We are living in an age in which we are witnessing an explosion of new therapeutic interventions based on new therapeutic tools including targeted antibody therapy, RNA silencing, personalized immune cell therapy, and gene editing to name a few. At the same time, the specificity of these therapies is allowing clinicians to identify new disease subtypes. As Caspard et al1 investigate in this issue, individual characteristics may influence baseline eosinophil counts in patients with asthma and chronic obstructive pulmonary disease. Increasingly, we are using and seeking to identify biomarkers that will allow us to administer the likely most beneficial intervention to the correct patient. This approach has been broadly termed “Precision Medicine.” We have witnessed this process in the area of asthma as well.

The development of biologics that target type 2, referred as T2, inflammation has changed the face of the treatment of severe asthma. Administered to patients with recurrent exacerbations and evidence of T2 inflammation, these agents reduce the population exacerbation rate by more than half and in many cases produce significant reductions in symptoms.

Are there biomarkers that identify patients with T2 inflammation responsive to these agents? In the case of drugs that target the IL-5 axis (currently mepolizumab, reslizumab, and benralizumab), peripheral blood eosinophils appear to be among the best biomarkers available. In the case of the drug that targets the IL-4/IL-13 axis (dupilumab), either eosinophils or fractional exhaled nitric oxide identify patients responsive to this therapy. Based on studies with these agents, minimum cutoffs of 150 to 300 eosinophils/μL have been proposed to identify patients “eligible” to receive these therapies (except in cases of patients chronically on oral corticosteroids where no minimum level is generally required).3 Using a cutoff of 300/μL, the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program data suggest that less than 40% of adult patients and just more than 50% of children with severe asthma would meet such criteria.3

Thus, it appears that asthma has entered the era of precision medicine. Is this enough? Are we now correctly identifying patients with severe asthma likely to respond to therapy and avoiding needless therapy to those least likely to respond by using blood eosinophil cutoffs for these medicines? The article in this issue of the journal by Caspard et al1 suggests that we may need to “personalize” our precision medicine cutoffs. Examining blood eosinophil numbers in the National Health and Nutrition Examination Surveys from 2001 to 2016, they identified about 2400 patients with physician-diagnosed asthma or chronic obstructive pulmonary disease. As expected, blood eosinophil counts were higher in patients with asthma than in patients with chronic obstructive pulmonary disease or controls. However, most interestingly as it relates to personalizing treatment of asthma, they found that blood eosinophils varied by demographic groups. Blood eosinophil counts were higher in men and those with higher body mass index. Most importantly, they found that blood eosinophil counts were lower in black individuals by 15% to 20%.

What do these findings mean as we try to apply precision medicine to decisions about biologics in asthma? Do biomarkers have the same significance regardless of demographic group? Or, considering the excess morbidity and mortality from asthma in blacks, is it possible that blacks with eosinophil counts lower than the 300/μL mark might be responsive to biologic therapy? Unfortunately, we may not be able to look to the studies that have been done with the currently existing agents to answer this question in blacks due to low levels of enrollment of this population in these clinical trials.

Another demographic group, not addressed by this study, is children. Airway eosinophilia and peripheral blood eosinophil numbers can be notably noncongruent in children. No large-scale studies of body mass index and severe asthma blood eosinophil numbers have been performed in children, leaving conflicting data reported between small studies. Variables of personal health such as race and sex and their influence on biomarker cutoffs are equally understudied in pediatric severe asthma. This is on a backdrop of pediatric normative values for peripheral eosinophil counts that are highly variable between as little as 2-year age difference.4 For example, the eosinophil cutoff for mepolizumab is noted to be greater than or equal to 150/μL at study entry or greater than or equal to 300/μL for children 6 years or older. These values stem from the DREAM (Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma) study, which was performed in children 12 years or older.4 From age 6 years to age 8 years the normal blood eosinophil count can vary by as much as 90 eosinophils/μL.4 Pediatric eosinophil biomarker studies in different age groups may find that a more personalized approach is needed.
to predicting best response in younger children with severe asthma.

This Caspard et al study suggests that even though we are approaching better medicine through the use of biomarkers, we may need to do larger studies in specific populations to validate our “precision” cutoffs. Studies need to be performed to determine whether a patient’s personal demographic information may influence which eosinophil level is best predictive for improvement when using biologic therapy in severe asthma. Precision medicine may ultimately require more “personalization.”

REFERENCES