



Reconsideration of Reference Ranges: Duffy Absolute Neutrophil Count (DANC) October 2023

Background and Rationale

Approximately two in three people in the United States who are of African or Middle Eastern ancestry have the Duffy-null phenotype, caused by a genetic variation in *ACKR1*, and defined as the non-expression of the Duffy antigen on red blood cells. This phenotype results in a clinically insignificant lower absolute neutrophil count (ANC) compared to the commonly used reference population which is often established from individuals of Asian or European descent of whom nearly 100% are Duffy non-null. Those with the Duffy-null phenotype have lower circulating neutrophils than Duffy non-null individuals, but similar total body neutrophil counts. Thus, individuals with the Duffy null phenotype have no increased risk of infection but are often incorrectly labeled as having neutropenia—a disease state that increases risk of infection or suggests disordered bone marrow function. This can result in unnecessary, expensive, and invasive testing, delayed or discontinued chemotherapy or other critical medications, exclusion from clinical trials, and other negative consequences.¹ This lower circulating neutrophil count frequently observed among those of African and Middle Eastern descent was previously referred to as “benign ethnic neutropenia” (BEN), but the preferred language is Duffy-null associated neutrophil count (DANC).²

Recent publications³ have highlighted the dangers of an incorrect diagnosis of neutropenia and the need to develop new ANC ranges that reflect populations with DANC. Recently, the experience developing and utilizing a Duffy-null specific ANC reference range at a single academic center was reported⁴. The lead authors report significant interest from other institutions in replicating this novel reference range within their hospital systems.

This creates an opportunity for ASH to lead a collaborative project to address this health equity issue. Such a project would lead to a better understanding of the impact of Duffy-null status and its implications for clinical decision making. The proposed project would include interventions with health care systems, health care professionals, and the affected populations.

Specific Goals

The overall goal for ASH’s proposed project is ensuring that ANC reference ranges reflect states of health for all patients which is foundational to ensure that all people, especially individuals with DANC, receive optimal care. This will be accomplished through three distinct aims: (1) empowering selected health care systems to set new ANC ranges for individuals with the Duffy null phenotype and sharing information about their efforts; (2) educating health care professionals about DANC; and (3) beginning interventions on a systems level such as advocating for lower ANC thresholds for clinical trials and integration of Duffy testing into Phase I and Phase II trials.

Methods or Process to Achieve Goals

The overarching effort is structured as a multifaceted approach targeting health care systems, health care professionals, clinical trialists and their funding sources, and patients. Undergirding this project will be a leadership team composed of key opinion leaders, project managers, and ASH staff. This group will be charged with overseeing activities in support of the three key goals outlined above.

¹ Merz, L., Achebe, M., - [When non-Whiteness Becomes a Condition](#)

² Merz, L., Story, C. M. et al, - [Absolute Neutrophil Count by Duffy Status Among Healthy Black and African American Adults](#)

³ Dickson, Alyson L. et. al, - Race, Genotype, and Azathioprine Discontinuation: A Cohort Study

⁴ Merz LE, Osei MA, Story CM, et al. [Development of Duffy Null–Specific Absolute Neutrophil Count Reference Ranges.](#)

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This request for proposals is focused specifically on the first aim of the overall work: Supporting Health Care Systems (HCS).

Using a collaborative approach, ASH will support HCS change by supporting a selection of HCS to validate new Duffy null adult ANC reference ranges and/or create new Duffy null pediatric ANC reference ranges. ASH will also work with selected HCS to unveil the clinical ramifications relevant for people with DANC. It is important to know that solutions to this issue will be locally developed as individual hospitals have their own policies, needs, and preferences for developing or validating reference ranges and that a commitment to central IRB and data sharing will facilitate development of replicable approaches and broader implementation. It is expected that this work will lead to a gathering consensus that would influence the adoption of the new reference ranges by non-participating health care systems. HCS approved to participate in this project are expected to:

1. Participate in an 16-month project to reconsider adult and pediatric ANC reference ranges for individuals with DANC as well as clinical ramifications and best practices for individuals with DANC.
2. Commit to centralized IRB and data sharing to facilitate implementation.
3. Meet for two in-person collaborative meetings to launch and conclude the effort.
4. Participate in ongoing teleconference meetings to advance work and share learnings.
5. Develop a data-informed understanding of the clinical ramifications of DANC.
6. Provide generalizable and specific replicable approaches (case studies), lessons learned, and themes to be disseminated broadly.

TIMELINE

Dates	Action
October – Nov. 2023	Health Care System (HCS) RFP and Selection Process
Nov. 30 2023	Application Deadline
Dec. 2023 – Jan. 2024	Review and Selection
Feb. – April 2024	Notification, Terms and Conditions, Contracting and IRB
May 2024 – Mar. 2025	HCS Implementation with On-going Collaboration Calls and PM Virtual Site Visits
Mar. - May 2025	HCS Lessons Learned Final Reports Due
June 2025	HCS Convening Meeting #2 Learning Community and development of case studies.
June 2025	Development of final report and future directions

REQUEST FOR PROPOSALS

Health Care Systems interested in participating in this effort are required to submit a proposal in response to this RFP. Proposals will be competitively reviewed with consideration for institutional support, reach, resources provided in support of success, commitment to participate in central IRB and data sharing, and representation of populations impacted by the proposed health care system change.

Application Deadline

Applications must be received at ASH by **11:59PM** Pacific Time on November 30, 2023, utilizing ASH's online application system available on ASH's website on October 31, 2023. Emailed submissions will not be accepted.

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Technical difficulties with the online application system should be directed to ASH staff at: diversity@hematology.org.

APPLICATION INSTRUCTIONS

To submit a complete application, applicants need to enter information directly into ASH's online application platform. The following instructions provide details about information that needs to be entered. Log into the ASH online application system available at <https://sso.hematology.org>. Create an ASH account if you do not already have one. A list of ASH awards will be displayed. Select “DANC - Health Care System Application”.

APPLICATION

- **Health Care System (HSC) Details (e.g., Name of Institution, ASH (Sales Force/Personify) ID)**
- **Multi-PI Details: Hematology/Oncology Project PI (e.g., Name, ASH ID)**
 - Upload biosketch
- **Multi-PI Details: Pathology Project PI (e.g., Name ASH ID)**
 - Upload biosketch
- **Primary Contact: Administrative Staff Responsible for Application**

Project Description

Provide a detailed description of how the institution intends to achieve the key goals of this project including an institution-driven, multi-disciplinary project to reconsider ANC reference ranges for individuals with Duffy null phenotype. Please describe:

- Population: Adult, Pediatric, or Both
- Anticipated number of samples (number and time to complete; e.g. 60 over 3 months):
 - Adult--Validation of reference range (typically 40-60 samples, flexible per institutional standards). Strong preference for each HCS to validate and publish their own adult Duffy-null ANC reference ranges.⁵
 - Pediatric—Development of new reference ranges (typically 200 samples per age category). Institutions are NOT expected to obtain all samples needed for development, but rather will plan to pool samples from other institutions to develop new reference ranges by age categories. Please provide pediatric age categories for ANC reference ranges utilized at your institution.
- Proposed collection method: Recruiting healthy participants from the community, identifying eligible individuals from primary care office or outpatient surgery center, etc. Please note that patients must be screened (chart review and/or interview) and found to be in reasonable health without conditions or medications that impact neutrophil count to be included in the study.
- Consent Approach: Verbal, Written, Both, None. Must agree to centralized IRB.
- Sample source: Residual blood versus fresh sample for complete blood count and Duffy testing.
- Duffy Typing Method: Available methods and preferred methods at your institution (genotyping versus phenotyping, in-house vs send-out) as well as approximate cost of available and preferred methods.

⁵ Merz LE, Osei MA, Story CM, et al. [Development of Duffy Null-Specific Absolute Neutrophil Count Reference Ranges](#).

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- Statement of agreement to participate in:
 - required meetings,
 - the development of best practices around DANC,
 - generalizable and specific replicable approaches (case studies), lessons learned, and
 - themes to be disseminated broadly.

Word Limit: 1000

Health Care System Description and Demographics

Describe the full HSC that will be included in and impacted by the development and implementation of the new reference range (e.g., multi-affiliate institution, community-based care organizations within the system). Include scope and demographics of the patients served by the HSC, including inpatient and outpatient numbers as well as description of race/ethnicity, age, levels of insurance/underinsurance, and rural/urban/suburban setting.

Word Limit: 400

HCS Support and Resources

Institution Leadership Letter of Support

Describe the resources that are committed by the health care system to ensure project success. This includes:

- Commitment to advancing principles of diversity, equity, and inclusion in general and health equity specifically.
- Engagement in the learning community and development of examples of replicable approaches.
- Commitment to operationalize results of the multi-disciplinary approach (inclusive of changes to EMRs).
- Access to resources needed for success such as laboratory testing, resources to support recruitment of consented participants.
- Commitment to prioritize and efficiently pursue institutional IRB approval and participate in centralized IRB through Western Copernicus, including anticipated local IRB review and approval timelines as well as intended actions to facilitate efficient legal review and point of contact responsible for the effort.
- ASH plans to provide a central IRB through Western Copernicus and Central IRB to facilitate the collection of de-identified data for this project. Please indicate expected local IRB level of review.
 - No local IRB requirement with reliance on Central IRB through WCG
 - Administrative review only with reliance on Central IRB through WCG
 - Full local IRB review required
- Agreement to participate in data sharing for purposes of publication and dissemination including responsible party.
 - Adult population: sharing consolidated de-identified results including sample population statistics (age, race/ethnicity, sex), Duffy-null prevalence, ANC reference range, and other relevant data to support development of best practices and case studies.
 - Pediatric population: Individual HCS will not be expected to collect 200 Duffy null samples in each pediatric age category. Rather, we will pool the pediatric data from multiple institutions to develop new pediatric reference ranges. Thus, HSC must agree to participate in consolidated sample collection and range development plan to adopt their new reference ranges at their HCS, and share consolidated de-identified results including sample population statistics, reference ranges developed and other relevant data to support development of best practices and case studies.

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Hematology and Pathology Letter of Engagement

Provide a brief letter that describes the relevant areas of the institution that will collaborate in this multidisciplinary project. Please specifically name a leader in patient-facing care (hematology/oncology, pediatrics, medicine) and a leader in pathology (blood bank, clinical pathology, lab director) who have communicated and have agreed to work on this project collaboratively for the HCS. The letter should include a brief description of the available methods to obtain blood samples from patients and obtain Duffy testing as well as affirm the preferred institutional approach (e.g. residual blood with in-house phenotyping; fresh sample for send-out to [company name] for genotyping) and commitment to provide needed resources inclusive of laboratory tech time, tests, etc.

Page Limit: 2 Pages Upload Letter

Resources

Provide an enumeration of the resources (staff, equipment, etc.) that will be committed to ensure the success of the project. Identify other existing, and potentially untapped, unique resources and/or opportunities that leverage novel or established intra- and interinstitutional collaborations.

Word Limit: 250

Project Funds and Budget Narrative

Awarded institutions will receive a stipend (\$20,000 for adult only reference range work and \$30,000 for reference range work that includes pediatric populations) to cover the anticipated hard expenses associated with the project (e.g., recruiting individuals to participate, lab test kits). For pediatric populations, because of the intention to pool samples, the minimum number of required samples by participating institutions is 200 (in total across all age brackets). Age brackets will likely be set as follows: 0-3 months, 3-6 months, 6mo to 5 years, 5-12, and 12-18 years. Please note that age at blood draw data will be reported to allow institutions to consolidate data using alternative age brackets if needed. Institutions that exceed the minimum pediatric requirement will be eligible for an increased stipend. Indirect costs are ineligible for this project. Please complete the [budget template](#) and provide a narrative for the budget line items.

Word Limit: 250

Institutional Commitment to Matching and Supplemental Funding

Institutions are invited to share a narrative of the anticipated uncovered costs that they will cover as a function of participating in this project.

Word Limit: 250