From Single Omics to Clinically Integrated Multiomics: Toward Bioclinical Artificial Intelligence

The analysis in biological fluids of carbohydrates, lipids, amino acids, nucleotides, and other small molecules produced during cellular activity (dubbed the *metabolome*) has been widely used to characterize disease states. From a molecular standpoint, asthma symptoms are underpinned by several pathogenetic mechanisms variably interacting with each other and resulting from the interplay between genetic predisposition and environmental influences (1). By this token, metabolomic analysis is particularly promising for the characterization of asthma and its endotypes (2). Several studies have already explored the association between the metabolite concentrations in different human samples and the risk for asthma and its different phenotypes in both children (3) and adults (4). Most of these studies have applied a metabolomic approach to characterize different well-defined subgroups of subjects with asthma: for example, subjects with severe (5) or obesity-related asthma (6). In this issue of the *Journal*, Mendez and colleagues (pp. 737–748) applied a metabolomic approach to assess plasma samples collected in two cohorts of children with mild-to-moderate asthma with similar clinical characteristics: the Childhood Asthma Management Program (CAMP) and the Genetic Epidemiology of Asthma in Costa Rica Study (GACRS) (7). Children with available plasma samples were included (from the GARCS cohort: 1,155 children, mean age, 9.2 yr; SD = 1.9; from the CAMP cohort: 953 children, mean age, 13 yr; SD = 2.1), and the samples were examined using a mass-spectrometry–based metabolomics approach. Through an extensive statistical analysis, the authors identified the metabolites associated with 22 prespecified clinical traits and with the five domains in which these clinical traits were grouped (airway hyperresponsiveness, atopy, lung function, blood eosinophils, and blood neutrophils).

Among the significant metabolites identified in this study, some were associated with more than one domain (multidomain metabolites), whereas others were uniquely associated with one domain (single-domain metabolites). Although the former are important for understanding the metabolic pathways transversally implicated in asthma pathogenesis (e.g., histamine and kyneurine, which resulted associated with all but one domain), the latter are useful to highlight the metabolic pathways specifically associated, and, therefore, likely pathogenetically related to each domain. An example is vitamin A, which showed a strong single-domain association with lung function.

The study by Mendez and colleagues (7), evaluating the metabolic profile associated with asthma clinical traits and domains, is interesting and promising, as it considers concomitantly the complexity of the biochemical–metabolic underlying processes and the variability of the phenotypic features that contribute to the overall clinical picture of the disease.

Recently, there has been a growing interest toward an approach to respiratory diseases that is based on the identification and treatment of the so-called clinical treatable traits, defined as recognizable phenotypic or endotypic characteristics that can be assessed and successfully targeted by therapy (8, 9). Although it does not include the characterization of treatable traits, the study by Mendez and colleagues describes the link between relevant clinical traits and the underlying biochemical–metabolic mechanisms that could become targets for specific therapeutic strategies. The investigation of the metabolic pathways associated with clinical traits, therefore, potentially paves the way to the development of personalized treatments (10).

Given these cogent findings, this study should be considered a first step and should be followed by other investigations of additional, key aspects of asthma. Mendez and colleagues' approach is cross-sectional, and this leaves the directionality of the results still unresolved. The stability over time of the measured metabolites and of their role in predicting the evolution of the disease is also unknown. A longitudinal approach has been recently applied in a multiomic setting to characterize the progression of asthma in children, from the asymptomatic state to recurrent wheezing and, finally, to asthma (11). If known, the molecular patterns that are predictive of a worse disease course could be used to devise targeted therapies, with the potential for modifying the natural history of asthma.

More fundamentally, Mendez and colleagues address only one of the multiple, layered determinants of health and disease. The molecular infrastructure of tissues and cells acts in an integrated way, and dissecting its components into different omic studies does not provide a full picture of its functional intricacy. Therefore, the need to refine methodologies for real-time multiomic analyses applied at the cellular level is urgent. Moreover, to be amenable for use in medical practice, omics information needs to be integrated with deeply characterized clinical phenotypes, and for this to happen, common data elements need to be defined (12), which would allow the collection of standardized data across populations and information platforms. Otherwise, harmonizing databases from heterogeneous sources is a difficult task, with results that are often too messy to be useful.

Persuasive single omics studies, such as that by Mendez and colleagues, thus anticipate a new era in which the extraordinary new analytical capacities provided by artificial intelligence (AI) are applied to real time, concurrently obtained, longitudinal assessment of multiple biological exposures, correlates, and functions (e.g., metabolomics, proteomics, genomics, epigenomics, microbiomics, exposomics, imaging, etc.). The AI instruments that are currently available are unprepared to tackle this specific task. A new AI instrument, which we propose to call BioClinical AI (Figure 1), needs to be designed as a collaborative effort between biologists,

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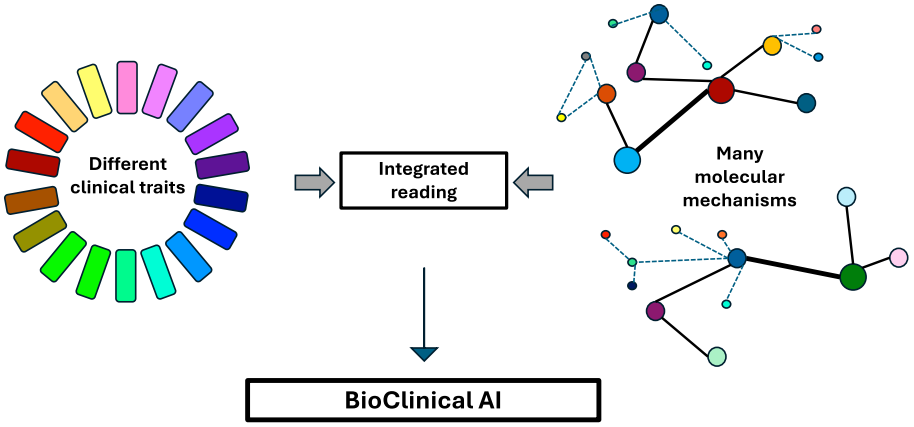

Figure 1. To increase likelihood of success in solving major medical challenges, biologists, clinicians, and information scientists must collaborate in the development of BioClinical AI, an ongoing analytical system that integrates real-time, longitudinal patient information with comprehensive omics data. AI = artificial intelligence.

clinicians, and information scientists. It will be embedded in biology (13), and, at the same time, it will deeply and accurately consider clinical features. As a result, such an approach will specifically address our most vexing medical challenges. We are convinced that asthma, the prototype of a developmental disease, which is really a heterogenous set of overlapping disorders, is a good place to start. As Mendez and colleagues have shown, there are, today, defined asthma phenotypes that provide consistent molecular signals underlying different endotypes. Validated clinical instruments exist that are widely used in clinical practice. What is missing is the assembly of the interdisciplinary teams that will get the job done.

We may be getting closer to solving the asthma riddle. ■

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