



Resolving Clinical Phenotypes into Endotypes in Allergy: Molecular and Omics Approaches

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Abstract

Allergic diseases are highly complex with respect to pathogenesis, inflammation, and response to treatment. Current efforts for allergic disease diagnosis have focused on clinical evidence as a binary outcome. Although outcome status based on clinical phenotypes (observable characteristics) is convenient and inexpensive to measure in large studies, it does not adequately provide insight into the complex molecular determinants of allergic disease. Individuals with similar clinical diagnoses do not necessarily have similar disease etiologies, natural histories, or responses to treatment. This heterogeneity contributes to the ineffective response to treatment leading to an annual estimated cost of \$350 billion in the USA alone. There has been a recent focus to deconvolute the clinical heterogeneity of allergic diseases into specific endotypes using molecular and omics approaches. Endotypes are a means to classify patients based on the underlying pathophysiological mechanisms involving distinct functions or treatment response. The advent of high-throughput molecular omics, immunophenotyping, and bioinformatics methods including machine learning algorithms is facilitating the development of endotype-based diagnosis. As we move to the next decade, we should truly start treating clinical endotypes not clinical phenotype. This review highlights current efforts taking place to improve allergic disease endotyping via molecular omics profiling, immunophenotyping, and machine learning approaches in the context of precision diagnostics in allergic diseases.

Keywords Allergic diseases · Endotype · Molecular profiling · Big data · Multi-omics · Machine learning

Introduction

Allergic diseases (asthma, atopic dermatitis (AD), allergic rhinitis (AR), food allergy (FA), and eosinophilic esophagitis (EoE)) are conditions caused by inappropriate immunological responses to normally harmless antigens. Collectively, they affect more than 50 million Americans each year making them the sixth leading cause of chronic illnesses in the USA [1, 2]. Although we may observe organ-specific symptoms, allergic

diseases are also systemic and are caused by partially shared etiologies. Individuals who have one allergic condition are more likely to develop other allergic conditions and the triggers for each may be shared. Such co-occurrence of allergic conditions in children has been estimated to be ~10-fold higher than one would expect by chance [3–5], suggesting a shared etiology or comorbidity caused in part by a process known as the allergic march (Fig. 1). While specific individuals may not have every disorder in the allergic march, the sequence starts with AD often in infancy, followed by FA and ending with AR or asthma [6, 7]. Furthermore, patients with AD, FA, asthma, or AR are at increased risk of being diagnosed with EoE [8]. The relationship between FA and EoE seems to be particularly strong, with FA patients developing EoE almost nine times more often than their healthy peers [9, 10]. Further, the risk relationship between EoE and AR seems to be bidirectional, with each condition imparting risk for the subsequent diagnosis of the other [8]. As a result of these various comorbidities, although a rare occurrence compared with other atopic diseases, EoE has been proposed as a fifth member of the allergic march [8, 11].

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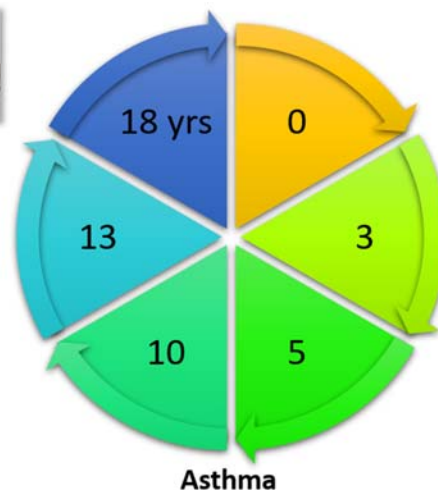
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Fig. 1 Schematic diagram illustrating progression, co-existence, and comorbidity of allergic diseases commonly known as “allergic march” in a single individual. FA, AD peak in the early years of life and decrease after a while. Asthma and AR increase over time as sensitization develops further

Eosinophilic Esophagitis



Allergic Rhinitis



Asthma



Eczema



Food allergy



Traditional classification of allergic diseases is typically based on severity, which relies on some form of “symptom score,” which is used as an indirect measure of risk and/or impairment. While this may be convenient and inexpensive to measure, it is a poor surrogate into the complex molecular determinants underlying allergic disease. Other prior attempts at classification of allergic disease used binary clinical outcomes such as atopy versus non-atopy implying suspected differences in underlying mechanisms. However, atopy is classically used to represent either genetic susceptibility or excessive immunoglobulin E (IgE) production regardless of whether this sensitization is contributory [12]. The problem is that atopy is likely too broad a category, and sensitization alone is unlikely to represent a true allergic endotype [12–15]. Notably, allergen-specific serum IgE and skin prick test (SPT) can assist in allergic diagnoses, but their diagnostic specificity and sensitivity remain limited. Indeed, for multiple allergic conditions, a detailed clinical history, additional provocation testing/challenges, or response to standard therapy together must guide diagnosis and treatment [16, 17]. Such heterogeneity, lack of robust biomarkers, and inadequate treatments warrant further research into the mechanisms underlying allergic diseases [17, 18].

Mechanism-based endotype classification can be different from patient to patient. Allergy endotypes are constantly evolving, and it is currently defined by the presence of a biologically tractable distinct pathophysiological mechanism, whereas phenotype is an observable physical characteristic

or binary outcome of disease without any implication of a mechanism [19–22]. Endotypes found in a specific biological pathway that explains the observable properties of a phenotype could provide an improved understanding of the distinct mechanisms driving the disease and advance precision medicine [23]. A natural result of these traditional classifications of allergic disease is that multiple molecular endotypes have been clustered together into a single phenotype (Fig. 2). Such oversimplification of phenotypes creates a confounding effect which hampers the efficacy of targeted treatment [24, 25]. As the development of targeted therapies has advanced, we are learning more about how molecular mechanisms play a role in phenotype definitions. Nowhere was this more apparent than with the initial trials of anti-IL-5 biologics in the treatment of asthma. The initial trials utilizing mild or moderate asthmatics (defined by severity) were a failure [26, 27], but when the target population was refined to the endotype of glucocorticoid-dependent eosinophilic asthma, the clinical studies were successful, leading to the approval of the first of a new class of asthma medicines in 12 years [28, 29].

This trend has continued with further development of cytokine-specific therapies, though there remains a large degree of variability in patient treatment response. This not only highlights the importance of molecular pathways in defining endotypes, but contributes to the rising cost of drug development with a current estimate of \$2.6 billion per drug [30, 31]. Thus, clinical phenotyping has been lagging behind other areas of medicine, mostly relying on data collection using

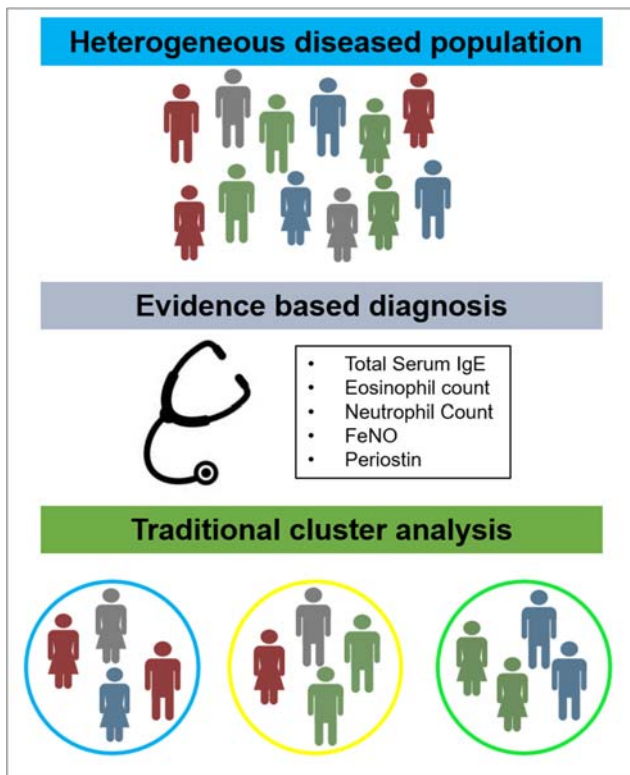


Fig. 2 Traditional methods of allergic disease diagnosis followed by cluster analysis leading patient classification with different endotypes and response to treatment

self-reported questionnaires and interviews. Biologic data is only as good as the associated clinical data collected. Given that there is a significant degree of heterogeneity between phenotypes and endotypes, it becomes very difficult to collect accurate clinical information in large populations that allows for selection of the most suitable treatment approaches for patients presenting with a spectrum of allergic disorders [20]. Such heterogeneity hinders the successful management of allergic diseases in the clinic as well.

The increased recognition among the scientific community that allergic diseases are comprised of a spectrum of different diseases with distinct clinical presentations and pathogenic mechanisms, along with the differences in prevalence and morbidity among different ethnic groups in the USA, is improving the way we study allergic conditions [32–37]. It is now clear that the traditional concept of phenotypes are a poor indicator of allergic disease severity and progression. Accurate reclassification of allergic diseases into clinically and biologically homogeneous subtypes could facilitate the understanding of disease pathophysiology and development of more targeted interventions [38]. A single phenotype may encompass multiple endotypes and such distinct endotypes likely have different genetic underpinnings [19]. The emergence of new biologic agents leads the way into the identification of clinically meaningful biomarkers that might help to stratify patients and identify those most likely to experience

benefit [21, 39]. Machine learning (ML) provides system-level opportunities, giving an improvement over conventional regression models by capturing complex, nonlinear relationships in multi-omics and clinical allergic data [40].

This review will highlight the current methods used to improve clinical phenotyping and molecular profiling of allergic diseases and outline how omics-based endotyping is transforming the traditional concepts of allergy through the discovery of novel endotypes. In addition, we will list the most common examples of ML approaches and new bioinformatics tools being utilized and integrated in clinical applications to study allergic disease endotypes and biomarkers. Finally, we will describe how this new knowledge is being utilized for the discovery and development of new treatment drugs.

Biomarkers for Allergic Diseases

Discovering and studying endotypes require the discovery and development of biological markers (biomarkers) in order to characterize the mechanisms and processes underlying different endotypes. Biomarkers are objectively measurable indicators that can be used to predict or monitor different aspects of a disease, such as risk, severity, clinical profile, and response to treatment. Types of biomarkers include genetic variation, epigenetic modifications, gene expression, protein levels, metabolites, and microbiomes [41–44]. An ideal biomarker will (a) link a disease endotype with its phenotype, (b) be stable or predictable over time, and (c) be detectable among populations with genetically distinct backgrounds [41]. The emergence of new biologic agents brings with it the challenge of identifying clinically meaningful biomarkers that might help stratify patients and identify those most likely to experience benefit [21]. Biomarkers also need to be available from relevant tissues with the least invasive methods possible. Systemic biomarkers relevant to allergy can be obtained from blood, serum, or plasma. Local biomarkers for AD may be available in the skin using tape stripping or skin biopsies. Nasal swabs or lavage, induced sputum, bronchoalveolar lavage (BAL), bronchial biopsies, or exhaled breath condensate can be used to obtain local asthma biomarkers, although bronchial biopsies, BAL, and sputum induction are fairly invasive, can only be performed in specialized medical settings by trained personnel, and may be unsuitable for young children. Biomarkers for allergic diseases have been reviewed extensively elsewhere [45–51].

Two broad asthma endotypes have been characterized based on the presence of type 2 (T2) inflammation. T2 inflammation is associated with eosinophilia and involves type 2

helper T cells (Th2 cells), which secrete the inflammatory cytokines IL-4, IL-5, and IL-13. Most established asthma biomarkers are directed toward the most common asthma endotype which is characterized by T2-high inflammation [52]. Eosinophil counts in peripheral blood have been shown to correlate with asthma severity in children with T2-high asthma, and may predict response to treatment with biologics. Eosinophil numbers in sputum, when available, can act as a predictor of asthma exacerbations [53] and may also predict response to treatment with glucocorticoids [54]. Total and allergen-specific IgE are markers for allergic asthma which assess atopy. The extracellular matrix protein periostin has been associated with T2-high asthma and has been suggested as a biomarker of T2-high inflammation in adult asthma patients [55]. Very few biomarkers for the less studied T2-low (or T1) asthma phenotypes are currently in use. T2-low asthma is often associated with neutrophilic inflammation, and high levels of IL-17 have been detected in neutrophilic asthma [52]. Several biomarkers have been suggested for the monitoring of AD severity. Serum levels of thymus- and activation-regulated chemokine (TARC/CCL17) have been reported to strongly correlate with disease activity [56], and among other potential monitoring biomarkers are IL-18 [57, 58], lactate dehydrogenase activity [59], and the chemokine +CTACK/CCL27 [60]. Recently, genetic variants have been identified that are specifically associated with the atopic march-like phenotype of AD + asthma comorbidity [61, 62], suggesting that such comorbidity constitutes an allergic endotype that may be predicted using biomarkers.

Skin prick testing to individual allergens has long been used to diagnose allergic rhinitis [63]. In addition to skin prick testing, TARC/CCL17 in nasal secretions may be used to distinguish allergic and nonallergic rhinitis [64]. Skin prick testing together with oral food challenge is used to diagnose food allergy. The basophil activation test and the more recently developed mast cell activation test have shown potential for distinguishing between food allergy and mere sensitization without the need for oral food challenge. Table 1 provides examples of established and emerging biomarkers for major allergic disorders, many of which may be of use for phenotyping. The table is not exhaustive, and the extensive literature on allergy biomarkers contains many reports of suggested biomarkers that may become useful in the future.

Genetic analysis of allergic diseases, including candidate gene studies, genome-wide linkage studies within pedigrees, and genome-wide association studies (GWAS), can provide useful biomarkers for endotyping of allergic diseases with an estimated heritability ranging from 35 to 95% [24, 82]. In the last 12 years, GWAS have identified loci shared across multiple allergic phenotypes, including asthma, allergic rhinitis, atopic dermatitis and food allergy. *IL13*, *IL4*, *IL33*, and *TSLP* are related to the “T2” immune response of type 2 helper T cells (Th2), and type 2 innate lymphoid cells (ILC2) are

biologically linked with immune function and implicated in allergy [82–85]. There are some loci that do appear to act specifically for certain asthma phenotypes and European ancestry. The chromosomal 17q12-21 locus has been associated with childhood asthma [86]. In particular, *ORMDL3/GSDMB/LRRC3C* is linked to childhood-onset asthma [87–89]. Loci such as *TLR1/TLR6* and *ADAD1/IL2* are linked to Th17-related mechanisms. GWAS have successfully identified numerous FA association loci in European ancestry [90–93]. Recently, there has been a focus on ethnicity-specific effects. For instance, *PYHIN1* is significantly associated with asthma, but only in individuals of African ancestry [88]. There is also an increasing focus on using admixture to map risk loci [24]. There is a strong heritable component to AD, and several candidate genes have been identified using association studies [94]. Filaggrin (*FLG*) mutations are found in 25–50% of AD patients [95] and are associated with severity and age of onset [96]. However, not all *FLG* mutation carriers develop AD [97], and *FLG* mutations alone are not sufficient to define a specific endotype.

Until recently, biomarkers for allergy were developed using hypothesis-based approaches focusing mainly on the abnormal immune responses to allergens. High-throughput omics technologies such as genomics, transcriptomics, epigenomics, proteomics, metabolomics, and microbiome analysis allow the screening for biomarkers in an unbiased fashion [98]. Biomarkers derived from an individual “omics” layer may not be sufficient to define all endotypes, underscoring the need for multi-omics approaches to achieve an integrated systems-level view of disease pathogenesis and endotypes [39]. The integration of endotypes, biomarker information, and data from omics technologies is creating large-scale biological databases [41]. These large-scale databases require strong computational power and new programming approaches to help sort and improve the prediction of outcomes for disease. Machine learning (ML) provides such opportunities, giving an improvement over conventional regression models by capturing complex, nonlinear relationships in multi-omics and clinical allergic data [40].

Immunophenotyping and Allergic Endotypes

Immunophenotyping has an important role in elucidating host immune responses. It is the analysis of heterogeneous populations of cells for the purpose of identifying the presence and proportions of cells in the populations of interest. Recent advances in RNA-sequencing and single-cell RNA-sequencing (scRNA-seq) technologies allow the detection of subpopulations that play important roles in host immune responses including the internal environment (obesity, co-morbidities, biome, etc) and external triggers (exposures, diet, infections, etc). ScRNA-seq studies have demonstrated that immune cells exhibit vastly heterogeneous expression profiles within

Table 1 Established and emerging biomarkers for major allergic disorders

Disease	Source	Marker	Phenotype/outcome	Reference(s)
Asthma	Blood, serum	Serum IgE		[65]
		Blood eosinophils	T2-high asthma, lung function	[51]
		Serum periostin	T2-high asthma	[54]
	Urine	LTE4	Asthma severity, aspirin-sensitive asthma, susceptibility to leukotriene receptor antagonists	[66]
		Metabolomic profile	asthma severity, corticosteroid-resistant asthma, early-onset asthma	[67–69]
	Exhaled breath	Volatile organic compounds	Eosinophilic asthma, neutrophilic asthma, persistent asthma	[70, 71]
		Fractional exhaled nitric oxide	Eosinophilic airway inflammation, response to treatment	[72]
AD	Sputum	Eosinophils	T2-high asthma, asthma severity, lung function, predictor of exacerbations, response to treatment	[51–53]
	Blood, serum	Serum TARC/CCL17	AD severity	[56]
	DNA	Filaggrin genotype	Screening and prognostic biomarker for AD risk, AD severity, early onset AD	[55]
	Skin	Transcriptome profile	Treatment response	[73]
		Microbiome profile	AD severity	[74]
Allergic rhinitis	Skin prick test	Allergen sensitization	Diagnosis, distinguishes allergic from nonallergic rhinitis	[63]
	Nasal secretions	TARC/CCL17, endothelin-1	Distinguishes allergic from nonallergic rhinitis	[75]
	Nasal lavage following nasal allergen challenge	Eosinophils, IL-5, IL-6, macrophage inflammatory protein	Diagnosis, monitoring of treatment	[76]
Food allergy	Skin prick test	Allergen sensitization	Diagnosis	[77]
	Blood, serum	Allergen-specific IgE levels	Diagnosis	[77]
	Blood	Basophil activation test	Diagnosis	[78]
	Plasma	Mast cell activation	Diagnosis	[79, 80]
	Blood	FOXP3 methylation in antigen-induced T _{reg} cells	Predictive of response to oral immunotherapy	[81]

seemingly homogeneous cell populations [99]. The immune response is affected by factors including immune predisposition based on immunologic history (including infection history), race, age, gender, and season. Immunophenotyping using *cytometry by time-of-flight* (CyTOF) has become the method of choice in identifying and sorting cells within complex populations, such as the analysis of immune cells in a blood sample [100, 101]. CyTOF profiles the immune cells in humans and identifies subpopulations and endotypes that are altered in allergic conditions [100, 101]. Databases like the Immunology Database and Analysis Portal (IMMPORT) are readily available to explore immune phenotypes [102].

Leveraging Omics for Allergy Endotyping

Since molecular phenotypes are assumed to be downstream of genetic variants in the causal pathway such as gene expression, epigenetics, proteomics, or metabolomics data, an understanding of the causal link needs to be established. Currently, efforts are underway to deconvolute distinct endotypes using molecular profiling approaches (e.g., gene expression or

epigenetics) to make therapeutic decisions feasible. For example, traditional diagnosis of AD depends on obtaining the patient's family history and visual assessment of the skin, as there is no specific laboratory test clinically available for confirming a diagnosis or assessing likelihood of treatment outcomes. With the advances in high-throughput platforms for transcriptomic analyses, many gene expression datasets are regularly deposited on publicly accessible repositories such as the NCBI Gene Expression Omnibus (GEO). GEO currently hosts over 90,000 datasets comprising over two million samples and presents an enormous opportunity for data mining across multiple studies (<https://www.ncbi.nlm.nih.gov/geo/>). These genome-wide expression studies identify differentially expressed genes (DEGs) for diagnosis and molecular profiling of the disease condition and to evaluate treatment outcomes. The expression of selected/prioritized DEGs can be readily quantified and compared between disease or treatment states for quick, accurate, and cost-effective diagnosis. Gene expression profiling has been widely applied as a tool for definitive diagnosis for many complex diseases like cancers [103–106] as well as several autoimmune and inflammatory diseases [107–112].

Transcriptomes from whole blood, neutrophils, CD4⁺ T cells, lung and airway tissues, airway smooth muscle cells, induced sputum, and nasal lavage fluids have been studied in asthma [113]. For example, genome-wide profiling of bronchial epithelial brushings in individuals can distinguish between T2-high and T2-low asthma endotypes [114, 115]. Th2-high and Th2-low phenotypes have shown differential responses to available therapies, whereby patients with non-Th2-driven asthma may be less responsive to glucocorticoids compared with a predominantly Th2-high disease phenotype [114]. T2-high asthma is associated with high levels of eosinophils in sputum and peripheral blood. Eosinophilic asthma is the most common endotype found among severe asthmatics and is thought to be more glucocorticoid responsive. In contrast, neutrophilic asthma is marked by elevated peripheral blood neutrophils (> 7000 cells/ μ L in patients ages 6 to 12 years, or > 8000 cells/ μ L for those 12 years and older) and is commonly steroid nonresponsive [14, 116]. From 2003 to 2015, only one biologic was approved for the treatment of moderate to severe asthma in the USA. Since 2015, four new asthma biologics were approved by the US (FDA) [117]. Currently, asthma biologics cost US \$30,000 or more annually [118].

Individuals with high levels of IL-5 and eosinophilic inflammation (determined by blood eosinophil count) are more likely to respond to mepolizumab, reslizumab, and benralizumab in addition to the IL-4 α monoclonal antibody, dupilumab, which have been approved as add-on therapy for the management of severe eosinophilic asthma by the US FDA [119]. Significant strides in our understanding of the pathogenesis, pharmacotherapies, and therapeutic treatment strategies for asthma are made, and five biologic agents to target specific endotypes of inflammatory mediators that are important in the pathogenesis of asthma are now available. The five FDA-approved biologics for the treatment of asthma are as follows: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab (Table 2). These targets include IgE (omalizumab), IL-5 (mepolizumab, reslizumab), IL-5 receptor (benralizumab) and IL-4 receptor α (dupilumab; shared part of receptor for both IL-4 and IL-13) [121]. Knowledge of a patient's endotype can inform clinicians' choice of appropriate therapies [122]. For example, asthmatic patients with eosinophilic airway inflammation respond better to inhaled glucocorticoids than patients without eosinophilic asthma [123]. Similarly, patients with the allergic asthma endotype, characterized by allergic hypersensitivity to airborne allergens, have been shown to respond better to omalizumab therapy than patients with other asthma endotypes.

Recently, we analyzed AD gene expression data generated from multiple independent studies that are publicly available on NCBI GEO database. We identified 89 genes (89 AD-gene signature panel, "89ADGES") that were consistently up-/downregulated (AD vs. controls; $P < 0.001$) in multiple

independent transcriptomic datasets [124]. Using a support vector machine, the 89 genes discriminated AD from controls with 98% predictive accuracy [124]. Furthermore, we found that this gene panel consists of gene clusters related to barrier function, inflammation, and lipid metabolism, processes germane to AD [124]. A similar approach has also been successfully used in the diagnosis of EoE, for which no molecular diagnostic tool was previously available [125]. This genome-wide expression profiling work led to the development of an EoE Diagnostic Panel (EDP) that has been used to diagnose EoE, differentiate it from other forms of esophagitis, uncover disease mechanisms, and identify at least three EoE endotypes [125–128].

Epigenetic modifications have also been associated with allergic disease. Several genome-wide methylation studies of allergic disorders have been conducted, and many of them offer the first step for new diagnostic and targeted treatment plans. In one study, methylation patterns in peripheral blood mononuclear cells were characterized in inner city children with persistent atopic asthma compared to healthy controls. They found 81 differentially methylated regions (55 of which remained significant after accounting for cell mixture), most of which were hypo-methylated [129]. Their results suggest that the epigenome is dysregulated in asthmatic patients [129]. Total serum IgE was independently assessed in two different genome-wide methylation studies of Hispanic and European ancestry children [130, 131]. When eosinophil methylation patterns of asthmatics with high IgE and low IgE levels were compared, they found that certain genes were hypo-methylated in patients with high IgE levels compared to those with low IgE levels, suggesting potential therapeutic targets for the different subgroups [131]. More recently, a study examining DNA methylation in cord blood mononuclear cells from children with and without asthma found that the *SMAD3* gene promoter was hyper-methylated in asthmatic versus nonasthmatic children ($P = 0.005$) [132], and these findings were replicated in three different birth cohorts. These types of studies are necessary to connect childhood asthma development to in utero exposures [132], and may help identify early life biomarkers that identify children at high risk for asthma development so prevention measures could be instituted earlier. Profiling molecular and cellular mechanisms that directly contribute to allergy pathogenesis and endotyping is likely to aid the discovery of novel biomarkers and drug targets (Fig. 3).

Proteomics provide a way to characterize the inflammatory state in allergic disease, and this approach has been used to identify asthma endotypes. The U-BIOPRED cohort was used to identify clusters with distinct proteomic signatures that were associated with differential counts of granulocytes in sputum [133]. In a recent study involving 12 patients with severe asthma, protein composition in lung epithelial structures was explored using data-independent acquisition mass

Table 2 Biologic agent for treating asthma [120]

Agent	Mechanism of action	FDA-labeled indications	Route of application	Dosing	Comments
Xolair (omalizumab, Genentech)	Binds to IgE, preventing binding to mast and other inflammatory cells and subsequent inflammatory mediator release	IgE-mediated allergic asthma, not controlled ICS ≥ 6 years of age	SC	Determined by IgE level and body weight Every 2 to 4 weeks	Preferred biologic agent for T2 high allergic asthma Administered in clinic setting
Nucala (mepolizumab, GlaxoSmithKline)	Binds to IL-5	Add-on therapy for severe asthma, eosinophilic phenotype ≥ 6 years of age	SC	Every 4 weeks	Administered in clinic setting
Cinqair (reslizumab, Teva Respiratory LLC)	Binds to IL-5	Add-on therapy for severe asthma, eosinophilic phenotype ≥ 18 years of age	IV	Every 4 weeks	Not labeled for pediatric use Administered in clinic setting
Fasenra (benralizumab, AstraZeneca)	Binds to IL-5R subunit on eosinophils and basophils, inducing cell toxicity	Add-on therapy for severe asthma, eosinophilic phenotype ≥ 12 years of age	SC	Every 4 weeks for the first 3 doses, then once every 8 weeks	Administered in clinic setting
Dupixent (dupilumab, Regeneron Pharmaceuticals and Sanofi)	Binds to IL-4R α , inhibiting IL-4 and IL-13 signaling	Add-on therapy for moderate to -severe asthma, eosinophilic phenotype or CS dependent ≥ 12 years of age	SC	Every 2 weeks	Can be administered at home Avoid concomitant use with live vaccines

CS, corticosteroid; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; IV, intravenous; SC, subcutaneous

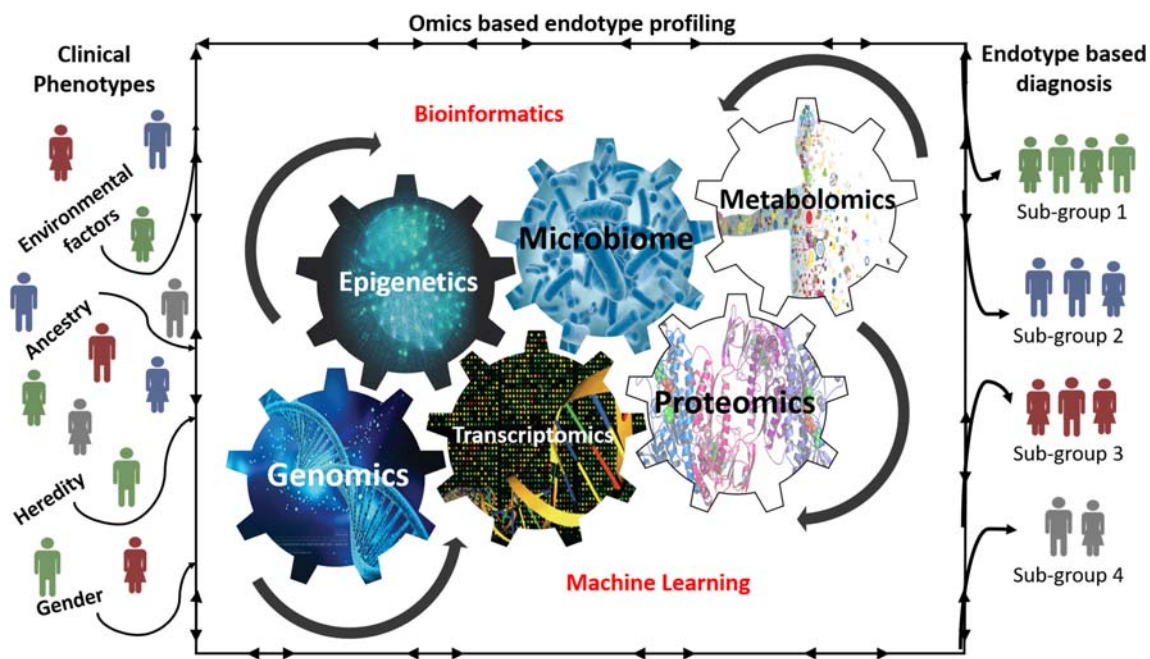


Fig. 3 Multi-omics integration representing the use of bioinformatics to integrate omics and generate molecular endotypes for precision diagnostics. The development of multi-omics platform capable of

measuring millions of analytes on a single specimen opened the flood gates for molecular phenotyping by vastly increasing the complexity and granularity of molecular data

spectrometry. Proteome differences were found in patients with stable severe asthma compared with patients with poor symptom control, as well as in metaplastic versus normal epithelium [134]. Proteomics-based approaches have also been used to explore inflammation in AD. A recent study found evidence of an inflammatory and cardiovascular proteomics signature in nonlesional skin of patients with moderate to severe AD [135]. Furthermore, inflammatory proteomics signatures in serum of AD patients have been found to be associated with sensitization to specific allergen classes [136].

Recent studies leveraging human microbiota showed that there are distinct microbiota associated with particular endotypes of allergy. The commensal microbiome on epithelial barrier structures, such as the skin barrier, the gut epithelium, and the upper airways, plays an important role in maintaining homeostatic conditions. There is a symbiotic relationship and a great amount of cross-talk between epithelial barrier tissues, immune cells, and microbes [137, 138], and as part of the wider exposome, the microbiome is also intimately associated with lifestyle factors and a changing environment [138, 139]. Next-generation sequencing has enabled the characterization of organ-specific microbiomes in health and disease, and changes in the composition of the gut microbiota in infants have been associated with the development of childhood allergies, including food allergy [140, 141], AD development [142, 143], and asthma [138, 144]. It has also been shown that AD is associated with changes in the skin microbiome, including colonization by *Staphylococcus aureus* and decreased diversity [142, 145, 146].

An increased understanding of the interplay between host and microbes in allergic disease may lead to the development of novel biomarkers for endotyping and disease prediction.

It is well established that prenatal and postnatal environmental factors play a large role in the development of allergic disorders and often interact with genetic variation to modulate the risk of disease. These exposures include physical components of the external environment such as food allergens and aeroallergens, air pollutants, tobacco smoke, diet, drugs, microorganisms, and various chemicals. Furthermore, less specific factors such as climate, social environment, and behavioral factors can also modify the risk of allergies [147, 148]. The concept of the exposome encompasses all environmental stimuli that impact an individual from conception and onwards [149]. It is often defined to include the internal environment in the body, including oxidative stress, inflammation, and specific biomarkers that result from external exposures [150]. A better and more complete understanding of the way the environment interacts with other factors to promote the development of allergic disease holds particular promise for the area of preventive intervention. Among ongoing initiatives with relevance to the field of allergy is the Human Early Life Exposome (HELIX) project, which involves six existing European birth cohorts [151]. HELIX aims to obtain comprehensive, longitudinal pre- and postnatal data in order to characterize the early-life exposome and explore associations with health outcomes, including allergy and asthma. EXPOsOMICS is a European project that aims to assess exposure to high priority environmental pollutants mainly in air and water [152], whereas the Health and Environment-wide Associations based on Large

Table 3 Omics technology status, diagnostic, prognostic and therapeutic applications

Sample type	Cost to assay	Ease of obtaining material	Sample size	Condition/context dependent	Relationship to endotype/phenotype	Completeness of assay	Maturity of analysis/technology	Potential applications
DNA	\$+	+++	+++++	No	+	++	++	Screening, prognostic, predictive
RNA	\$	+ to ++	++(++)	Yes	++	++	+	Prognostic
Methylation	\$+	+++	+++((++))	Yes	+ to ++	++	+	Screening, prognostic
Proteomics	\$	+ to ++	++(+)	Yes	+++	+	+	Monitoring, prognostic
Metabolomics	\$	+ to ++	++(+)	Yes	+++	+	+	Monitoring
Microbiome	\$	+ to ++	++(++)	Yes	+++	+	+	Screening, treatment
Exposome	\$	+ to ++	++(++)	Yes	+++	+	+	Prevention
cyTOF	\$	+ to ++	++(+)	Yes	+++	+	+	Monitoring, predictive
scRNA-seq	\$	+ to ++	++(+)	Yes	+++	+	+	Predictive/treatment

population Surveys (HEALS; www.heals-eu.eu) aims to disentangle the influence of the exposome from genetic effects using monozygotic twin data. The Exposome-Explorer (<http://exposome-explorer.iarc.fr>) is a database with extensive information about biomarkers associated with exposures to environmental risk factors. The European multicohort study of allergies known as Mechanisms of the Development of Allergy (MeDALL), integrating 14 European birth cohorts that included 44,010 participants and 160 cohort follow-up study from pregnancy to age 20 [153], is a great example to advance this field through characterization of the exposome within multiple time windows, development of exposure assessment and analytic methods, and examination of exposome–response relationships related to a number of health end points [154]. In the USA, the National Institute of Environmental Health Sciences (NIEHS) has supported efforts to advance the field of exposome within environmental health research [155]. The NIEHS has established an infrastructure to promote the incorporation of the exposome within child health research studies. The Children’s Health Exposure Analysis Resource (CHEAR; <https://www.niehs.nih.gov/research/supported/exposure/chea/>) includes a network of laboratories with extensive analytic abilities for exposure assessment and measures of biologic response in a variety of biological samples. Although there are tremendous opportunities, exposomics is a young area of research, and challenges to be overcome include extremely complex statistics, exposure misclassification, and the limits of exposure assessment technology [156]. Table 3 shows omics cost, maturity of the technology, and applications.

From Omics to Multi-omics

The promise of the genome-scale multi-omics molecular phenotyping approach to decipher the endotypes of allergic diseases has been well-described, and several investigators have proposed potential biomarkers and endotypes using omics resources [39, 56, 157–159]. However, although the role of “multi-omics-level” studies have been very useful in understanding the mechanism of allergic diseases manifestation, current analyses are primarily based on individual omics data, and there have not been sufficient attempts to integrate multi-omics data including machine learning methods in allergy endotyping [160]. Each omics approach can capture one of many dimensions underlying allergic pathology. Recent high-throughput next-generation sequencing technologies now make it possible to sequence and profile hundreds of thousands of biomarkers across the human genome. As a result, the development of multiple omic platforms capable of measuring millions of analytes on a single specimen opened the flood gates for molecular phenotyping by resolving the complexity and granularity of molecular data in allergic research (Fig. 4). Deep phenotyping into endotypes, multi-omics

profiling, and ML methodology will bring allergic diseases to a new era of precision diagnosis [161].

MeDALL combined omics data that included GWAS, DNA methylation, targeted multiplex biomarker, and transcriptomic studies to define novel phenotypes and endotypes of allergic diseases. The multi-omics and longitudinal data were able to identify comorbidity of AD, AR, and asthma regardless of IgE sensitization [5], and two distinct phenotypes of monosensitization and polysensitization in allergies associated with specific IgE [5, 153]. The MeDALL project is an example of how multilayered integration of classic data collection and new and advanced analyses can come together to improve diagnosis of allergic diseases. Another resource is the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED). Studies from U-BIOPRED cohort suggest multiple asthma endotype clusters based on transcriptomics data [162–167]. Recent studies have tried to understand the endotypes of pulmonary function impairment and their relationship with allergic diseases. A recent study by Kelly et al. used an integrative approach of transcriptomics and metabolomics to study pulmonary function in children with asthma [168]. Their approach involved using a weighted gene co-expression network analysis (WGCNA) to identify modules of co-regulated gene transcripts and metabolites (specifically 25,060 gene probes and 8185 metabolite features) from 325 children with asthma from the Genetic Epidemiology of Asthma in Costa Rica study. They found three gene modules and six metabolite modules associated with pulmonary function at $p < 0.05$. When they integrated the gene and metabolite modules, they were able

to link FEV1/FVC ratio with ORM DL3 and dysregulated lipid metabolism. This study is one of the first studies to integrate omics to assess pulmonary function in asthma [168]. Using both microbiome and metabolomics data, a recent study identified intestinal microbial-derived sphingolipids that are inversely associated with food allergy [169]. Other studies have integrated genetic and metabolomic data using networks and identified biological relationships between an asthma gene, ORM DL3, lipid metabolism, and asthma phenotypes [170]. Additional examples include a multi-omics approach involving transcriptomics and metabolomics that characterized altered platelet function in severe food-associated respiratory allergy [171], and an ongoing study that aims to explore associations between AD and obesity by integrating metabolome, immune biomarkers, and microbiome biomarkers [172].

Machine Learning and Allergic Disease Diagnosis

ML approaches can use computer algorithms to identify homogeneous patterns with similar underlying biologic mechanisms of allergic diseases and are based on systematically collected large molecular profile data along with clinical metadata. There are many commonly used supervised and unsupervised ML algorithms such as latent class, random forest, support vector machine, naïve Bayes, K-means, decision tree, etc [173]. These methodologies can be employed to identify at-risk patients for which good risk prediction methods do not exist or are found to have relatively poor performance.

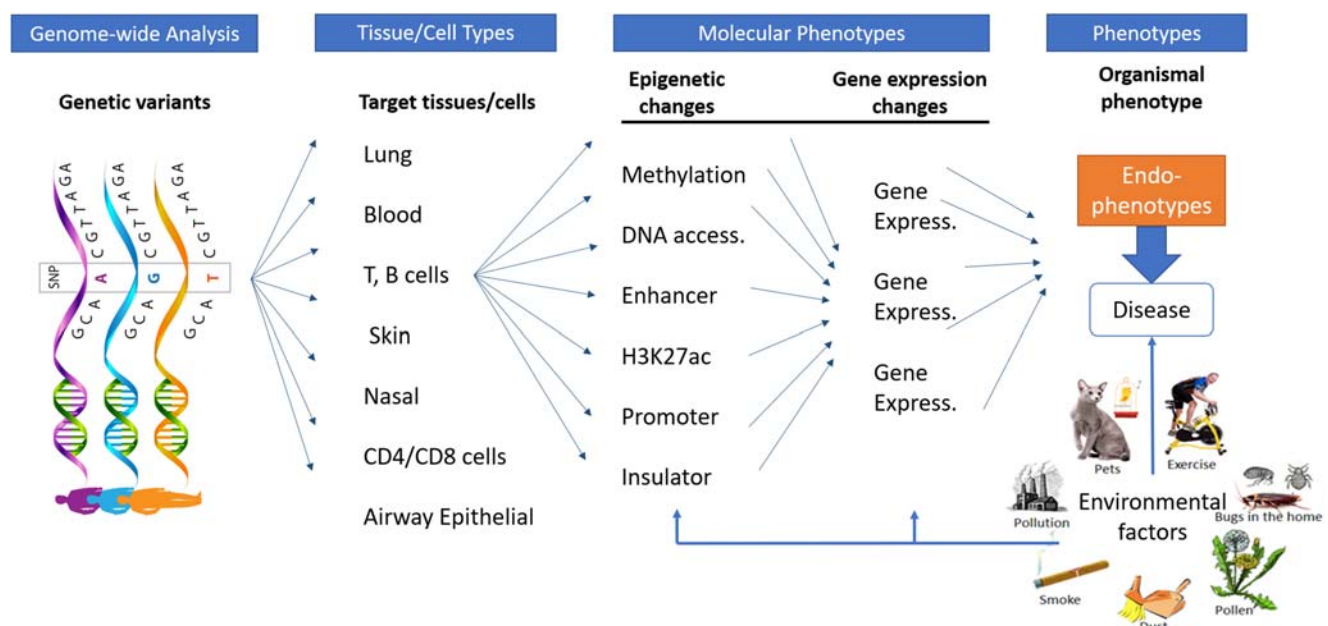


Fig. 4 Roadmap from genome-wide genotype to molecular and cellular phenotypes to endo-phenotype and diseases as influenced by environmental risk factors

ML methods such as latent class analysis (LCA)—an unsupervised statistical method developed to identify a small set of underlying subgroups [174]—are an alternative to the traditional approaches where one or more disease phenotype is used to compare treatment response. Recent studies on allergy classification and diagnosis have taken advantage of LCA and have made progress in clustering disease phenotypes that will potentially represent more accurately defined disease endotypes. For example, the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) used LCA to characterize four different phenotypes in food allergy: (1) low to no sensitization, (2) highly sensitized, (3) milk and egg dominated sensitization, and (4) peanut and/or inhalant allergen—no milk sensitization. Total IgE levels showed variations among the groups [175]. Doctor-diagnosed AD and asthma (at age 4 years) also varied according to specific IgE levels. The highly sensitized group presented with the highest rates of diagnosis, and the low to no sensitized group showed the lowest rates of diagnosis. Data from this study suggests that the use of LCA, rather than the traditional definition of atopy for IgE presence (allergen-specific IgE), better identifies children with allergic disease diagnosis [175]. LCA was also used in the Protection Against Allergy Study in Rural Environment (PASTURE), a European-based birth cohort [176]. They found four phenotypes for eczema, two of them before age onset 2 years, namely: early transient, and early persistent; the late phenotype with onset 2 years or older, and finally the never/infrequent phenotype. Using multivariate logistic regressions, they found that early phenotypes were strongly associated with food allergy. Asthma diagnosis at age 6 years and allergic rhinitis were only associated with the late phenotype [176]. A very similar study was carried out using the Canadian Healthy Infant Longitudinal Development (CHILD) study [177]. They used LCA to investigate the patterns of sensitization and AD from infancy to age 3. The study yielded five distinct classes of phenotypes, and similar to the PASTURE study, children with persistent sensitization appeared to be prone to other allergic disease diagnosis with age [177]. These studies are examples of how ML can yield advancement not only in allergic disease prediction and diagnosis, but also in clinical care. Stratification of AD endotypes on the basis of allergen sensitization profiles by Leonard et al. [136] further reveals differential systemic inflammatory profiles and anti-*Staphylococcus aureus* toxin antibody levels, highlighting the need to further characterize allergen-specific responses in AD patients, since adequate therapeutic intervention may require specific treatment of systemic inflammatory components in addition to microbial responses.

Another ML method was used to predict asthma on the basis of response to controller medications in the Childhood Asthma Management Program (CAMP) study [178]. The authors of the study used an algorithm called predictor pursuit (PP), a method that has two capabilities: first, it iteratively discovers phenotypes

in a dataset until there are no statistical differences that lead to further division, and second, it predicts clinical outcome on the basis of all available features (variables) sequentially dividing the feature space until there are no prediction performance improvements that can lead to further divisions [178]. PP identified four groups of phenotypes overall, namely allergic not obese (A^+/O^-), obese not allergic (A^-/O^+), allergic and obese (A^+/O^+), and not allergic not obese (A^-/O^-). Obesity was a factor for the effect of two control medications, nonobese children treated with budesonide instead of nedocromil had well-controlled asthma, whereas the opposite was true for obese children [178]. Pulmonary function impairment is recognized as an important endotype for asthma and AR diseases [179]. A recent study by the National Heart, Lung, and Blood Institute Severe Asthma Research Program (NHBLI-SARP) cohort indicated the predictive role of pulmonary function test in asthma [180, 181]. Pulmonary function tests include forced vital capacity (FVC, a measure of lung size), forced expiratory volume in 1 s (FEV₁, a standard measure of lung function), and FEV₁/FVC ratio (a commonly used outcome to assess airway obstruction). As outlined in the Guidelines of Asthma Severity [182], a patient is classified as having “mild” asthma if the FEV₁ level is > 80%, “moderate” asthma if the FEV₁ level is 60 to 80%, and “severe” asthma if the FEV₁ level is < 60%. ML approaches are being used to explore allergy heterogeneity and to probe the pathophysiological patterns or “endotypes” [183]. Ideally, these large datasets would integrate existing clinical and “omics” data (e.g., genomic, proteomic, lipidomic, and microbiomic). The use of harmonized terminology for patient characteristics and outcomes and of standardized protocols and the open access to repositories for biospecimen collection are of critical importance. The challenge of accessing large sample sizes is that it introduces heterogeneity in cases and controls, thus obscuring findings, the so-called Faustian bargain [184]. A similar problem is the “winner’s curse” [185] where significant results in a genome-wide study tend to exhibit larger effect sizes than what they are in reality.

Omics-Driven Endotype Identification to Enable Allergic Disease Drug Discovery

Prior to the GWAS era, numerous pharmacological approaches including anti-IgE (omalizumab), anti-IL5 (mepolizumab), anti-IL13 (lebrikizumab), anti-IL4R (dupilumab), and anti-IL2RA (daclizumab) antibodies had been trialed for allergy with varying degrees of success [186–189]. Recently, other therapies (anti-IL33, IL6R, TSLP, etc) have been tested [186, 190]. Recent high-throughput omics technologies such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics and exposomics have enabled the construction of regulatory networks and biological pathway models. Parallel advances in bioinformatics and computational techniques have enabled the integration and interpretation of these exponentially

growing data sets and opens the possibility of endotype-based precision medicine for allergic diseases [171, 191]. High-throughput measurements of molecular phenotypes provide an unprecedented opportunity to model cellular processes and their impact on disease. By integrating proteomics and genomics data, proteo-genomics allows for the analysis of the correlation of mRNA and protein pairs across samples, of mutations, post-translational modifications, and signaling pathways, and of correlations of the regulatory effects on RNA and protein expression levels caused by genetic variants (eQTL), microRNAs (miRNAs), and copy number aberrations (CNAs) [192]. The growing availability of biologics for the treatment of allergic diseases makes it increasingly important to accurately characterize endotypes so that therapy can be appropriately prescribed to improve each condition. Understanding the impact of endotypes may ultimately help explain the disease etiology and help drug discovery.

The goals of the omics-based endotype-driven deep phenotyping approach in allergic diseases are to link drug responses with the biological profile and to provide a safe and efficacious drug for a selected patient population. Besides the therapeutic purpose, omics-driven approaches should be able to open new avenues for prevention in high-risk individuals, early diagnosis, and intervention strategies [23, 41, 45, 193–195]. Although there is no pharmacogenetics (PGx) testing for any allergic disease, PGx studies targeting the response to treatment of the main drugs used for asthma treatment (i.e., short- and long-acting β_2 -antagonists [SABA and LABA, respectively], inhaled corticosteroids [ICSs], and leukotriene modifiers [LTMs]) are being conducted [196]. Several factors involved in the response to drug reaction include host factors and the chemical structure of the drug. A major advance over the last few decades has been the discovery of genetic variants associated with specific drugs to a given allergic disease [85, 197, 198]. Association of specific HLA genotypes and vancomycin allergy as well as drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported [199].

Recently, Thijs et al. published a retrospective study on the effects of mycophenolic acid (MPA) in 65 patients with severe AD with and without the presence of polymorphisms in the metabolizing enzyme uridine diphosphate-glucuronosyltransferase 1A9 (UGT1A9). Their results showed that 85% of patients with UGT1A9 polymorphisms were nonresponsive to MPA treatment [200]. An additional example of AD therapeutics focused on nemolizumab (CIM331), a humanized antibody against IL-31 receptor A. The IL-31 receptor plays a role in the occurrence of pruritus in AD, and a recent phase 2, randomized, double-blind, placebo-controlled, 12-week trial was conducted on 264 adults with moderate to severe AD who received subcutaneous nemolizumab [201]. This trial showed that nemolizumab significantly improved AD symptoms when compared to placebo by inhibiting the IL31 signaling, but longer studies should be carried out to confirm the results [201]. Similarly, a highly potent and specific inhibitor of human IL-13 activity in cell-based in vitro

assay, QAX576, significantly improved intraepithelial esophageal eosinophil counts and dysregulated esophageal disease-related transcripts in adults with EoE; baseline transcripts in the esophagus were associated with responsiveness to therapy [202].

As we embrace the era of precision medicine aiming at developing diagnostics and therapeutics that account for individual's unique genetic information, lifestyle, and environmental exposure to select the best treatment for their condition, large-scale omics, omics integration, and ML will be crucial for discovering biomarkers and designing therapeutic strategies for allergic diseases. Clinicians will be able to treat the molecular drivers of disease (endotypes), which can be better understood by analyzing a patient's genetic and gene expression profiles, rather than clinical phenotypes or manifestations. In addition, pathway analysis will also facilitate the prediction of response to therapy and outcome, as well as identify novel therapeutic targets close to disease pathogenesis (Fig. 5). With current and emerging public resources, we can potentially match allergy-associated CpGs against the ChEMBL database (v22.1) (<https://www.ebi.ac.uk/chembl/>) to identify whether any are targets of approved drugs or drugs in development. Databases of Encyclopedia of DNA Elements (ENCODE), the Ensembl regulatory build, and Functional ANnotation Of the Mammalian genome (FANTOM) project, the VISTA Enhancer Browser, expression quantitative trait loci (eQTLs), enhancer RNA (eRNA) co-expression, transcription factor (TF) co-expression, and capture Hi-C (CHi-C) are all useful to understand the role of genetic variants in health and diseases. Treatable targets can be identified in gene expression studies that encode proteins with predicted drug targets. We also can use the Ingenuity Pathway Analysis (IPA, www.ingenuity.com) to identify drug targets and upstream regulators of the gene lists. Studies have shown that several of the newly identified genes linked to lung function are treatable targets, highlighting the clinical relevance of an integrative omics approach [203, 204]. The long-term goal or roadmap is to tailor therapies to individual patients depending on their underlying endotype or pattern of pathophysiology (e.g., anti-T2 biologic treatment for allergic asthma; combined anti-Th2/Th17 treatment for steroid-resistant disease), through the implementation of precision medicine.

Conclusion

The evolution of our understanding of allergic disease endotypes reflects the interplay of both the clinically recognized phenotypes observed and the technologies and treatments available to study them (Fig. 6). Asthma is an illustrative example of how a broadly defined clinical entity can be gradually subdivided based on pathophysiologically distinct endotypes. The first clinical definition of phenotype

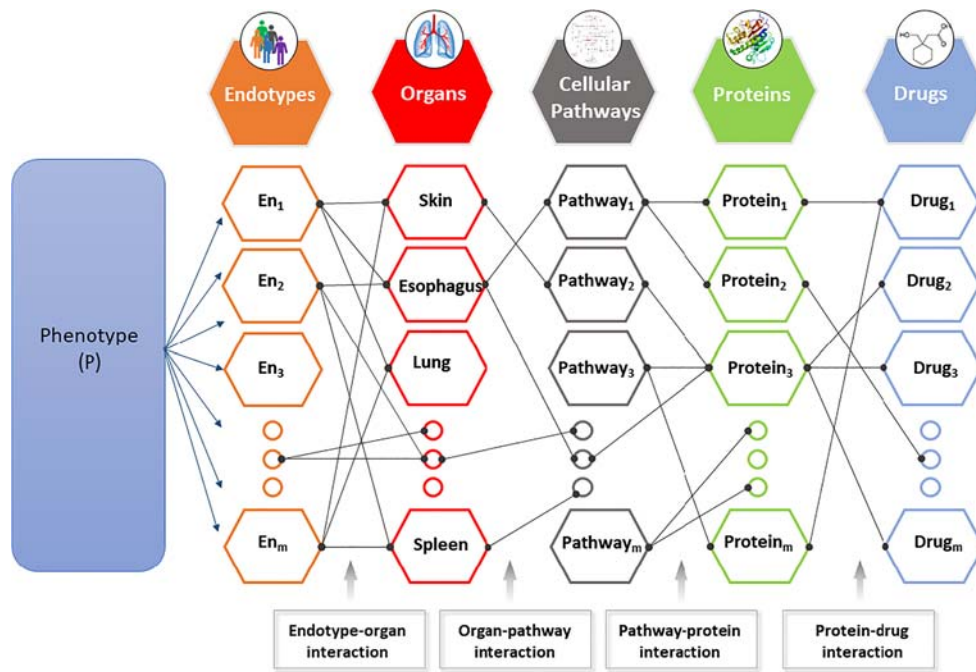


Fig. 5 An interaction and integrative molecular map showing an allergy phenotype (P) mapped to multiple endotypes (En_m) which interact in certain organs and leading cellular pathways (Path_m) interacting with proteins (P_m) and target drugs (D_m) (adopted from Huang et al. [161])

heterogeneity for asthma was made by Francis Rackemann in the 1940s [205], and the application of spirometric measurement of airflow limitation with reversible improvement as a recognized diagnosis was made in the 1980s [206]. Although not universally, clinical trials of broad anti-inflammatory therapy in the 1990s were largely successful for asthma. Around this time, researchers recognized the Th2 pathway as particularly relevant for many asthmatics, and broader availability of sequencing and early omics technologies reignited the interest in clinical heterogeneity of asthma [207, 208]. Only after the initially negative results of anti-IgE and anti-IL-5 antibody therapy in larger asthma clinical trials in the 2000s did the

field begin to realize the importance of careful focus on targeted endotypes in allergic disease [209]. The last 10 years has brought significant advancement in treatment of allergic disease with the rollout of multiple biologics to target the Th2 pathway. The next 5–10 years will not only see an increased number of targeted therapeutics (especially non-Th2 targeted), but there will also be a large investment in multi-omics integration and the use of machine learning to help recognize patterns in large datasets/cohorts as these new therapeutics enter the field. The challenge of our field in the next 10–20 years is using the multiple biologic/targeted therapies and the technological advances of multi-omics integration and

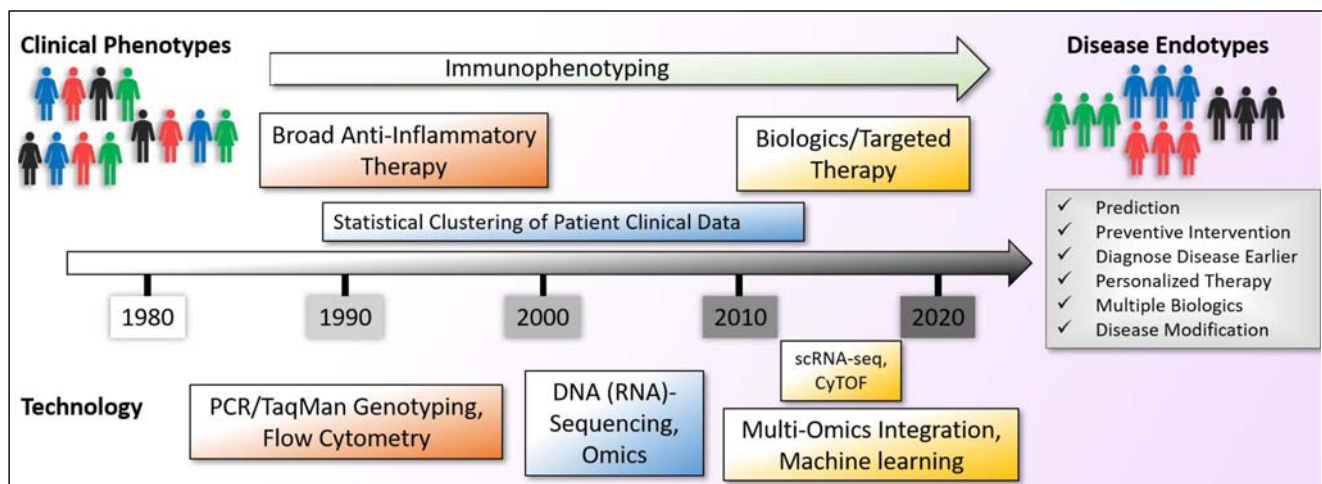


Fig. 6 Brief history of allergy phenotype/endotype research

machine learning to define the nuances of the many atopic endotypes, to set the stage for the next generation of trials in allergic disease.

Despite advances made in the understanding, diagnosis, and treatment of allergic diseases and an increasing interest in omics technologies, the search for endotype-specific biomarkers remains an unmet need. Recent efforts are underway to unravel allergy-specific endotypes and environmental exposures which impact the underlying biological systems [210]. One of the most promising sources of information to be used for endotyping of allergic diseases are multi-omics profiling, which now can be generated in real time for clinical use. With the advent of omics-based big data-driven and unbiased approaches to define and characterize endotypes, including more accessible tools for human immunophenotyping, we can now gather detailed molecular information to deconvolute and identify patterns from the data, and gather further insights into the biology of diseases and health states of individual patients [211, 212]. The availability of “omics” data and integrative omics approaches has created unique opportunities to unravel the molecular underpinnings of target endotypes to develop personalized risk stratification and therapy. Statistical methods to integrate multi-omics data are emerging to provide important insights into disease pathophysiology of allergic diseases [213]. As we move forward, accounting for individual’s unique race-specific lifestyle and environmental exposure along with clinical and multi-omics-based data-driven ML framework and integration will be crucial for discovering and designing therapeutic strategies for specific allergic endotypes. Such an approach will help to develop precision treatment options tailored to distinct endotypes in allergic diseases [214, 215].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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