Duke Foundation along with institutions across the United States are underway to verify Duffy null adult ANC reference intervals and build Duffy null ANC reference intervals for the pediatric population.

How are people with the Duffy null variant impacted by current clinical trial standards?

Decades of ANC reference intervals that do not reflect health for people with the Duffy null variant likely contributed to inequitable access to clinical trials.

- There is disproportionate ineligibility for clinical trials among Black patients due to restrictive hematological criteria like ANC thresholds ***(10,11)***.
- One study reported that 76.5% of phase III trial protocols from 2021-2023 of 5 cancer types had eligibility criteria that required ANC levels within the Duffy null variant reference interval (any ANC threshold >1200/uL) and 53.5% of trials recommended dose modifications within this range.
- Many people with the Duffy null phenotype have grade 2 neutropenia (ANC 1000-1500) by current Common Terminology Criteria for Adverse Events (CTCAE) at their healthy baseline.
- Remission criteria for many hematological malignancies may not be adequate for people with the Duffy null phenotype. For example, the International Workshop of chronic lymphocytic leukemia (CLL) includes an ANC of >1500 as part of the remission criteria which is above the lower limit of normal ANC for healthy Duffy null people ***(12)***. Another study showed that adults with the Duffy null variant with multiple myeloma undergoing CAR-T therapy had delayed ANC recovery (median, 68 vs 40 days; P =0.04), but without the negative corresponding risk for poor outcomes typically correlated with prolonged ANC recovery including severe infection (3.6% vs 7.3%; P =0.69) ***(13)***.

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What do we know about the impact of the Duffy null variant on outcomes to date?

Given the deficits in many current clinical trial designs, there are also differences in outcomes and medication dosing by Duffy status.

- A sub-analysis of the PALINA trial in women with breast cancer showed that patients with the Duffy null variant had higher rates of ANC<1000/uL (72% vs 23%) and more dose reductions (55% vs 8%) than patients who are Duffy non-null without any increased risk of febrile neutropenia ***(14)***.

- There are significantly higher rates of discontinuation of azathioprine for autoimmune conditions due to concerns about hematopoietic toxicity for Duffy null patients compared to Duffy non-null patients, even when adjusted by race (HR=2.61, 95%CI: 1.01–6.71, P=0.047) ***(15)***.

- Duffy null black children with acute lymphoblastic leukemia were given lower dose intensity of 6-mercaptopurine (6-MP) compared Duffy non-null children (0.83 [0.70–0.94] vs 0.94 [0.73–1.13]; P=0.013) ***(15)***.

These studies are compelling, but more research is needed to fully understand the differences in and consequences of clinical trial eligibility, dose modifications or discontinuation, remission criteria, neutropenia CTCAE, and disease response or survival outcomes by Duffy status.

What is already being done in clinical trials to account for the Duffy null variant?

Some trial protocols have already made changes in their eligibility criteria, dose-modification criteria, and/or planned endpoints to better account for variations due to the Duffy null variant.

- A protocol on CAR-T Cell Therapy for Desensitization in Kidney Transplantation (NCT06056102) has an eligibility criteria of ANC ≥ 1,800/μL but allows for ANC > 1,200/μL for patients with Duffy-null associated neutrophil count (DANC).

- SWOG 1803 (NCT04071457) in multiple myeloma changed dose modification guidance for Duffy null patients to hold lenalidomide when ANC is <750/uL instead <1000/uL.

- The Multiple Myeloma Research Foundation Horizon One Adaptive Platform Trial (NCT06171685) is allowing growth factor support before enrollment and obtaining Duffy status on all patients (either reported from screening for transplant work-up or obtained from banked specimens) to allow for sub-analysis by Duffy status.

- DETERMINATION 2 (recruitment active summer 2025) plans to require assessment of Duffy status in all trial patients, allow more permissive ANC criteria for eligibility and dose modifications for those with the Duffy null variant, and plans to analyze outcomes by Duffy status.

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