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Invisible Infrastructure in Haematology: Neutrophil Reference Ranges and the Duffy-null Phenotype

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Historically, the term benign ethnic neutropenia was used to describe absolute neutrophil counts (ANC) <1500/μL without an increased risk of infection, which was commonly observed in people of African, Arab or Yemenite Jewish ancestry. In 2008, researchers showed that the mechanism is a polymorphism in the Duffy antigen receptor for chemokines (*DARC*) gene, which results in red cells lacking Duffy antigens.[1] Individuals who have the Duffy-null phenotype have reduced susceptibility to *Plasmodium vivax*, and the polymorphism is found more frequently in individuals whose ancestors lived in malaria-endemic regions such as Sub-Saharan Africa and the Arabian Peninsula. In June, Dr Lauren Merz and colleagues published ANC ranges for individuals who are Duffy-null.[2] Here, she discusses with *HemaSphere* Scientific Editor, Stephen Hibbs, the relevance of this work, the limitations of ethnicity as a concept, and other unquestioned practices within haematology.

SH: Could you explain why it matters to have Duffy-null specific neutrophil ranges rather than assuming someone has "benign ethnic neutropenia?"

LM: It matters because we want to make sure that we're giving the best possible healthcare and the most personalized healthcare to all individuals that we serve. It is especially important in this case because not recognizing Duffy-null associated neutrophil counts mainly impacts minoritized populations – people that haven't always been served as well as they should be served. I also think it's important for the integrity of medicine in general: the terminology "benign ethnic neutropenia" clearly blurs that line because we are calling something a disease simply because it's different than normal values for White males. And that's just unacceptable on its face.

Laboratory medicine is the foundation of everything that we do in medicine. And if we don't have an accurate reference range, everything else is broken down the line: clinical trial eligibility, describing someone as having disease or not, medication thresholds for when we withhold and when we can give – everything is broken because we have this crumbling foundation.

SH: In a world with a different history and where the textbooks were written in another location, I wonder if we might have had the term "benign ethnic neutro*philia*" – with a different group of individuals excluded from trials or medication, or getting unnecessary antibiotics and spurious CRP testing, because a different group of people were seen as "normal" and formed the reference range.

Haematology practice has often assumed neat differences between discrete ethnic groups. Many people assume that sickle cell disease (SCD) is solely found in people of African ancestry and they only look for it in those who they deem are "at risk," often on the basis of skin tone. But SCD is found in people of all skin tones and who have a vast range of geographical ancestry, though some ancestries are associated with higher prevalence.

There are some comparable issues in deciding which individuals require Duffy testing – how would you approach this?

LM: I think we should think about it similar to the work-up for thalassaemia. We think about testing for thalassaemia or thal-trait if we are working up a microcytic anaemia. The diagnostic schema we learned in medical school tells us that thalassemia is typically found in individuals from Africa, South/South-East Asia and the Mediterranean basin. But it doesn't mean someone who has the appearance of or identifies as predominantly having English or German heritage couldn't have thalassaemia. If we've ruled out other more likely causes of microcytic anaemia, most of us would still test for thalassemia regardless of patient ancestry. I have a similar approach to understanding lower neutrophil counts in an otherwise healthy individual. Suspicion is higher for the Duffy null phenotype in those who endorse African or Middle Eastern ancestry, but I may still send it in those who identify as Asian or White. I have

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a low threshold to obtain Duffy testing because it's cheap and it's easy and then you have a clearer answer to your hypothesis.

SH: Can your published reference be used by all hospitals for their Duffy-null patients? And if you do confirm that someone is Duffy-null, how should this affect treatment decisions?

LM: Yes! We have a grant with the American Society of Hematology and funded by the Doris Duke Charitable Foundation. We're working on partnering with different healthcare systems around the country to accelerate the dissemination and adoption of these Duffy-null specific ANC reference ranges. After this process is completed and the experience disseminated, we hope that then other laboratories independently without our funding will also adopt Duffy-null specific reference ranges. We hope that from a year from now we will have more hospital systems that are using Duffy-null specific reference ranges for adults. We are also working on developing paediatric reference ranges. Since no one has published paediatric ranges yet and there are more age subdivisions for ANC in this population, it'll probably be more like 2 or 3 years before we have enough samples.

Once we have widely accepted Duffy-null ANC reference ranges, then we'll hopefully be able to address some of the bigger and more common questions that I get: what do we do with clinical trial eligibility criteria? What do we do with medications that we dose based on ANC? How low is too low? All questions where we have answers based on expert opinion, but no real strong data to say anything definitive. We need to start at the foundation of understanding normal for individuals with the Duffy-null phenotype first. And I can't give an answer about the third floor if we don't even have a solid foundation yet.

SH: I recently read a paper that startled me with its first sentence: "This article is in a way a call to study boring things."[3] The author, Susan Leigh Star, encourages research on infrastructure to understand how institutions and organisations work: things like building architecture, how phone books are organised, or how sewers are designed. These things are invisible until they stop working – and they stop working sooner for some than others (think of someone negotiating an old hospital building in a wheelchair, for instance). She notes how infrastructure becomes invisible in science: the "process by which a scientific fact is gradually stripped of the circumstances of its development, and the attendant uncertainties, and becomes an unvarnished truth."[3]

This might be a good lens to understand the way that reference ranges operate – they are invisible infrastructure that has over time become "an unvarnished truth," stripped of historical circumstance. At first glance, studying reference ranges might seem dull, but they may tell us a great deal about why some patients are served better than others. Does this resonate, and have you seen any other examples of taken-for-granted infrastructure in haematology?

LM: Yes, this fits so well! A lot of these reference ranges including ANC were built by and for White men in the early 1900s. If and when we re-evaluate them, we often use a convenience sample from people who work in the lab. In the United States, the majority of these healthcare workers identify as White or Asian which skews heavily towards Duffy positive or Duffy heterozygote phenotypes.

The example of how you don't really notice that a building isn't built for you until you're in a wheelchair – it's the exact same thing for Duffy-null individuals. A person presents for routine care and they're told, "well, you're totally healthy, but your neutrophils are low," and they get sent to haematology and are told they may need a bone marrow biopsy. Our haematology departments are often housed within the cancer centres so many patients are under the impression that maybe they have leukaemia, maybe they don't, we don't really know. Seeing a couple of individuals go through the trauma of all of that made me look at the fundamental infrastructure, recognize where it isn't working for certain groups, and do my best to update our system to make that invisible infrastructure work for everyone.

Now I'm asking myself: what else is broken? There's a lot of stuff that we need to re-evaluate. The one I'm getting more into right now is iron deficiency and haemoglobin levels. Why are there different reference ranges for men and women? If you look at haemoglobin by age, you have similar haemoglobin levels for boys and girls up until menarche, then they significantly separate, and then when you look at older people after menopause, you see those lines come back together. So what is happening during those reproductive years? We've assumed it is differences in hormones – it may be, but has anyone really looked at blood loss and the pandemic of iron deficiency in premenopausal women and how that may be impacting haemoglobin reference ranges?

What else have we assumed is gospel, fundamental, something that is unshakable – that really is harming people?

AUTHOR CONTRIBUTIONS

LM and SPH devised the initial concepts. SPH wrote the first draft and LM edited the final draft. All authors approved the final article.

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