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On behalf of all the authors

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## The Visible and Invisible Faces of the Iceberg of Type 2 Asthma

*To the Editor*:

We read with great interest the review article by Dr. Wenzel (1). The author has well illustrated the importance of the asthma phenotype and endotype, and biomarkers and the role of advances in this area in biologically targeted therapies, especially in type 2 (T2)-high severe asthma. In this report, the author stated that integrated approaches, including clinical and molecular phenotyping, regarding responses to biological therapy significantly improved our understanding of phenotypes and even endotypes of severe asthma (1). We would like to thank Dr. Wenzel for her contribution to the literature with such a valuable review. We also would like to share our opinions on this report.

In clinical practice, inexpensive and easily accessible biomarkers and observable clinical conditions are used for the T2 asthma phenotype, which can reflect the T2 asthma endotype. We can think of it as the visible side of an iceberg. The Global Initiative for Asthma main report defined the T2 asthma phenotype by one or more of the following features: skin prick test against aeroallergens and/or specific IgE positivity, blood eosinophilia, sputum eosinophilia, fractionated exhaled nitric oxide elevation, and oral corticosteroid dependence (2).

The association of phenotypes of asthma, which is quite heterogeneous, with cellular, molecular, immunological, and pathophysiological mechanisms is called endotype (3, 4). We can think of it as the invisible side of an iceberg. T-helper cell type 2 (Th2) and IgE, and innate lymphoid cell 2 (ILC2) and IL-5–IL-13 pathways, play a role in the T2 asthma endotype (5, 6). In the Th2 and IgE-dominant subendotype of the T2 asthma endotype, in the presence of coactivators such as alarmins (TSLP, IL-33, and IL-25) released from the epithelium, Th2 cells of the adaptive immune response are stimulated by dendritic cells, and as a result, they produce IL-4, IL-5, and IL-13 (5, 7). IL-5 is an essential cytokine for the proliferation, survival, maturation, and activity of eosinophils. Both IL-4 and IL-13 induce IgE switching and IgE synthesis by B cells activated by $CD4^+$ T cells. The allergen-specific IgEs lead to mast cell activation by binding to the FcεR1 receptors on mast cells, thus revealing early- and late-phase allergic inflammation. In addition, these cytokines contribute to the migration of inflammatory cells to the airway, bronchial hyperreactivity, and airway remodeling (5, 7). In the ILC2-dominant subendotype of the T2 asthma endotype, epithelial-derived alarmins released after epithelial damage caused by toxins (especially Staphylococcal enterotoxins), irritants, aeroallergens, and microorganisms activate ILC2. IL-5 and IL-13 are produced in response to prostaglandin D2 by PGD2 receptors expressed on ILC2 (5). The underlying inflammatory pathways (endotype and subendotypes), observable features (phenotypes), and biological markers reflecting T2 inflammation are shown in Figure 1.

As a result, studies on asthma phenotypes and endotypes have gained momentum in recent years. There are no more simple distinctions in asthma such as intrinsic and extrinsic asthma. Understanding asthma phenotypes, endotypes, and biomarkers that reflect them has become even more important as many biologic treatments have begun to offer a targeted approach aimed at treating underlying inflammation in asthma. ■



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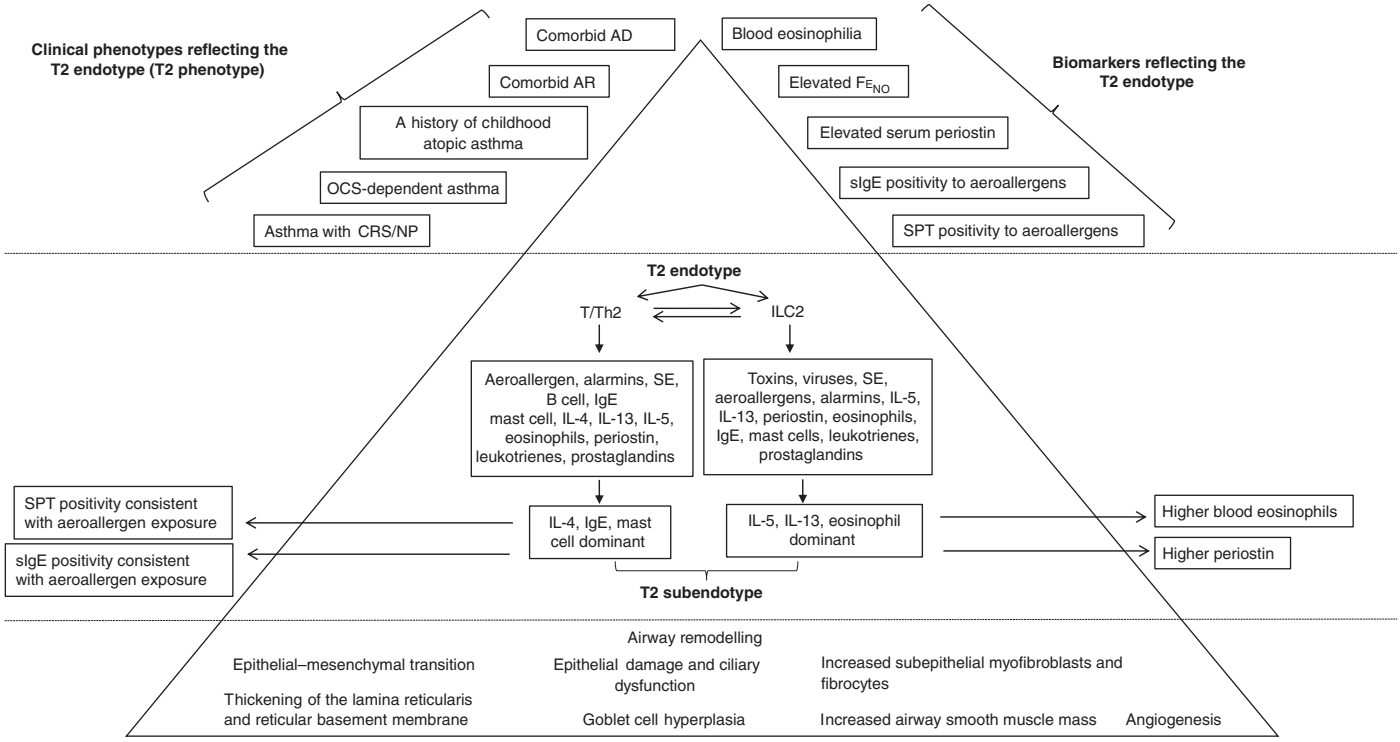


**Figure 1.** T2 asthma phenotype/endotype and biologic markers reflecting the T2 endotype. AD = atopic dermatitis; AR = allergic rhinitis; CRS/NP = chronic rhinosinusitis/nasal polyps; $F_{ENO}$ = fractional exhaled nitric oxide; ILC = innate lymphoid cells; OCS = oral corticosteroid; SE = *Staphylococcus aureus* enterotoxins; sIgE = specific IgE; SPT = skin prick test; T = type; Th2 = T-helper cell type 2.

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## Reply to Yilmaz and Çetin

*From the Author*:

I am delighted by the thoughtful response to my recent article (1). I believe the overall concept of defining visible and invisible sides of the iceberg is an excellent approach. It allows us to begin to conceptualize the relationships of clinical, physiologic, and biologic characteristics, which in composite we refer to as *phenotypes*, to the underlying complex immunoinflammatory characteristics, which constitute the *molecular phenotype* and eventually lead us to *endotypes*. Combining clinical features with type 2 (T2) biomarkers has allowed us to identify a "visible" T2 asthma phenotype. Yet, even this *visibly* defined broad clinical phenotype of T2 asthma is still evolving. Incorporating clinical features such as age at onset and responses to targeted therapies allows clinicians to move beyond



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