



Perspective

The future of omics for clinical practice



Andrew Long, PharmD^{*,†,‡}; Bryan Bunning, BS^{*,†,‡}; Matteo Borro, MD^{*,†,‡};
Vanitha Sampath, PhD^{*,†}; Kari C. Nadeau, MD, PhD^{*,†}

^{*} Sean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford University, Stanford, California

[†] Division of Pulmonary and Critical Care Medicine and Division of Allergy, Immunology and Rheumatology, Stanford University, Stanford, California

[‡] Department of Internal Medicine, Clinical Immunology Unit, University of Genoa and Policlinico San Martino, Genoa, Italy

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The future of clinical practice lies in precision medicine and personalized care, offering individuals safe and effective care based on the specific pathophysiologic mechanism, or endotype, unique to each patient. Traditional approaches in the treatment of atopic diseases have focused on the management of patients based on phenotype or the observable characteristics of disease; however, despite similar clinical symptoms and appearance, multiple patients often have variability in treatment response and disease trajectory. Although there are indications that atopic diseases may be manifestations of the same disease, with atopic dermatitis presenting first during infancy with progression to food allergy, allergic asthma, and allergic rhinitis, increased understanding of the pathophysiologic heterogeneity within each atopic phenotype has shifted current efforts away from grouping and treating patients based on clinical observations and toward the identification of underlying mechanistic pathways and biomarkers to better inform diagnosis, treatment selection, and prognosis on an

individual basis. To this aim, exponential advances in omic and bioinformatic technologies have begun to allow for the generation and analysis of large-scale biological data sets. Omics is a collective set of high-throughput technologies designed to empirically analyze large sets of pathophysiologic data, including genetic makeup (genomics), epigenetic modifications (epigenomics), gene and protein expression (transcriptomics and proteomics, respectively), metabolite production (metabolomics), and microbial flora (microbiomics). Unlike traditional hypothesis-driven and reductionist approaches, the omics approach to biological studies is holistic, integrative, and hypothesis generating, attempting to characterize and quantify a wide spectrum of analytes and cellular components from a single biological sample with the goal of identifying complex patterns and associations that better define endotypes and allow for treatment decisions tailored toward the underlying pathologic mechanism (Fig 1).¹

Completed in 2003, the human genome project took 13 years to sequence the entire human genome at a cost of \$2.7 billion. With advancements in technology, whole genome sequencing can now be completed for less than \$1000 and rapidly enough to potentially allow for practical application. Twenty-five genome-wide association studies (GWASs) of asthma were published between 2007 and 2016, the largest with a sample size of 157,242 individuals. Collectively, these studies uncovered approximately 39 genomic variations significantly associated with risk of asthma. Although the mechanisms that drive many of these associations have not been well elucidated, the GWAS findings have still been of use in guiding the development and use of several novel therapeutics specific to individual patient polymorphisms. For example, tocilizumab, an anti–interleukin 6 receptor antibody, has been considered for the treatment of patients with mild to moderate asthma based on the identification of an association between variation in the *IL6R* gene and asthma risk and severity as reported across several of the GWASs.¹

Reprints: Kari C. Nadeau, MD, PhD, Sean N. Parker Center for Allergy and Asthma Research at Stanford University, 269 Campus Dr, CCSR 3215, Mail Code 5366, Stanford, CA 94305-5101; E-mail: knadeau@stanford.edu.

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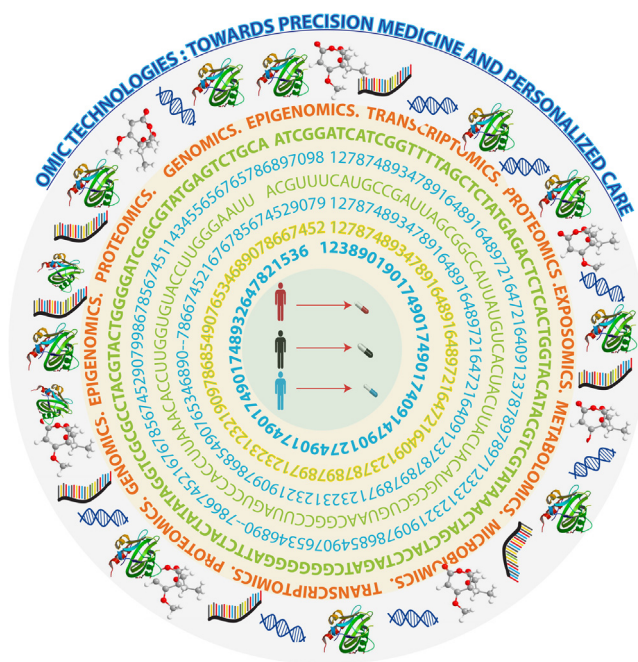


Figure 1. Omic technologies, such as proteomics, genomics, epigenomics, metabolomics, and microbiomics, are enabling precision medicine and personalized care.

Similar to genomic research, differences in epigenetic signatures, most commonly DNA methylation and histone modifications, have also been studied at the omic level, with several positive findings, particularly as markers of response to therapy and tolerance in the field of food allergy. Desensitization and tolerance after oral immunotherapy are associated with the hypomethylation and increased transcription of the *FOXP3* gene in regulatory T cells of patients receiving immunotherapy. Monitoring epigenetic changes in this region may aid in guiding aspects of therapy, such as treatment duration and long-term prognosis. Additional efforts have identified a 96-CpG DNA methylation signature that is highly predictive of reactions on food challenges in multifood allergic infants, distinguishing between allergic and nonallergic or sensitized infants.² The panel outperformed both egg and peanut specific serum IgE levels as a indicator of clinical allergy, suggesting it may serve to replace the need for oral food challenges after further refinement.

In addition to genomic and epigenomic studies, microarray technology and RNA sequencing have provided a powerful means of comprehensively defining the entire transcriptome of a tissue; however, transcriptomes are cell and tissue specific, and multiple transcripts can arise from a single gene, thus presenting challenges in the generation of practical, meaningful

insights into the pathogenesis of allergy or asthma. Proteomics, on the other hand, has enabled our understanding of the structural features of more than 850 allergens,³ including their immune epitopes, posttranslational modifications, abundance, degradation in gastrointestinal environment, and protein-protein interactions. This knowledge has significantly assisted in evaluating differences in the severity of reactions by allergen type and cross-reactivity between allergens. For example, the presence of intact bovine α -S1-casein has been detected in human breast milk, which may explain some forms of milk allergy in infants.⁴ Current research indicates that allergies to profilins and/or pathogenesis-related protein 10 are associated with mild oral allergic syndrome, whereas lipid transfer proteins, seed storage proteins, and thaumatococins are responsible for more severe clinical reactions.⁴ In addition, proteomics research may assist practitioners through the identification of other allergy endotypes, such as those directed against the proteins ω -5 gliadin or α -gal, resulting in the increased risk for exercise-induced anaphylaxis or severe delayed IgE-mediated reactions, respectively. Such findings may help establish patient-specific dietary recommendations.

Recently, interest in microbiomics has increased, in particular, the gastrointestinal, respiratory, and epithelial microbiome and its association with allergic disorders. The sequencing of bacterial 16S ribosomal RNA has enabled the identification of certain microbiota, namely, *Clostridia*, *Bifidobacterium*, and *Bacteroides*, as protective against food allergy. Microbial colonization in mice promotes expansion of regulatory T cells and the release of IgA, both of which contribute to tolerance.⁵ Although the role of microbes in pathogenesis remains unclear, further study appears to be warranted given their potential use in clinical practice as individualized diagnostic or treatment targets.

As sophisticated and novel omic technologies continue to develop, they are poised to allow researchers to analyze expansive data sets in the attempt to better define the underlying pathophysiologic mechanism of atopic disease. Although challenges still lie in the integration of different omic layers to map the complex network of pathways that mediate allergy and asthma, the future of clinical practice lies in the precise characterization of the endotypes driving atopy, enabling diagnosis, prognosis, and treatment on a highly individualized basis.

References

1. Vicente CT, Revez JA, Ferreira MAR. Lessons from ten years of genome-wide association studies of asthma. *Clin Transl Immunol*. 2017;6:e165.
2. Dhondalay GK, Rael E, Acharya S, et al. Food allergy and omics. *J Allergy Clin Immunol*. 2018;141:20–29.
3. Nony E, Le Mignon M, Brier S, Martelet A, Moingeon P. Proteomics for allergy: from proteins to the patients. *Curr Allergy Asthma Rep*. 2016;16:64.
4. Arasi S, Mennini M, Valluzzi R, Riccardi C, Flocchi A. Precision medicine in food allergy. *Curr Opin Allergy Clin Immunol*. 2018;18:438–443.
5. Ho HE, Bunyavanich S. Role of the microbiome in food allergy. *Curr Allergy Asthma Rep*. 2018;18:27.