

"Asthma" or "Asthma Spectrum Disorder"?



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The World Health Organization defines asthma as a "disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person," which is due "to inflammation of the air passages in the lungs..."¹ Asthma diagnosis is usually made on the basis of patient-reported symptoms such as wheezing, shortness of breath, chest tightness, and cough, coupled with the evidence of variable expiratory airflow limitation. Notable in their absence in most definitions and diagnostic algorithms, and most asthma management guidelines, is consideration of the mechanisms underlying clinical presentations (apart from a broad reference to airway inflammation). However, asthma is multifactorial and cannot be explained by a single underlying mechanism. There is a plethora of evidence that this condition that we agreed to call asthma comprises a spectrum of disorders that are underpinned by different mechanisms (often called asthma endotypes²). However, although there is a general consensus that there are different asthma endotypes,³ there is little agreement on what these are or how best to define them.⁴ Data-driven methodologies have been used to this purpose, with inconsistent results.⁵ These inconsistencies are partly because the number and type of asthma subtypes identified by data-driven methods are influenced by the choice of algorithm, as well as the sample size, age, and follow-up frequency.⁶ In the current issue of this journal, Fitzpatrick et al⁷ applied latent class analysis to more than 2500 well-characterized children with mild to moderate persistent asthma and identified 5 latent classes that differed primarily in allergic sensitization and lung function patterns. Children in the class with poorest asthma control (9.4% of the study population) were characterized by the multiple sensitization and partially reversible airflow limitation, and had the highest blood eosinophils, and high total serum IgE. Children in this class had more exacerbations than those in any other class. Despite suboptimal asthma control and relatively diminished lung function, 41% of children in this class were not receiving controller therapy. The largest class (35.7% children) was characterized by multiple sensitization, but reversible airflow limitation. Two classes included children with normal lung function, either with

multiple sensitization (27.6%) or with lesser sensitization (15.0%). The final class was that of the lesser sensitization with reversible airflow limitation (12.1%), with most children with no sensitization or monosensitization, but with high tobacco smoke exposure. The class membership probability was reassuringly high for all participants,⁷ which contrasts the pooled analysis of 5 birth cohorts that has shown that more than 10% of patients cannot be assigned to a specific latent class with high certainty.⁸ Importantly, although the study population comprised patients with mild/moderate asthma, asthma exacerbations were observed in each of the latent classes.⁷ This is consistent with recent population-based analysis that deployed machine learning to characterize 2 longitudinal trajectories of asthma exacerbations throughout childhood (infrequent and early-onset frequent exacerbations), and that also identified a subgroup of patients with mild asthma, with good symptom control and normal lung function, who experienced frequent exacerbations.⁹ Another study that applied data-driven methods to 4 domains of asthma (age of onset, sensitization, severity, and exacerbations) also described 5 clusters,¹⁰ which were similar to those reported by Fitzpatrick et al.⁷ Of interest for clinicians, in all these studies children with varying asthma severities and with exacerbations were present in each cluster, suggesting that "severe asthma" is not a unique endotype, but a severe end of the spectrum of different asthma endotypes. In all studies, markers of type 2 inflammation were associated with poorer outcomes.⁶⁻¹⁰

Despite major ongoing efforts to disaggregate asthma, the reductionist view of asthma as a single disease is still the norm in clinical practice and most research studies, and underpins most asthma management guidelines. This is one of the key barriers preventing genuine advances toward personalized treatment.^{3,4} The current approach to management is focusing on treating the diagnosis or "asthma disease," rather than treating the pathological mechanism that causes ill health in an individual patient, and for most physicians, the primary goal is the treatment of symptoms. A direct consequence of such approach is that patients with multiple asthma subtypes are forced into a single diagnostic category for empirical treatment.³ Regulatory approvals for asthma therapies are mostly based on randomized controlled trials focused on relatively short-term improvements in clinical indices, such as symptoms scores, lung function, or airway hyperreactivity. Group mean data are often used to summarize and compare the effects of investigational medicinal products (active ingredient or placebo, or one active treatment with another), and the results of such trials, and systematic reviews thereof, constitute the backbone of evidence-based medicine. However, there is no such thing as a "mean asthma patient" who would respond equally and consistently to a prepackaged "average asthma treatment plan." Although we recognize that we have to shift our attention from treating the disease toward treating the patient, when discussing personalization the focus of the attention is mostly on patient-reported

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outcomes and on consideration of issues that are important to the individual patient when deciding how to proceed with any intervention. For example, the Global Initiative for Asthma Guide suggests that asthma management should be customized to the individual, and that personalization should take into account symptom control, phenotypic characteristics, the risk factors for exacerbations, and patients' personal preferences including the cost of available medications.¹¹ However, although all these issues are undeniably important, there is much more to personalized management than these relatively narrow perspectives. One key aspect and a prerequisite for delivering a truly personalized approach in asthma is the understanding of pathophysiological mechanism(s) that give rise to symptoms in an individual patient, and the ability to use this knowledge to deploy mechanism-based treatment(s).¹² That is, only a move away from diagnosis-based or symptom-based toward mechanism-based treatment will enable a genuinely personalized approach. Such approach recognizes that drug efficacy and safety vary between groups of patients, and uses biomarkers to facilitate targeted prescribing, with the aim of improving the benefit/risk ratio of treatment. Personalized medicine requires that genuinely mechanism-based treatment are available or can be developed.³ Oncology has been at the forefront of the development and implementation of mechanism-based personalized medicine, in part because most of the cancer drugs have side effects, and the treatment is often very expensive. We now must follow the suite to help the translation of evidence-based medicine to a specific patient.

So, can data-driven methods help identify meaningful phenotypes for the purpose of personalized treatment? Although the application of novel analytical techniques to patient and birth cohorts may provide pointers to mechanisms, no single data source or methodology can uncover the complex mechanisms underpinning disease heterogeneity. Without careful mechanistic studies in human and animal models, we will not be able to develop novel mechanism-based treatments or target the existing ones to individual patients to improve outcomes. We must therefore move toward a more integrated approach, wherein cross-disciplinary collaborations ensure rigorous scientific scrutiny and interpretation of findings.¹²

To conclude, one of the key areas of asthma research is to understand its heterogeneity and facilitate the provision of personalized, mechanism-based treatments, for the benefit of our patients. But there is a broader picture here: as a community, we must remove the divisions separating clinical research, basic science, and data science. We must abolish the artificial dichotomy of data-driven hypothesis-generating *versus* hypothesis-driven approaches. This effort may ultimately result

in a change in taxonomy of obstructive airway diseases to better reflect underlying mechanisms. The study by Fitzpatrick et al⁷ demonstrates that asthma encompasses a range of linked conditions. Until the time comes when we have discovered and genuinely understood asthma endotypes, we should consider categorizing asthma as a spectrum, and use the term "asthma spectrum disorder," which is better suited to the current state of knowledge than the term "asthma."

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