Review article

Multiomics approach to evaluating personalized biomarkers of allergen immunotherapy

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Recent advancements in genomics and "omic" technologies have ushered in a transformative era referred to as personalized or precision medicine. This innovative approach considers the unique genetic profiles of individuals, along with a range of variability factors, to devise tailored disease treatments and prevention strategies that cater to the distinct needs of each patient. Although the terms *personalized medicine* and *precision medicine* are frequently utilized interchangeably, it is essential to delineate the subtle distinctions between them. Personalized medicine concentrates on bespoke treatments and prevention strategies that are meticulously tailored for each individual. Conversely, precision medicine utilizes advanced gene sequencing and comprehensive data analytics to formulate specific treatments and prevention strategies for defined groups of individuals based on genetic, environmental, and lifestyle factors rather than focusing exclusively on individual patients. Therefore, precision medicine constitutes an extension of traditional personalized care, improving the accuracy of diagnosis, prognosis, and therapy estimations for each patient through the application of sophisticated molecular diagnostics and advanced imaging techniques enabled by recent technological innovations. The shift from personalized to precision medicine has gained considerable traction, particularly in the wake of the 2015 US Precision Medicine Initiative, which has further stimulated advancements in this domain. This review will explore multiomics approaches that have facilitated the evaluation of personalized biomarkers associated with allergen immunotherapy, particularly in the treatment of allergic diseases. By leveraging these innovative methodologies, we aspire to cultivate more effective and individualized patient care, ultimately enhancing health outcomes for individuals with allergies. (J Allergy Clin Immunol 2025;156:523-34.)

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PATHOPHYSIOLOGIC MECHANISMS OF ENVIRONMENTALLY AND ALLERGEN-INDUCED ALLERGIC RHINITIS

Allergic inflammation is an immune reaction triggered by allergens in genetically predisposed individuals, leading to chronic T_H2 cell–driven inflammation and tissue remodeling. It plays a key role in allergic rhinitis (AR), asthma, atopic dermatitis, and food allergies. AR, a chronic IgE-mediated inflammation of the nasal mucosa, is triggered by allergens such as pollen, dust mites, and pet dander. It affects up to 25% of adults and 40% of children globally, with rising prevalence owing to urbanization, pollution, and lifestyle factors.[1] Over the years, there has been growing evidence of the role that environmental exposure (the "exposome") plays in the development of allergic diseases. These exposomes can be further categorized as internal (ie, aging, hormones, and metabolic processes) or external (ie, chemical pollutants, lifestyle factors, and socioeconomic factors),[2-4] with the latter being implicated with recent climate change, which has led to longer pollen seasons, increased pollen production, and allergenic potency.

Abbreviations used
AI: Artificial intelligence
AIT: Allergen immunotherapy
AR: Allergic rhinitis
Ara h: *Arachis hypogaea*
CRD: Component-resolved diagnostics
DC: Dendritic cell
DC2: Type 2 dendritic cell
Der p: *Dermatophagoides pteronyssinus*
GWAS: Genome-wide association study
HETE: Hydroxyeicosatetraenoic acid
ILC: Innate lymphoid cell
mTOR: Mammalian target of rapamycin
NAC: Nasal allergen challenge
Phl p: *Phleum pratense*
PPARG: Peroxisome proliferator-activated receptor gamma
RNA-seq: RNA sequencing
scRNA-seq: Single-cell RNA sequencing
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
T_H2A: Allergen-specific T_H2
Treg: Regulatory T

A recent proposal of the epithelial barrier hypothesis underscored its importance as a first line of defense against allergens. It is suggested that disruption of this barrier contributes to the development of allergic diseases by increasing permeability, enhancing allergen penetration, and triggering immune activation, hence creating a vicious cycle to enhance dysregulation of the subepithelial immune response.[5] Patients with AR have been associated with elevated expression of occludin and claudin-7, proteins associated with exposure to secondhand smoke and urban location.[6] Disruption in intestinal permeability, which can alter microbial composition and disruption to the intestinal tight junctions, have also been positively associated with a high-fat diet and the use of antibiotics.[7,8]

The mechanisms of allergic inflammation involve a complex process including an interplay of the epithelial barrier, innate and adaptive immune cells, and humoral responses. Allergens can penetrate the nasal epithelial barriers, resulting in the loss of epithelial integrity and the generation of epithelial-derived mediators (IL-33, IL-25, and TSLP) which can activate group 2 innate lymphoid cells (ILC2s) and type 2 dendritic cells (DC2s). In individuals with allergy, DC2s are proficient in promoting the differentiation of T_H2 cells, allergen-specific T_H2 (T_H2A) cells, and type 2 T follicular helper cells, the latter being derived from the marginal zones of lymph nodes. The differentiation of these proallergenic T-cell subsets promotes the differentiation of B cells into IgE-producing plasma cells. Cross-linking of allergen-specific IgE and FcεRI on the surface of mast cells subsequently results in their activation and degranulation, which in turn leads to the release of granule-derived mediators (ie, tryptase and histamine) and membrane-associated lipid mediators (ie, prostaglandin D_2 and leukotrienes) (Fig 1).

Clinical symptoms associated with AR include nasal congestion, sneezing, rhinorrhea, and itching. Antihistamines and corticosteroids are effective symptom relievers; however, in more severe cases, biologics may offer faster symptom relief by directly targeting specific immune molecules, although the benefit is not persistent over time. Allergen immunotherapy (AIT) is currently the only disease-modifying treatment for AR; it works by gradually desensitizing the immune system to allergens over time, providing a long-term clinical benefit after cessation of therapy. Combining biologics and AIT has also been indicated as a potentially more effective approach to treating patients with severe AR. Despite the evidence supporting the efficacy of AIT and its role in modulating the proallergic immune response, the challenge of accurately identifying individuals who are likely to respond, as opposed to those who will not, remains a significant hurdle to determining biomarkers of efficacy and immune tolerance.

BIOMARKERS

Biomarkers are biologic molecules that act as an indicator of health and disease. The identification of a reliable biomarker(s), whether cellular, molecular, or clinical, holds the key potential for personalized medicine and overall enhanced clinical outcome. In the context of allergic diseases and AIT, several candidate biomarkers have been proposed over the years; however, no validated clinical biomarker to predict the clinical response to AIT has been identified. These biomarkers can be broadly categorized into (1) biomarkers for diagnosis, (2) biomarkers for immune monitoring and treatment efficacy, (3) biomarkers of responses, and (4) biomarkers predictive of efficacy.

Biomarkers for allergy diagnosis

Diagnosis of AR typically combines clinical history with allergen tests such as the skin prick test and testing for specific IgE level. Although specific IgE is routinely used in clinical practice to diagnose patients, its reliability as a biomarker for immune monitoring has been questioned, as AIT has been associated with a transient increase in level of specific IgE before it falls back down, often not correlating with clinical symptoms.[9-12] Novel diagnostic tests, such as epitope mapping, the basophil activation, and the mast cell activation test, have been explored but are not yet widely used.[9,12,13] Nasal allergen challenge (NAC) has also been explored as a clinical biomarker for diagnosis. A retrospective study investigating the safety and reproducibility of NACs performed over 12 years in Spain showed that in both adults and pediatric patients with allergy, they were well tolerated without delayed, severe local, or systemic adverse events.[14] Although NAC may not be a necessity for diagnosis in AR, it can prove to be extremely beneficial in diagnosing local allergic rhinitis (LAR), which is characterized by a localized IgE-mediated response in the nasal mucosa despite negative results of both skin prick testing and specific IgE level testing.

Diagnosing allergic conditions often involves measuring specific IgE levels in the blood, typically by using allergen extracts from common sources such as pollen, house dust mites, or pet dander.[15] However, these extracts can vary significantly in their allergen content and may include nonrelevant molecules, leading to potential misinterpretations. In recent years, the advent of molecular component-resolved diagnostics (CRD) has revolutionized allergy testing.[16] This approach utilizes highly purified native or recombinant allergens optimized for low immunoassay interference (such as cross-reactive carbohydrate determinant) in specific IgE level testing, allowing for a more precise understanding of sensitization patterns and cross-reactivity among allergens. This enhanced specificity aids in better risk assessment and more targeted AIT selection.[17,18] A substantial portion of clinically relevant allergens are grouped into a few major protein families. In the case of plant allergens, more than 40% fall into 6 families: 2S albumins, nonspecific lipid transfer proteins,

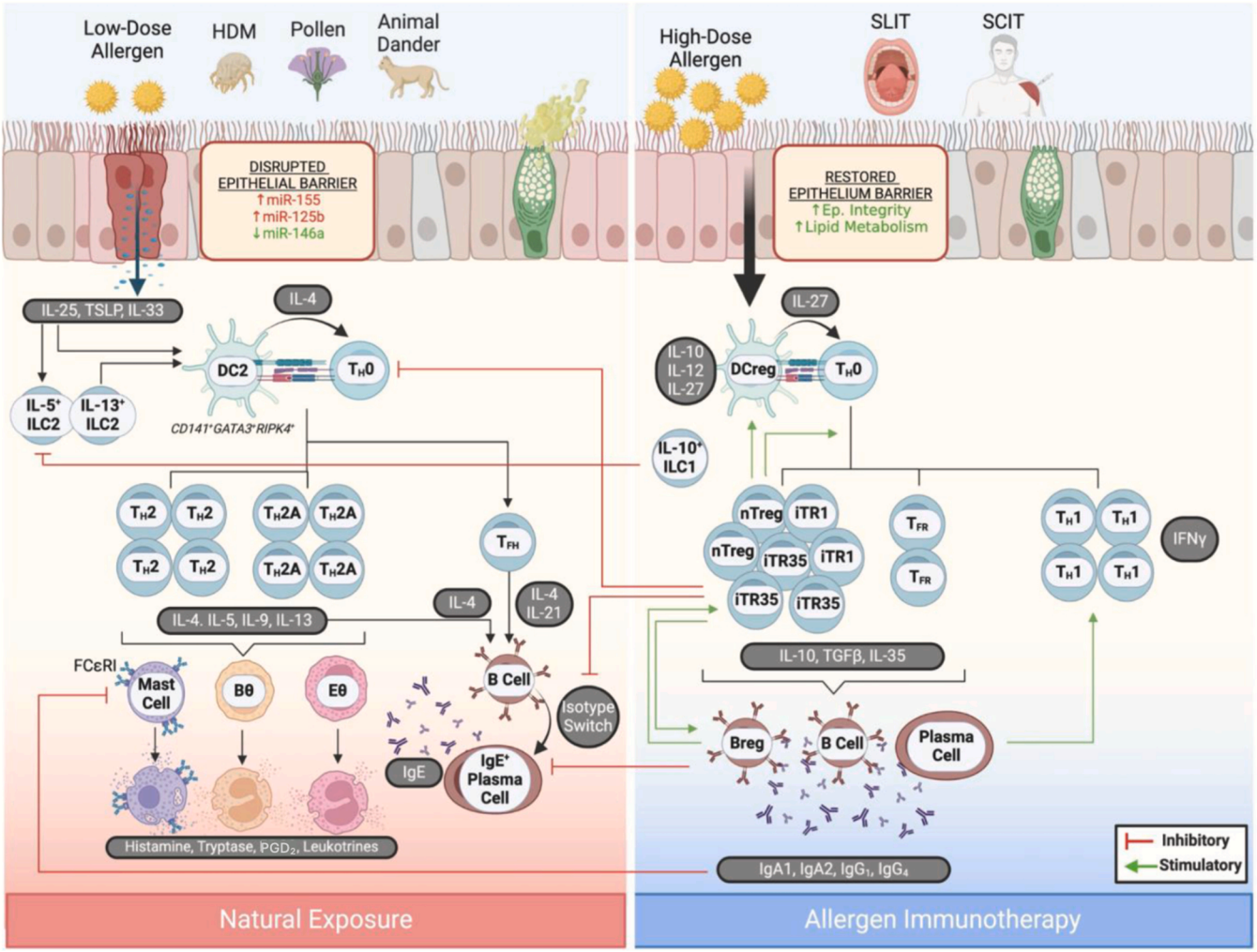


FIG 1. Mechanism of AIT. Natural low-dose allergen exposure drives epithelial barrier dysregulation, activation of group 2 innate lymphoid cells (ILC2s) and DC2 cells, and differentiation of proallergenic T_H2/T_H2A cells that promote IgE production by B cells. Allergen- specific IgE and FcεRI complex cross-linking on effector cell surfaces induces cell activation, degranulation, and secretion of immunomediators. High-dose allergen exposure administered through AIT restores epithelial barriers and induces group 1 ILC (ILC1) subsets and regulatory DC (DCreg) cells, which promote T_H1 cell and follicular regulatory T (T_{FR}) cell differentiation and expansion of Treg subsets. IL-10, TGF-β, and IL-35 drive B cells to produce inhibitory antibodies, IgA_1, IgA_2, IgG_1, and IgG_4. Inhibitory antibodies compete with IgE, preventing formation of allergen-IgE FCεRI complexes on effector cells. Red lines indicate inhibitory pathways, and green lines indicate stimulatory pathways as mediated by allergen immunotherapy. *Bθ*, Basophil; *BC*, B cell; *Eθ*, eosinophil; *Ep*, Epithelial; *HDM*, house dust mite; *iT_R1*, inducible IL-10^+ Treg cell; *iT_R35*, inducible IL-35^+ Treg cell; *MC*, mast cell; *nTreg*, natural Treg; *PGD_2*, prostaglandin D_2; *T_H0*, naive T cell; *T_{FH}*, follicular T_H cell; *TSLP*, thymic stromal lymphopoietin. Figure created using BioRender.com.

legumins, vicilins, profilins, and the pathogenesis-related (PR) proteins known as PR-10 proteins.[16,17] In the case of animal allergens, 4 families—cysteine proteases, lipocalins, tropomyosins, and parvalbumins—account for more than 70% of significant allergens.[16,17] Additionally, Hymenoptera insect venom allergens represent another critical category.[18,19]

Birth cohort studies have identified allergen molecules that drive disease and predict the progression from IgE sensitization to allergy.[20] Early-life IgE reactivity to select molecules (eg, *Betula verrucosa* 1, *Felinus domesticus* 1, *Phleum pratense* [Phl p] 1, Phl p 5, *Dermatophagoides pteronyssinus* [Der p] 1, Der p 2, and *Arachis hypogaea* [Ara h 2]) signals a high risk of asthma and rhinitis in adolescence.[21] Polysensitization to cat or dog allergens predicts allergy better than extract-based tests do,[22] whereas Der p 23, alongside Der p 1 and Der p 2, is linked to a higher risk of allergic asthma.[23] Furthermore, measuring IgE reactivity to grass allergen molecules in childhood improves detection of grass pollen sensitization. In the Barn/Children Allergy/Asthma Milieu Stockholm Epidemiologic (BAMSE) cohort, sensitization to Phl p 1, Phl p 4, and/or Phl p 5 was more prevalent than sensitivity to timothy extract.[24] CRD often serves as a key step in refining the diagnosis, either through initial testing or in follow-up patient visits. CRD can be performed in various formats, such as singleplex,[16] oligoplex,[19] or multiplex immunoassays,[25,26] tailoring the testing to individual translational research or patient needs and health care settings for effective patient management.[17,27]

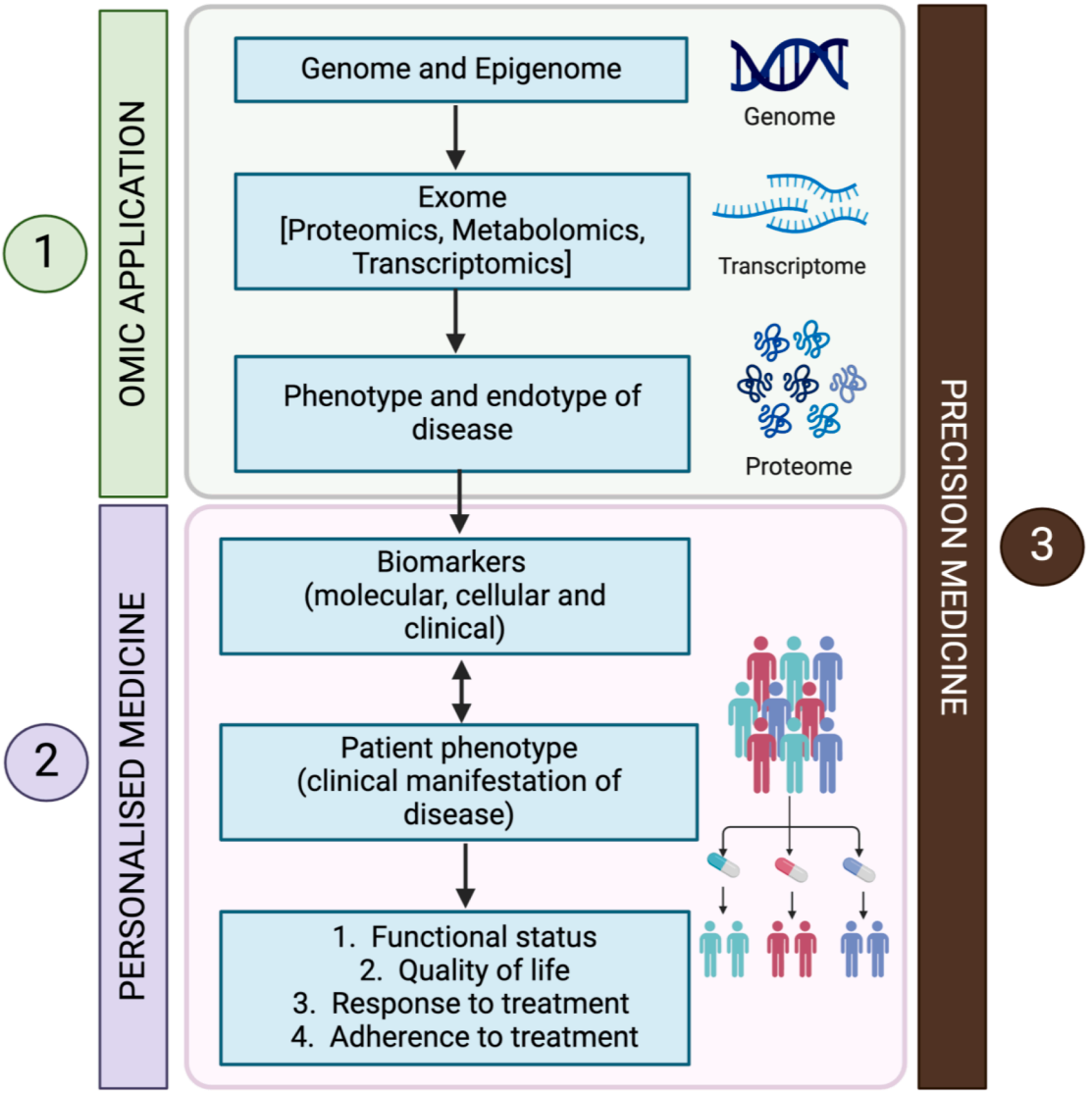


FIG 2. Personalized medicine versus precision medicine. Personalized medicine and precision medicine are related concepts in health care, but they have subtle differences in focus and application. Although both terms can be used interchangeably, precision medicine offers an approach more focused on the biologic aspects of disease, whereas personalized medicine incorporates a broader range of patient-specific factors to guide treatment. Combining data obtained from omics applications (ie, genomic, epigenomic, transcriptomic, metabolomic, and proteomic) and data obtained through personalized medicine (ie, biomarkers, patient phenotype, and clinical data) allows for precision medicine.

Biomarkers for AIT: Immune monitoring, treatment efficacy, and predictive biomarkers

For the treatment of allergic diseases, patients are traditionally treated on the basis of their phenotyping profile (eg, AR or asthma) rather than on the basis of underlying immunologic or endotype profile.[28] A better understanding of various (sub)endotypes of allergic diseases may enable clinicians to optimize treatment modalities in the future (eg, by exploiting candidate biomarkers for both initiation and monitoring of therapeutic interventions such as AIT). AIT is currently the only disease-modifying treatment for IgE-mediated inhalant allergies,[29,30] with proven efficacy and safety for both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT).[31,32]

Many proposed biomarkers for immune monitoring, treatment efficacy, and prediction remain under investigation in small studies, making their validation challenging. Humoral biomarkers such as specific IgG (sIgG1 and sIgG4)[33-36] and IgA (sIgA1 and sIgA2)[37] antibodies show potential, with a typical 10- to 100-fold increase in IgG4 particularly linked to treatment adherence and clinical outcomes. A task force initiative of the European Academy of Allergy and Clinical Immunology has reviewed possible biomarkers to be used in clinical trials of AIT.[10] Clinical trials indicate that nasal IgG4 levels correlate with effectiveness of grass pollen SCIT.[38,39] The functional blocking capacity of IgG4 antibodies can in turn be assessed by using the IgE-facilitated allergen binding assay and basophil activation test, both of which are valuable diagnostic

tools to assess immune monitoring and treatment efficacy.[13,40] Cells within the innate (dendritic cells [DCs] and innate lymphoid cells [ILCs]) and adaptive (T_H2, regulatory T [Treg], and regulatory B cells) immune compartments have also been proposed as potential biomarkers of AIT efficacy. Successful SCIT and SLIT have been associated with induction of regulatory DCs,[41,42] IL-10–producing ILCs,[43-46] and inducible Treg cells with the capacity to produce IL-10 and IL-35 cytokines,[47-49] which correlate with clinical symptoms. Moreover, AIT has also been associated with the induction of IL-10–producing regulatory B cells[50-52] and allergen-specific memory B cells displaying upregulated CD29 expression.[53,54] Although promising, these have been investigated only in small clinical trials or explorative studies and have the caveat of complexity, thus limiting their use as routine clinical laboratory testing.

Biomarkers to delineate precision versus personalized medicine

The delineation of personalized versus precision medicine can be made by using a combination of biomarkers. Precision medicine generally defines an approach that uses data (ie, genetics, biomarkers, and environmental factor) to classify individuals into subgroups that respond differently to treatments. Hence, the overarching goal of precision medicine lies in identifying the right treatment for the right group of people based on similar characteristics. An example of this includes the utility of CRD to determine specific IgE reactivity to specific allergen components and thereby obtain a thorough molecular profile, which will allow the clinician to recommend a specific AIT treatment that is likely to benefit the patient owing to his or her sensitization profile to the major allergen. On the other hand, personalized medicine can be defined as a treatment that is tailored to the individual characteristics of each patient and also gives consideration to patient-centric factors. For example, beyond selecting the appropriate AIT treatment for an individual based on CRD, the clinician would typically engage with the patient in a shared decision-making approach, allowing the recommendation of treatment to be driven and optimized on the basis of other factors such as adherence and satisfaction (Fig 2).

PANOMICS APPROACHES TO IDENTIFY BIOMARKERS OF AIT

Omics approaches, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics, play a pivotal role in discovering biomarkers to allow personalized treatment approaches.

Genomics and epigenomics

Genomics is a tool that can be used to understand the function of genes and noncoding regions of the genome and study differences in DNA sequences between individuals that may underlie variation in traits and susceptibility to diseases. Many genome-wide association studies (GWASs) have been performed to identify the association of certain gene variants with AR. A previous GWAS analysis led to the identification of 11 risk variants (the variants rs7009110 in ZBTB10 and rs62026376 in CLEC16A) associated with asthma with AR.[55] Furthermore, a combined GWAS and HLA fine-mapping study identified 25 new loci that had not previously been associated with AR.[56] Most recently, genetic variants underlying differences in immune responsiveness against allergen components were also identified through GWAS in a pediatric cohort in Japan. Although genomic approaches can be useful to identify gene variants for disease susceptibility and also identify biomarkers of diagnosis, other omics-based approaches may be more valuable to assess predictive biomarkers, treatment efficacy, and treatment response.

Epigenomics focuses on the study of reversible epigenetic modification of a cell, without altering the underlying DNA sequence. Key aspects of epigenomics include DNA methylation, histone modification, chromatic accessibility, and noncoding RNA modification. DNA methylation is key in the differentiation and function of T cells, with intergenic regions of both the *IL4* and *IFNG* genes being methylated in resting $CD4^+$ T cells.[57] In children with allergic asthma, hypomethylation of the *IL4* gene is associated with elevated gene expression versus that in healthy controls. A recent study demonstrated changes in DNA methylation of tryptase gamma 1 (*TPSG1*), schlafen (*SLFN12*), and mucin 4 (*MUC4*) genes following NAC, suggesting that these baseline features may act as potential indicators of symptom severity in AR.[58] More recently, differential methylation of CpGs associated with asthma, fractional exhaled nitric oxide, and IgE was also found locally within the nasal compartment, serving as a biomarker of asthma, allergy, and airway inflammation in children.[59]

There is growing evidence that AIT can modify epigenetic mechanisms to induce allergen tolerance.[60] For example, grass pollen SCIT and SLIT showed differential chromatin accessibility in follicular helper T (T_{FH}) and follicular regulatory T (T_{FR}) cells,[61] whereas combined timothy grass and dust mite SLIT induced allergen-specific $FOXP3^+$ memory Treg cells with reduced DNA methylation at the FOXP3 locus.[62] Demethylation of the Treg cell–specific demethylated region (TSDR) of FOXP3 is a prerequisite for stable maintenance of the suppressive activity of Treg cells. Epigenetic modification following Der p SCIT in children with allergic asthma resulted in increased DNA methylation at the *IL4* promoter,[63] whereas grass pollen SCIT and SLIT resulted in hypermethylation of the *SATB1* locus, but not *FOXP3*, at 12 months. This highlights the fact that SATB1, a known transcriptional suppressor of FOXP3 that regulates Treg cell function, plays a critical role following AIT.[64] Although promising, there is currently a lack of robust, easy-to-measure, and preferentially nucleic acid–based biomarkers to tailor therapies to individual patients.

Transcriptomics

Transcriptomics, the study of all RNA molecules within a cell or population of cells, has revolutionized our understanding of the heterogeneity underlying complex allergic diseases, leading to discovery of multiple allergic disease phenotypes and endotypes, as well as to development of biomarkers and targeted biologic therapies. Also known as RNA sequencing (RNA-seq), it has become one of the fastest-growing areas of omics-based approaches evolving from (1) classic bulk RNA-seq to (2) single-cell RNA-seq (scRNA-seq) and toward the newly emerged (3) spatial RNA-seq.

Bulk RNA-seq. Bulk RNA-seq, once the standard for gene expression analysis, provides an averaged "crude" measure across diverse cells. Although bulk RNA-seq allows inference of proportions of cell types, and despite its low cost, its low resolution results in an inability to associate changes in gene expression (and therefore, important information such as signaling and pathway interpretation) with specific cell types. A side-by-side comparison of bulk RNA-seq and scRNA-seq highlighted the fact that bulk RNA-seq fails to capture asthma-specific features whereas

scRNA-seq reveals T_H cell heterogeneity, thus identifying IL-9–expressing house dust mite–reactive T_H cells in individuals with allergy.[65] Bulk RNA-seq analyses have highlighted the fact that grass pollen SCIT and SLIT induce similar gene expression changes over time, downregulating mucus hypersecretion and leukocyte activation while enhancing epithelial development. In PBMCs, AIT reduced type 2 cytokine signaling, correlating with clinical improvements.[66]

Single-cell RNA-seq. The use of scRNA-seq has increased substantially since 2017 (ie, since the introduction of various single-cell platforms, particularly 10*x* Genomics, to the market), offering a more cost-effective and user-friendly platform. Gene expression at a single-cell resolution enables similar cells to be clustered together and identified, including those that are rare but immunologically significant (eg, ILCs, ionocytes, DC subsets), even within subsets that were previously thought to be homogenous (eg, cDC2s).[67] Additionally, a more nuanced understanding may be obtained by associating expression with individual cells. For example, the developmental trajectory and precursors of DCs were revised, and heterogeneity in cDC2 cells has revealed new subsets through scRNA-seq.[67,68]

More recently, many single-cell multiomics approaches that can simultaneously measure 2 modes of information have been developed, and an accompanying explosion in development of single-cell multiomics–specific tools has been under way to take advantage of the linked modalities. For example, using both gene expression and chromatin accessibility (ATAC-seq) greatly improves inference of gene regulatory networks over that enabled by either modality alone.[69]

Advances in scRNA-seq technology have advanced our understanding of the underlying mechanisms of AIT through the ability to hone into specific cell types in an unbiased manner. A cellular indexing of transcriptomes and epitopes based on sequencing (scCITE-seq) approach demonstrated that grass pollen SLIT treatment can modify retinol metabolic pathways, cytokine-cytokine receptor interaction, and Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathways within the ILC compartment, highlighting their potential as candidate biomarkers of AIT.[43] Iinuma et al used scRNA-seq and single-cell variable diversity joining (scVDJ) sequencing to uncover both a potential mechanism and a biomarker of SLIT for Japanese cedar pollinosis.[70] Expansion of T_H2 cell and Treg cell subsets has been observed in responsive patients; specifically, SLIT was associated with an increased subset of a trans-type T_H2 cell population that expresses musculin gene (*MSC), TFGB,* and *IL2,* which subsequently differentiated into Treg cells. Elevated *MSC* expression was observed within the active SLIT group that remained unresponsive after 1 year of treatment, highlighting its potential as a biomarker of AIT efficacy. More recently, a short preseason grass pollen SLIT treatment was shown to be effective in inducing allergen-specific memory B-cell subsets with unique transcriptional profiles that include upregulated *IgHG4*, *CD23,* and *CD29* expression and may act as a biomarker for treatment effect.[54] Finally, scRNA-seq to investigate the mechanism of tolerance induction by depigmented and polymerized (DPG-POL Phl p) allergoid for use in SCIT revealed that DPG-POL Phl p induces its immunomodulatory properties by dampening T_H2 cell–associated signaling, induction of functional Treg cells exhibiting immunosuppressive roles through CD52 and Singlec-10, and modulation of genes encoding immunoproteasome that dysregulate the allergen processing and presentation to T cells.[51] Although these may all act as promising candidate biomarkers, further validation in a larger study cohort would be required.

scRNA-seq faces challenges owing to noisy, sparse, high-dimensional data, as well as to diverse experimental designs. The appropriate tools and parameters are highly data set–specific, requiring collaboration between clinicians, researchers, bioinformaticians, and technicians to ensure accurate analysis and meaningful insights into disease mechanisms and treatments.

Spatial RNA-seq. A major limitation of scRNA-seq is the loss of spatial information, which is crucial in allergic diseases in which local changes in epithelial and immune cells occur following allergen exposure. Emerging spatial sequencing technologies that capture gene and protein expression along with their tissue locations are providing deeper insights into allergic inflammation, although their application to AIT remains limited. Through spRNA-seq of endobronchial biopsy samples from asthmatic children, Joulia et al demonstrated that genetic changes in vessel-rich areas are associated with cellular stress, remodeling, and mast cell activation.[71] Furthermore, the integration of spatial RNA-seq, scRNA-seq, and proteomics in skin biopsy samples demonstrated a potential cross talk between $CD45RO^+$ T cells, M2 macrophages, $LAMP3^+$ DCs, and $COL18A1^+$ fibroblasts in atopic dermatitis skin lesions.[72] Unveiling these networks and mechanisms may allow endotype-specific treatment and novel disease-modifying targets for anti-inflammatory and immunomodulatory treatments. Despite its promise, spatial sequencing is still developing, with challenges in resolution and sampling; however, it holds great potential for advancing understanding and treatment of allergic disease.

Metagenomics

Human cohort studies have linked composition of the early-life microbiota with allergic diseases, but the mechanisms and host-microbe interactions are still being explored.[73,74] Metagenomics, which sequences DNA from environmental samples, is key in studying microbial communities and holds promise for diagnosing immune-mediated and allergic diseases.[75] Through detailed analyses of microbiota from skin, gut, or airway mucosa, distinct microbial profiles that have been associated with various allergic conditions were identified.[76] Thus, specific microbial signatures that could serve as biomarkers for early diagnosis and risk assessment (eg, in asthma or food allergy) have been identified.[74,77] Specific alterations in microbial diversity and the presence of certain taxa have been linked to heightened allergic reactions to common food allergens such as ovalbumin and peanuts at the intestinal barrier.[78] Specifically, depriving dietary fiber increases mucin-degrading bacteria, such as *Akkermansia muciniphila*, leading to intestinal barrier dysfunction and elevated type 1 and 2 cytokine levels, along with IgE-coated commensals.[79] These insights underscore the need for further exploration of the microbiome's role in allergic diseases, highlighting potential prevention and treatment strategies. Integrating metagenomics with clinical data could lead to the establishment of robust biomarkers, paving the way for improved management and prevention strategies for allergic diseases.[80] Other important technologies in the context of discovery of biomarkers from healthy or diseased microbiomes are metatranscriptomics[75] (which focuses on the RNA transcripts present in a community, providing more functional insights by analyzing microbial gene expression and activity at a given time) and metaproteomics[81] (which is the large-scale study of proteins expressed by microbial communities). Metaproteomics complements metagenomics and metatranscriptomics by providing insights into the actual

proteins produced. Along with bacterial cultures and biochemical profiles, metaproteomics is a vital tool for understanding the functional dynamics of microbial communities.

Metabolomics and immune metabolism

Systemic and cellular omics approaches during AIT offer insights into biologic systems affected by AIT. Few studies have analyzed metabolomic signatures during AIT. Barker-Tejeda et al[82] performed serum metabolomics and PBMC transcriptomics in a trial of grass pollen SLIT. At baseline, polysensitized patients had lower levels of linoleic acid, linolenic acid (18:3), arachidonic acid, and adrenic acid (22:4), suggesting a higher use for proinflammatory lipid mediators. After AIT, patients showed higher levels of lysophosphatidylcholine (LysoPC), docosahexaenoic acid, and hydrophilic bile acids (taurocholic and glycochenodeoxycholic acids), indicating a shift toward anti-inflammatory mediators. Additionally, lower levels of tyramine and p-cresol in the active arm suggest that AIT alters amino acid metabolism, warranting further investigation into p-cresol's protective role in allergy.[83]

An open, controlled study confirmed that AIT-induced lipid metabolism changes in children undergoing 3-year SCIT via eicosanoid metabolomics.[84] Levels of 5(S)-, 12(S)-, and 15(S)-hydroperoxyeicosatetraenoic acids (HPETEs) and 5(S)-, 8(S)-, 11(S)-, 12(S)-, and 15(S)-hydroxyeicosatetraenoic acids (HETEs) rose in year 1 before declining by year 3, with levels of 12(S)- and 15(S)-HETE decreasing only at year 3, thus highlighting the need for prolonged treatment to induce systemic anti-inflammatory effects. In ultrarush wasp venom immunotherapy, prostaglandin E_2 release and COX2 expression decreased at 3 and 6 months, correlating negatively with IL-10 release.[85] Peroxisome proliferator-activated receptor-gamma (PPARG) is a key transcription factor in lipid metabolism, with reduced PPARG signaling observed in patients undergoing venom immunotherapy.[86] Similarly, allergen challenge in patients with allergy and asthma resulted in increased bronchoalveolar lavage fluid levels of T_H2, Treg cells, and antigen-activated ($CD154^+$) T cells, expressing genes responsible for their "pathogenic" receptor, cytokine, lipid, and transcription factor signatures such as PTGDR2 (CRTH2), HPGDS, IL1RL1 (IL-33R), and IL17RB (IL-25R), as well as IL-9, PPARG, and IRF4.[87] Importantly, these CRTH2+ T_H2 cells and CRTH2+ Treg cells are downregulated during AIT.[88,89]

Glycolysis and mammalian target of rapamycin (mTOR) signaling are other key immune metabolism pathways in type 2 inflammation in DCs, T_H2 cells, and ILCs. Activated T_H2 cells upregulate the glucose transporter GLUT1, resulting in high glucose uptake.[90] L-Phenylalanine, an essential amino acid, regulates mTOR signaling, which is impaired in patients with severe allergy.[91] One year of SLIT with the allergen *Dermatophagoides farinae* reduces mRNA expression of glycogen synthase kinase 3b and *MTOR* in whole blood of patients.[92] Novel AIT approaches using vaccines adjuvated by monophosphoryl lipid A (MPLA), mannan, or other bacterial products, have been proved to affect DC metabolism.[93-95]

Proteomics

Very few protein biomarkers for AIT are available to allow patient stratification, early identification of responders, or monitoring of treatment efficacy. This is due to difficulties in identifying general biomarkers given the long duration of the treatment with different intervention schedules and various routes of administration, the time-dependent immunologic events along the course of treatment, the different types of allergens, and differences in allergic diseases.[10,96,97] Candidate biomarkers, such as periostin, MMP-12, ALCAM, and MIF, have been suggested to differentiate responders from nonresponders.[97] These biomarkers are typically measured using ELISAs, whereas high-throughput mass spectrometry–based proteomics provides a broader, unbiased view of differential protein levels during AIT. This approach has identified marker proteins in monocyte-derived DCs that distinguish AIT responders from nonresponders or placebo-treated patients.[41,42]

Mass spectrometry–based proteomics also plays a key role in cancer immunotherapy by identifying protein signatures and neoantigens that predict clinical outcomes.[98] A similar approach could be applied to allergic diseases in the future. In immunopeptidomics, HLA-bound peptides can be identified by using data-dependent, data-independent, or targeted proteomics.[99,100] This approach is initiated with immunoaffinity purification of either MHC class I or MHC class II complexes.[99] Peptides presented onto MHC class I complexes are derived primarily from intracellular proteins (ie, neoantigens in cancers) that then get presented to cytotoxic T cells,[99,101] whereas those presented onto class II MHC complexes come from extracellular proteins that then get presented to $CD4^+$ T cells and are important in autoimmune and allergic diseases. The sequences of the mass spectrometry–identified eluted MHC class I and class II peptides combined with genomic and ribosome profiling data, as well as with binding affinity data, are instrumental for the reliable prediction of the T-cell epitopes,[102,103] which is of crucial importance in AIT approaches.

High-dimensional immune profiling and single-cell cytometry

Advancements in multiomics approaches, such as scRNA-seq and advanced flow cytometry, have greatly improved immune profiling in AIT and allergic diseases.[100] These techniques address challenges such as limited resolution and data complexity, enabling more precise identification of biomarkers for personalized treatment strategies.[27,43,104]

Large-scale longitudinal studies generate vast cytometry data sets, often with millions of cells. Traditional analysis methods, which relied heavily on manual gating, were both time-consuming and prone to bias. However, the emergence of unsupervised clustering and dimension reduction algorithms, such as GigaSOM, has significantly improved the efficiency and accuracy of these analyses.[105,106] Its unprecedented capability to handle high-dimensional data allows researchers to uncover rare immune cell populations and their functional states, providing deeper insights into the mechanisms underlying allergic responses.[104,107] Despite these advancements, annotating clustered data remains challenging. Semiautomated annotation tools are being developed to streamline the process, improving reliability and reducing researcher workload.[108] Ultimately, these innovations aim to enable personalized medicine for allergic diseases, tailoring treatments such as AIT to individual patient responses and thereby improving outcomes and reducing adverse effects.[27,43,100,104]

ROLE OF AI FOR DATA INTEGRATION TO ACHIEVE PERSONALIZED MEDICINE

The integration of artificial intelligence (AI) with multiomics data represents a pivotal advancement in personalized medicine,

enabling precise health care interventions tailored to individual patient profiles. Multiomics approaches, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, generate complex data sets. The ability of AI to integrate and analyze these data sets is crucial for understanding disease mechanisms, identifying biomarkers, and developing personalized treatments.[109,110] Key strategies for integrating multiomics data include (1) horizontal or vertical integration methodologies, (2) AI-driven strategies, (3) AI tools for personalized medication, and (4) integration of omics and clinical data.

Horizontal integration, a method requiring the synthesis of data from the same omics layer across different conditions or samples, is essential for identifying shared biomarkers and pathways across various biologic contexts. For instance, in oncology, this approach facilitates the comparison of genomic data from multiple tumor samples, aiding in the identification of mutations associated with disease progression. In contrast, vertical integration combines different omics data from the same biologic system, providing a comprehensive view of gene expression and protein function, which is crucial for more effective and personalized treatment options.[111-113]

AI enhances multiomics integration by using 3 main approaches. The "early" integration approach merges multiple omics layers into a single data set before analysis, utilizing deep learning to mitigate challenges posed by high dimensionality and thereby ensuring robust analysis by focusing on the most informative features.[112,114] The "intermediate" integration approach relies on the transformation of each data set into intermediate representations before integration, allowing a more meaningful biologic insight. AI models, particularly those using latent factor analysis, excel at capturing complex interomics relationships, reducing noise, and enhancing data interpretability.[112,114] Finally, "late" integration involves the analyses of each omics layer separately, with results integrated at a higher level. AI models that incorporate cross-omics interactions during this phase are particularly effective, allowing for specialized analyses tailored to the specific characteristics of each data type.[112,115]

In the context of precision medicine, several AI tools have been developed to facilitate integration of multiomics data. For instance, multiomics factor analysis (MOFA) and MOFA+ analyze multiomics data sets to identify latent factors. AI platforms such as the Molecular Twin integrate multiomics data with clinical information to predict disease outcomes, advancing personalized treatments,[101-103] This integration allows for the development of predictive models that anticipate disease onset, progression, and response to therapy, paving the way for more personalized and effective health care (Fig 3).

REGULATORY PERSPECTIVE ON OMICS BIOMARKERS IN DISCOVERY, THERAPEUTIC MANAGEMENT, AND TOLERANCE

The past decade has been fruitful toward identifying several candidate biomarkers in drug development and personalized therapeutic management of respiratory and food allergy. Some candidate biomarkers may serve both goals. For example, a prognostic biomarker that differentiates children who will "grow out of" respiratory or food allergy from those who will have sustained chronic allergic disease will both guide clinicians toward those who are most in need of intervention and aid toward participant selection for therapeutic clinical trials. Similarly, a diagnostic biomarker or surrogate end point that replaces oral food challenge will be of immense value to clinical and industry stakeholders alike. Conversely, some biomarkers, such as rare lymphocyte subsets with multiple cellular markers, may require technology (eg, 20- to 30-color flow cytometry) that is unusual in the clinical setting. As stated at a recent US Food and Drug Administration public workshop, the margin of error for acceptance or qualification of biomarkers in allergic diseases is narrow, so stakeholders should focus on candidate biomarkers for personalized medicine that are highly sensitive and specific, consider that a composite of measurements will have greater value than any one biomarker alone, and choose biomarkers for which there are robust assays that can be validated for accuracy and precision.[116] In addition, strategies for validation should consider the fact that the context in which a biomarker is used will determine the regulatory pathway (ie, approval as a diagnostic test or device vs qualification or acceptance as an end point in clinical trials) because the indication or context of use may vary accordingly.

CHALLENGES IN APPLYING MULTIOMICS AND AI APPROACHES TO IDENTIFY BIOMARKERS OF AIT

Although multiomics technologies and AI-driven approaches offer promising avenues for biomarker discovery in AIT, significant challenges remain in translating these innovations into routine clinical practice. To date, many AIT studies have primarily used single-omic approaches—such as transcriptomics or proteomics—rather than fully integrated multiomics strategies. This is largely due to the high cost associated with each omics platform, limited availability of high-quality samples, and technical challenges around reproducibility and standardization of methodologies. Although single-omic data have provided valuable insights, the added complexity and cost of generating and integrating multiomics data sets have constrained their widespread adoption.

However, as technological advances continue to reduce sequencing and analysis costs, the need for integrative approaches is becoming more apparent. The future of precision medicine in AIT likely lies in the ability to combine multiomics data with clinical phenotyping and environmental exposure information (the exposome). Such integration could enhance our understanding of disease endotypes and treatment response variability at a systems level, although some challenges will remain. The integration of multiomics—encompassing genomics, transcriptomics, proteomics, metabolomics, and epigenomics—requires a high degree of technical and analytic coordination. The volume, dimensionality, and heterogeneity of these data demand robust bioinformatics infrastructure, specialized computational tools, and personnel skilled in both biology and data science. Many clinical institutions, especially those without dedicated translational research capabilities, may find these demands prohibitive.

The application of AI and machine learning in biomarker discovery further complicates the landscape. Despite growing sophistication, challenges such as model overfitting, lack of methodologic standardization, and limited generalizability are common. These issues are especially pronounced in AIT, in which sample sizes tend to be small and cross-study harmonization is limited. Without access to large, diverse, and high-quality data sets, predictive models may fail to perform reliably across different patient populations.

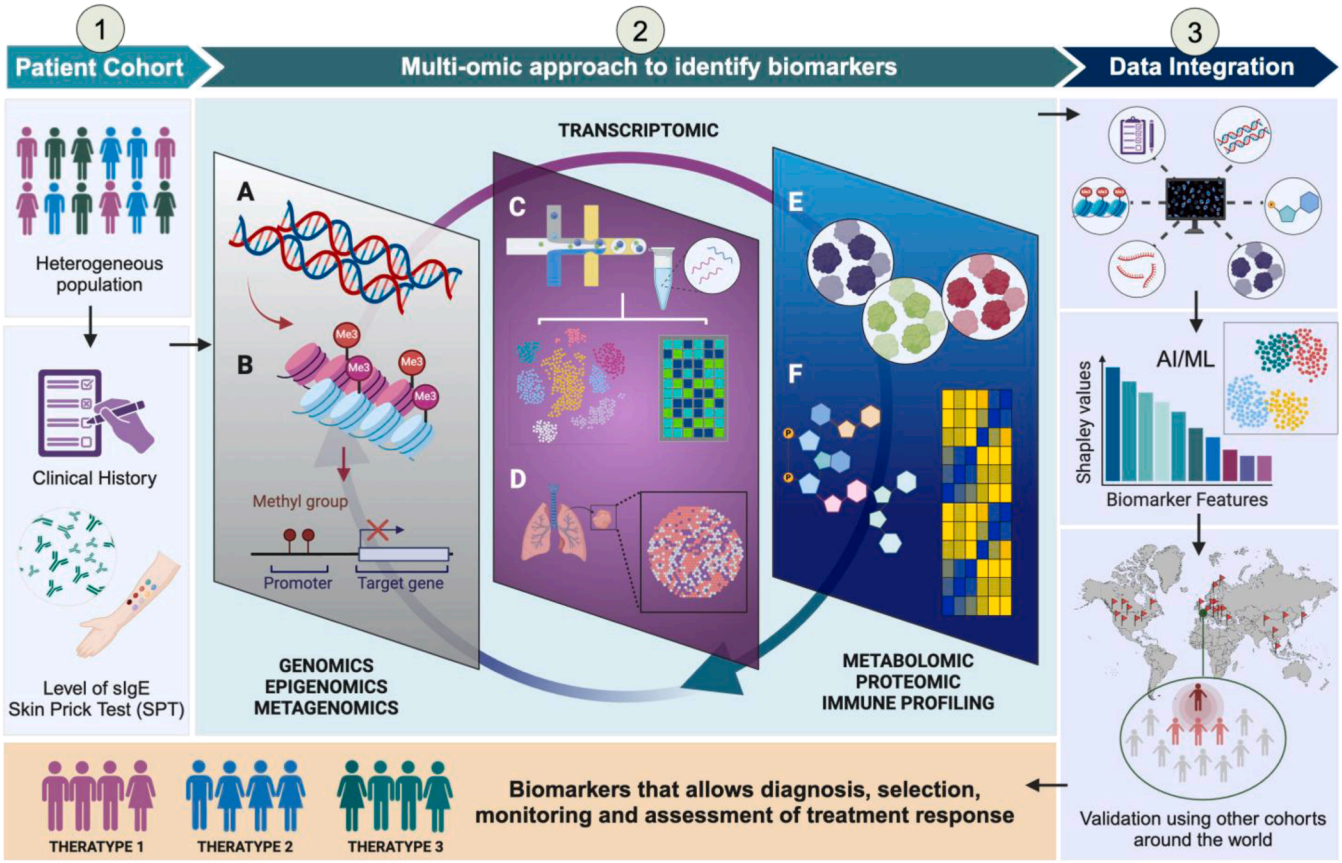


FIG 3. Multiomics approach to identify biomarkers of AIT. The identification of biomarkers of AIT can be achieved through 3 key stages as follows: (1) identification of patient cohort, (2) multiomics approach to identify biomarkers, and (3) data integration. A patient cohort from a single site consisting of a heterogeneous population with a clear clinical history and data (ie, level of specific IgE and skin prick test) should be collected before multiomics analysis. Samples are collected from each patient cohort and can be subjected to various multiomics analyses consisting of genomics and epigenomics (**A** and **B**), transcriptomic (single-cell and spatial) (**C** and **D**), and proteomic and metabolomic (**E** and **F**) studies. Clinical and omics data can be pooled by using machine learning (ML) algorithm tools that allow data integration to identify biomarker features. Candidate biomarkers will then be validated in another cohort of patients, allowing patient stratification and identification of disease endotype. *sIgE,* Specific IgE. Figure created using BioRender.com.

A final and crucial hurdle is the validation of biomarkers identified through these approaches. Most studies to date have been exploratory or of a proof-of-concept nature, often lacking replication in independent cohorts. Progress toward clinical implementation requires a stepwise process that includes (1) replication in larger, independent populations; (2) standardization of assays and analytic protocols; (3) prospective validation in multicenter trials; and (4) establishment of regulatory and ethical frameworks for biomarker qualification. In summary, although multiomics and AI-driven approaches hold significant promise for advancing precision medicine in AIT, their successful translation into clinical settings will depend on overcoming current cost, technical, and methodologic challenges, and increasingly, on integrating patient-specific data, multiomics profiles, and environmental exposures.

CONCLUSION

A multiomics approach for evaluating personalized biomarkers in allergic diseases and AIT leverages data from genomics, epigenomics, transcriptomics, proteomics, and metabolomics. The integration of these layers will pave the way toward the identification of biomarkers that predict treatment efficacy, stratify patient responses, and enhance understanding of disease mechanisms. Despite the advancement in these approaches, challenges in the context of data integration to harmonize diverse data types, validation to translate to clinical practice, and scalability to increase accessibility remain to be addressed. Their clinical translation will depend on overcoming key practical, financial, and methodologic challenges. A concerted effort toward standardization, interdisciplinary collaboration, and infrastructure development will be essential to realize the promise of precision allergy immunotherapy.

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