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Donna Pickett, RHIA, MPH
Chief, Classification & Public Health Data Standards
National Center for Health Statistics
HHS/Centers for Disease Control and Prevention
3311 Toledo Road
Hyattsville, Maryland 20782

Re: ICD-10-CM Code Request for Duffy Phenotype

Dear Ms. Pickett,

The American Society of Hematology (ASH) requests the creation of new ICD-10-CM codes to describe the Duffy phenotype. ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases.

The association between lower absolute neutrophil count (ANC) and African or Arab ancestry has been well established since the 1970s, and then genome wide association sequencing in the 2000s established a genetic cause. Homozygosity for a single nucleotide polymorphism (SNP) rs2814778 in the promoter region of the *Duffy antigen receptor for chemokines DARC* [also known as *atypical chemokine receptor ACKR1* (rs2814778)] gene produce the Duffy null or Fy(a-b-) phenotype which is the driver of the lower ANC observed for decades in those of African and Arab ancestry.[1] The Fy+ allele at rs2814778 is found in 99.3% of Europeans but only 0.2% of Africans.[1] Further, the Fy(a-b-) phenotype is found in <1% of those with White or Asian ancestry but is very common in individuals from Sub-Saharan Africa (80-100%) and the Arabian Peninsula (50-70%).[2-6] Homozygosity of the SNP at rs2814778 is very strongly associated with lower neutrophil count ($p = 4.09\times10^{-53}$), and association of lower ANC with race is abrogated when accounting for Duffy status.[7] A prospective study in the United States among healthy Black individuals presenting for primary care found no difference in ANC among Black Duffy non-null individuals than the institutional reference range, but Black Duffy null individuals had a significantly lower median ANC (2820 cells/uL).[8] Additionally, nearly a quarter of healthy Duffy null individuals had ANC below the institutional lower limit of normal.[9] This normal, healthy variant of lower circulating neutrophils is now referred to as Duffy-null associated neutrophil count (DANC).[8]

Thus, the current ANC range in the United States is neither inclusive of nor accurate for a significant percentage of individuals with the Fy(a-b-) phenotype. An accurate ANC reference range is foundational to adequate care.

Inaccurate reference ranges lead to over-testing, unnecessary referrals, inappropriate medication discontinuation, and delays in chemotherapy administration.[10-12] Additionally, ANC is used to assess eligibility and toxicity grading in clinical trials: inaccurate ANC reference ranges impact enrollment and lead to reporting of false "adverse events."[13,14] In a study examining potential barriers to participation in prostate cancer clinical trials, 47.2% of trials required an ANC of 1500 or higher for participation.[15] A recent study recommended a new ANC reference range of 1210-5390 cells/uL for those with Duffy null phenotype, significantly different than the ANC reference range of 1900-7500 cells/uL for all other individuals.[16] This hospital system currently publishes the Duffy null range as a comment below the institutional reference range as there is no simple demographic status or ICD-10-CM code to encode into an electronic medical record to call up the Duffy null-specific reference range like there is, for instance, for sex-specific hemoglobin reference ranges. Additionally, there is no ICD-10-CM code to associate with Duffy testing that would allow for accurate documentation, allay clinical concerns and, importantly, prevent unnecessary further testing. Most clinicians use D70.9 (neutropenia, unspecified); this is not, however, an accurate diagnosis code to use when reporting the existence of the Duffy null phenotype as this implies an abnormal state as well as assumes that all Duffy null patients will have an ANC below traditional neutropenia threshold (<1500 cells/uL) which is only seen in ~10% of Duffy null patients.

There is much evidence that shows that Duffy null status is associated with lower circulating neutrophil counts without any known negative clinical consequences. Several studies have indicated that the Duffy-null genotype causes a change in the morphology of neutrophils, facilitating their migration into tissues, thus reducing the number of circulating neutrophils and causing an apparent neutropenia.[17] This mechanism is thought to be clinically benign because the production and functioning of neutrophils is not reduced and so their ability to fight infection remains unchanged.[18] The importance of this is that it is an "apparent neutropenia" and not at all a true neutropenia, which is covered by the existing ICD code.

Duffy is an antigen on the red blood cell membrane, easily tested and documented, and analogous to the major blood types or Rh status. **ASH recommends and proposes adding codes for Duffy phenotype status within the Z code section paralleling how Rh status is listed. We request codes for all four phenotypes, specifically:**

- Duffy null [Fy(a-b-)]
- Duffy a positive [Fy(a+b-)]
- Duffy b positive [Fy(a-b+)]
- Duffy a and b positive [Fy(a+b+)]

Specific Z codes will help document the Duffy status for individuals in a consistent and longitudinal manner. An ICD-10-CM code will also be critical for proper reimbursement, accurate documentation, appropriate clinical care and management, and augmented ability to conduct research. For prospective clinical trial participants, it will permit inclusion of diverse populations in research, currently excluded by inappropriate eligibility criteria. For patients, it will decrease duplicative testing and permit medication (e.g., chemotherapy) administration consistent with need. In the United States specifically, it will help

redress an underappreciated cause of health disparities. Additionally, an ICD-10-CM code will be the bedrock for the development of electronic medical record advanced functions, providing an accurate ANC reference range that automatically populates based on Duffy status.

Tabular Modifications:

Z00-Z99 Factors influencing health status and contact with health services.

Z67.A Fy(a-b) Duffy Phenotype

Duffy null [Fy(a-b-)]
Duffy a positive [Fy(a+b-)]
Duffy b positive [Fy(a-b+)]
Duffy a and b positive [Fy(a+b+)]

ASH appreciates your consideration of this request. A list of references is provided below. Should you have any questions, please use Suzanne Leous, Chief Policy Officer (sleous@hematology.org), as your point of contact.

Sincerely,

Robert A. Brodsky, MD
President

References

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