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Immune monitoring for precision medicine in allergy and asthma

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Abstract

"Precision Medicine" embodies the analyses of extensive data collected from patients and their environments to identify and apply patient-specific prophylactic strategies and medical treatments to improve clinical outcomes and healthcare cost-effectiveness. Many new methods have been developed for evaluating the activity of the human immune system. Such "immune monitoring" approaches are now being used in studies of allergy and asthma in the hope of identifying better correlates of disease status, predictors of therapeutic outcomes, and potential side-effects of treatment. Together with analyses of family histories, genetic and other biometric data, and measurements of exposures to environmental and other risk factors for developing or exacerbating disease, immune monitoring approaches promise to enable "Precision Medicine" for allergic diseases and asthma.

Keywords

Allergy; asthma; atopic dermatitis; exposome; gene-environment interactions; immune monitoring; metabolome; microbiome; personalized medicine; pharmacogenomics

Precision Medicine and Immune Monitoring

Concepts of "Precision Medicine" (i.e., the patient-specific tailoring of medical treatment based on detailed phenotyping and characterization of the patient, their disease, and their environment) have long been applied in Clinical Allergy/Allergology. In their seminal

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description of therapeutic immunization with grass pollen extract of subjects suffering from grass pollen allergic rhinitis, Noon and Freeman recognized that the allergen therapy needed to match the cause of the patient's disease[1–3]. Accordingly, as recently reviewed[4], a foundation of "Precision Medicine" in modern allergology is the initial identification of the patient's allergic sensitivities prior to forming a plan of treatment, and the assessment of how those sensitivities may be altered by immunotherapy (IT).

The development of genome sequencing, as well as microbiome and virome characterization, stemming from improvements in DNA sequencing methods, has opened the possibility of collecting unprecedentedly detailed genetic data from allergic or asthmatic patients and their commensal or pathogenic microbes. Other 'omic' analyses that can be applied to the analysis of allergic disorders and asthma include measurement of 'epigenetic' chemical modifications of a person's genome, characterization of proteins and other macromolecules in bodily fluids or tissues, and measurement of glycan modifications of proteins. Similarly, characterization of the patient's 'exposome' (i.e., the carefully documented record of exposure to components of the patient's environment, including allergenic plants, animals, fungi, and foods, as well as to therapeutics, tobacco, pollutants, and irradiation) should be considered critical for understanding allergic or asthmatic patients in the context of Precision Medicine (Table 1).

A report from the U.S.A. National Research Council[5] proposed a framework for making sense of large datasets from patients to guide Precision Medicine therapeutic interventions, and to revise disease classifications based on new data gained through such efforts (Fig. 1). The traditional randomized clinical trial[4,5] will still remain the gold standard for assessing the safety and efficacy of any medical intervention. However, recent studies suggest that improved immune monitoring assays may be able to improve our ability to diagnose and evaluate immunological diseases, and predict therapeutic outcomes and side effects. In this review, we will provide some recent examples of work in this broad area.

Allergic Disease and Asthma Diagnosis and Patient Stratification

Efforts to identify patients with "subtypes" of allergic disorders involve both defining the observable characteristics of their disease (i.e., the disease "phenotype") and attempting to determine the underlying biological mechanisms involved in the origins and manifestations of the disease (i.e., the disease "endotype"). For example, increasing understanding of the mechanisms underlying food allergy[6–10] is helping to improve diagnosis and stratification of patients[11]. Notably, while allergen-specific serum immunoglobulin E (IgE) and skin prick tests (SPTs) can assist in food allergy diagnoses, these assays are not perfectly sensitive or specific[12]. The more expensive, laborious and higher-risk double-blind, placebo-controlled food challenge (DBPCFC), in which food allergens are administered to patients under carefully monitored conditions to detect clinical reactivity, is the diagnostic gold standard[13]. Alternative tests that do not involve triggering an allergic reaction would represent a significant advance. The use of recombinant allergens[14], and approaches for identifying the allergen epitopes recognized by a patient's IgE[15–17], may accelerate improvements in diagnostic specificity.

Other promising non-invasive immune monitoring tests include basophil activation tests (BATs), which measure blood basophil activation upon allergen challenge[18,19]. Blood basophil phenotype and function *in vitro* may be useful in distinguishing between peanut-sensitized children who have clinical allergy versus those who are sensitized but tolerant to peanut[19]. Moreover, it recently was shown that both conventional BATs (i.e., assessment of surface levels of CD63 or CD203c) and cytometry by time-of-flight mass spectrometry (CyTOF) analysis of basophils are robust assays that can be applied to samples shipped overnight, promising improved standardization of such testing at specialized reference laboratories[20]. The application of CyTOF technology[21] to the analysis of basophils[20,22] may reveal previously unsuspected heterogeneity in these cells, and provide additional diagnostic, prognostic and therapeutically-relevant data. Further, two recent reports of new fluorescent-avidin-based assays for basophil activation in whole blood describe a fast and inexpensive BAT that could reveal basophil heterogeneity between different individuals at diagnosis or during therapy[23,24].

In the asthma field, diagnostic classification is evolving rapidly[25], and several new subcategories or "endotypes" of asthma (i.e., variants of asthma that appear to differ in underlying biological mechanisms) were recently reported[26–31], encompassing different genetic variants, patterns of gene expression, and clinical phenotypic features. Efforts to further refine the classification of clinically important subtypes of asthma now include large clinical trial groups in several countries. This work should clarify the requirement for allergen-specific IgE in the pathogenesis of asthma endotypes from early life onward[32–34]. The proposed asthma endotype categories often rely on identifying common downstream pathways (e.g., the detection of a "T_H2 cell signature"[31,35]). These downstream pathways are, in some cases, susceptible to targeting with particular biologic therapies[36].

Therapy Selection and Monitoring

Diagnostic methods and classification schemes are of greatest value if they guide selection of effective therapies, and decrease rates of serious side effects. Even if there are reproducible biological differences between subcategories of a disease, unless there are meaningful therapeutic options for each subcategory, or other advantages such as improved prognostication of the disease course, the clinical relevance of the classification will be questionable[4,37,38]. Validation of new classification schemes via testing of different therapies, such as monoclonal antibody drugs, will have major clinical and financial consequences for patients, and for companies developing novel therapies and "companion diagnostics" intended to evaluate whether a therapy would be effective in an individual patient.

In asthma, there are several examples of therapeutic selection based in part on characterization of patient immune responses. Improved identification of patients whose disease has a "T_H2 endotype"[31,35], using biomarkers including periostin[39,40] and high levels of blood eosinophils[41], has been used to recommend therapies targeting T_H2 response components (e.g., IL-4, IL-5, IL-13 and/or their receptors)[42–47]. However, it appears that there are many pitfalls in attempts to develop these new diagnostic categories

for patient populations differing by age, race, or other factors that may alter the correlation of disease phenotype with individual biomarkers. For example, blood periostin levels may not be a useful biomarker of asthma in pediatric populations[48,49], while biomarkers such as exhaled NO and blood eosinophil counts may better predict asthma morbidity in this population[49]. As another example, therapies targeting eosinophils might be most helpful in patients with elevated levels of blood or tissue eosinophils[41,50–54].

Of course, immune monitoring approaches need to be evaluated in clinical trials to determine their merit. A recent study[55] of over 1,000 patients found that optimal “asthma control signatures” identified in whole peripheral blood specimens were enriched for immature lymphocytic gene expression patterns, and that suboptimal control was associated with signatures of eosinophilic and granulocytic inflammation, suggesting that such transcriptional data could guide treatment choices. However, we agree with Gomez and Kaminski[56] in thinking that large prospective clinical studies will be needed to test the usefulness of these immune signatures in predicting suboptimal asthma control over time. It may be possible to refine such approaches by identifying specific cells and regulatory events underlying such immune signatures, both in asthma and other settings[57–60]. The need for large prospective studies to evaluate the clinical utility of immune monitoring assays is similar to proposals for validating pharmacogenomic assays and predictions, including in the area of asthma therapy[61,62].

Similar points can be made regarding identifying any proposed biomarkers for allergic disorders and asthma, as described in recent papers on the potential use of immune monitoring and other data to improve the classification and management of allergic disease, including allergic rhinoconjunctivitis[63] and asthma[36]. As noted by Muraro et al., the heterogeneity of asthma, rhinitis, and AD biomarkers, and variation in the onset, clinical presentation and rates of remission or progression in these diseases combine to generate difficulties in determining the appropriate clinical management strategies, and in selecting biomarkers of therapeutic efficacy[36]. For example, a recent paper suggests that the tyrosine kinase inhibitor, imatinib, may have utility in the treatment of certain patients with severe asthma, but it is unclear whether the critical target is mast cells or other KIT positive cells, or may be due in part to effects of the drug on other tyrosine kinases[64,65]. Perhaps the development of immune profiling tools for assessing the importance of mast cells in asthma could be used to refine the selection of patients for this targeted treatment. That study, which included measurements of the mast cell product, tryptase, in the blood, as well as bronchial biopsies to quantify mast cell numbers in the airways, raises a general point about the extent to which measurements of cell populations and other analytes in the blood can be useful in efforts to “monitor” immune responses whose clinical manifestations reflect the pathology which they induce at specific sites of disease (e.g., the lungs, GI system, or skin). This is an important general problem for the field, and one that is not trivial to study.

Improved immune monitoring approaches could also be relevant in efforts to prevent the development of allergic disease. For example, it is known that genetic predisposition, and the phenotypic manifestation of clinical atopy, are correlated with the development of allergies, including food allergies[66–68]. The recently published LEAP (Learning Early About Peanut) randomized clinical trial provided convincing evidence that children in an

intention-to-treat population who had atopy (and therefore had a high probability of developing clinical allergy to peanuts), but who had negative results in SPTs for peanut, had an approximately 85% reduction in development of peanut allergy by 5 years of age if peanut products were introduced into their diet within their first year of life, in contrast to infants avoiding peanuts[69]. This surprising result has led to a reversal of decades of pediatrician advice that parents should avoid exposing their infants to allergenic foods until later in childhood. It may be the case that additional phenotyping of infants, based on the collection of immunological and other clinical data, family histories, and genetic data, could provide the basis for further improvements in decreasing the risk of developing severe allergies by guiding the timing and extent of exposures to environmental factors such as foods associated with allergies. In principle, immune monitoring tests could be less expensive and invasive alternatives to DBPCFC studies for assessing the efficacy of these interventions. Similarly, such assays could be used to evaluate factors that can influence a patient's threshold for developing a clinical reaction to allergen exposure, such as exercise, alcohol consumption, and concurrent infection[70–72].

A critically important area for implementing Precision Medicine concepts in allergy treatment is in the improvement of Allergen-Specific Immunotherapy (AIT) protocols. Ideally, detailed patient phenotyping could help tailor the allergen dose escalation schedule for AIT for allergic rhinitis[73–75] or oral immunotherapy (OIT) for food allergies, and predict which patients will become permanently desensitized or tolerized[76–78] rather than achieving desensitization dependent on continuing exposure to the allergen[74]. Recent studies provide proof-of-concept data indicating that certain biological measurements can better classify patients and guide their AIT regimens. A recent small phase I single-center clinical trial of OIT for peanut identified *FOXP3* gene methylation levels in regulatory T cells as a correlate in patients who achieved more sustained unresponsiveness to peanut after a period without peanut ingestion[77]. Another recent paper based on a small number of subjects identified expanded allergen-specific CD4+ T cells with an "anergic" T_H2 T cell phenotype as a feature of patients undergoing OIT[79]. Others have reported that patients undergoing allergen-specific IT show an increased proportion of regulatory T follicular helper T cells to T follicular helper cells[80]. Similarly, analysis of the frequencies of peanut allergen-specific B cells in patients undergoing peanut OIT showed increased levels of specific cells as a correlate of treatment[81,82]. As noted above, recent work indicates that blood basophil phenotype and function analyzed *in vitro* may be able to distinguish between peanut-sensitized children who have clinical allergy, in contrast to those who are sensitized but tolerant to peanut[19]. Basophil assays also are under investigation for monitoring the efficacy of IT for SAR[83] or omalizumab treatment for severe peanut allergy[84].

Further work with much larger patient cohorts and integrated analyses of different leukocyte populations and other immunological parameters will offer the prospect of identifying the immunological changes that are most closely correlated with the safety and efficacy of treatment, as well as the durability of patient responses. It also will be important to define which of such immune monitoring tests have the greatest clinical utility (and are most cost-effective) for use in routine "check-ups" of patients with allergic diseases, or those at substantial risk to develop such disorders, to enable early detection of allergic diseases, document sustained favorable responses to treatment, and/or give an early indication of the

need to consider altering that individual's management. The results of such efforts, that should include studies of people representing the full diversity of the human population in terms of sex, life stage, genetic background, environmental exposures, and socioeconomic circumstances, will be critical for generating sufficient scientific and clinical data to determine whether a new diagnostic classification of allergic disorders (i.e., a "new taxonomy[5]" of these diseases) should be considered.

Summary

The concepts of Precision Medicine are clearly applicable to the study and classification of allergic disorders and asthma, as well as the selection and monitoring of therapeutic strategies for patients (Table 1, Fig. 2). We feel that the field is only at the beginning of the process of critically evaluating the clinical utility of such "immune monitoring" approaches, some of which involve very newly developed assays. Fundamental questions remain about such approaches, including the extent to which the evaluation of features of immune responses that can be measured in the peripheral blood accurately reflect immunopathology at the tissue sites of disease (Table 2). Ongoing and future work will determine whether immune monitoring approaches will improve disease classification, therapeutic choice, and monitoring of disease status and responses to treatment, as well as the cost-effectiveness of care, in patients with allergic diseases and asthma.

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Abbreviations

AIT	allergen-specific immunotherapy
BAT	basophil activation test
CD-sens	basophil allergen threshold sensitivity
CyTOF	cytometry by time-of-flight mass spectrometry
DAO	diamine oxidase
DBPCFC	double-blind, placebo-controlled food challenge (DBPCFC)
IgE	Immunoglobulin E (antibody)
IT	immunotherapy
LEAP	Learning Early About Peanut (a clinical trial)

OIT	oral immunotherapy
SAR	seasonal allergic rhinitis
sIgE	specific Immunoglobulin E (antibody)
SLIT	sublingual immunotherapy
SPT	skin prick test
Tfh	T follicular helper cell
T_H2	T helper cell type 2

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Management Program cohorts, and employing gene set enrichment analyses of asthma control and the immunologic signatures gene set collections of the Molecular Signatures Database, the authors identified molecular pathways associated with a modified version of the asthma control test. They provide evidence that optimal asthma control signatures were enriched for immature lymphocytic gene expression patterns, and that suboptimal control was associated with signatures of eosinophilic and granulocytic inflammation. Notably, their work suggests that the triggering receptor expressed on myeloid cells 1 (TREM1 or CD354, a cell surface receptor expressed on activated monocytes, neutrophils, granulocytes, dendritic cells, and natural killer cells) is involved in asthma control, suggesting that patients with suboptimal asthma control exhibit signs of persistent innate immune activation. [PubMed: 27494826]

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peanut allergic patients, measurements of basophil allergen threshold sensitivity (CD-sens) (which correlate with the outcome of DBPCFC with peanut) were used to measure omalizumab treatment efficacy. The authors found that participants who needed an elevated omalizumab dose (ED) to suppress CD-sens had significantly higher CD-sens values at baseline compared to those who managed with a normal dose, and that the median ratios for anti-Ara h 2 IgE-ab/IgE were significantly higher in the ED group (17%) compared to the ND group (11%). This hypothesis generating study, which had a one-armed study design, provided evidence that the ratio of anti-Ara h 2 IgE-ab/total IgE, as well as basophil CD-sens to peanut, may predict the need for a higher dose of omalizumab in this setting. [PubMed: 27883239]

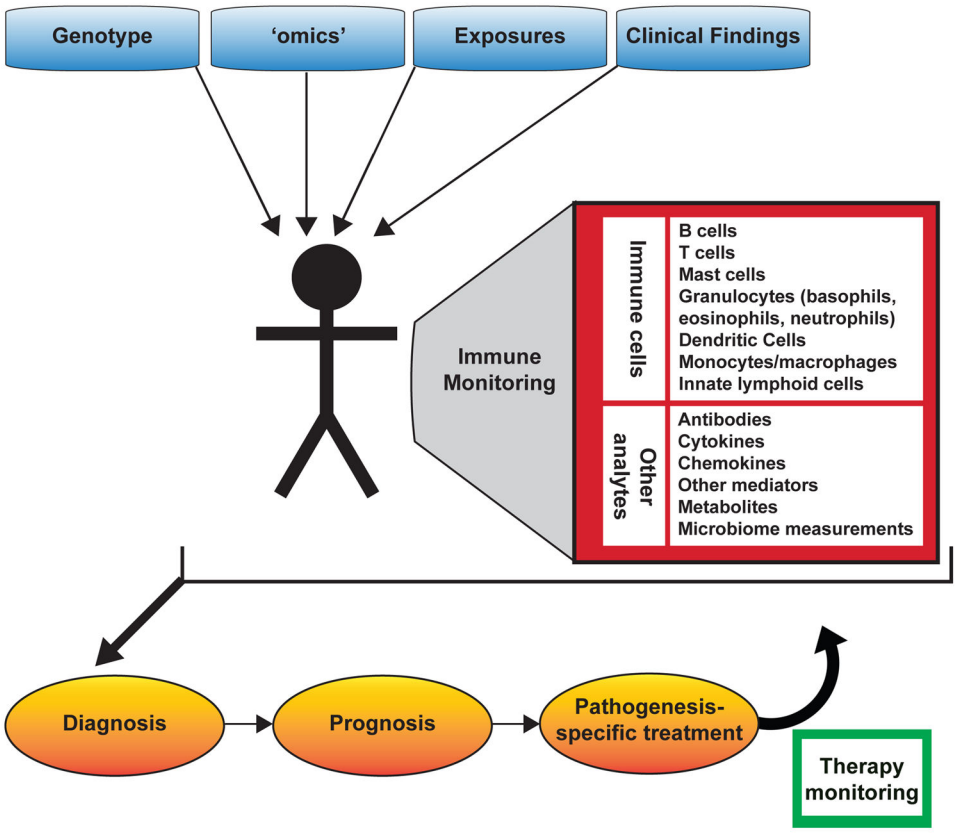

Figure 1.

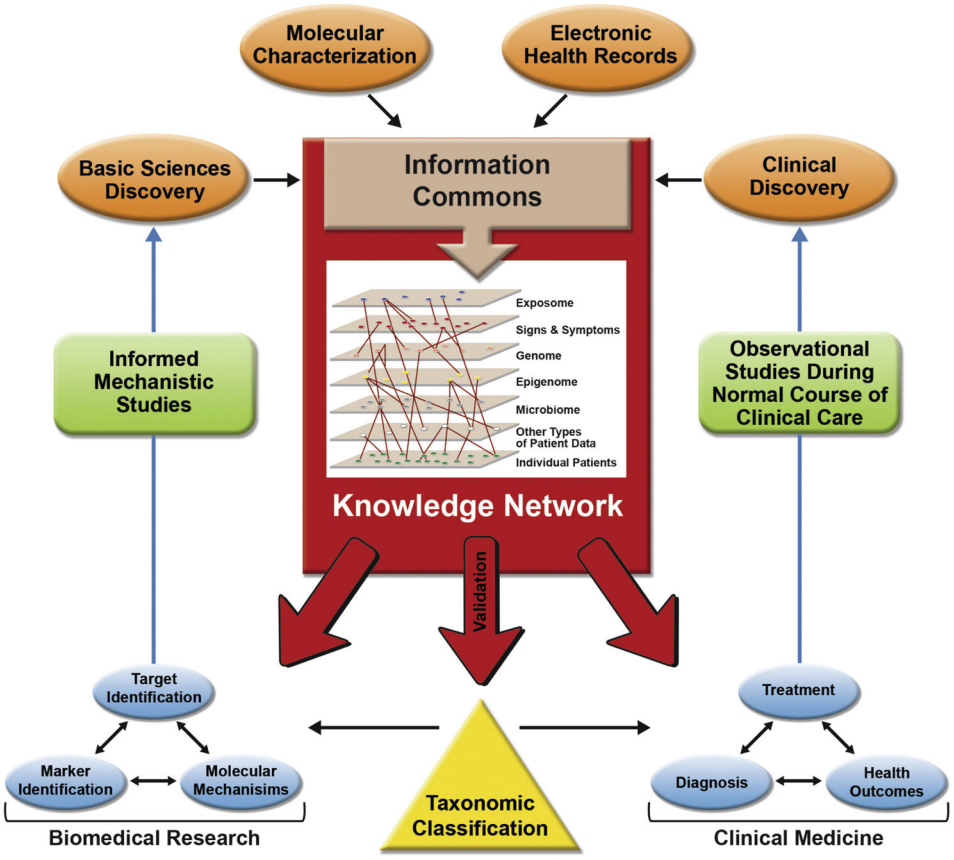

Figure 2.

Table 1

General principles of precision medicine for allergic disorders and asthma*

Characterize the disease: Identify the disease and, if applicable, the subtype of allergic disorder or asthma; for allergic disorders, precisely define the offending allergen proteins.
Profile the patient: Characterize patient genotype and phenotype (and in some cases microbiomes) and their environment (i.e., their "exposome"); assess patient's likelihood to respond to pharmacological or biological agents, AIT or other forms of management.
Select optimal management: Based on the individual's subtype of disease, offending allergens, genetic and phenotypic characteristics, and an evidence-based assessment of her/his likelihood to respond to various treatment/management options.
Monitor disease and response to management: Perform appropriate biometric monitoring during treatment (e.g., with pharmacological or biological agents or with AIT) to assess favorable or adverse effects of the intervention and duration of favorable effects.
Develop algorithms to select the most cost-effective management approach for that patient: Based on the characteristics of the patient and his or her test results and the evidence-based assessment of the clinical utility of the treatment options and the type of health care system in which that patient receives his or her care.

* By taking advantage of ongoing basic, translational and clinical research, and having access to patient-specific data obtained during the course of clinical care, these approaches can be continuously and iteratively refined and improved (see Fig 1). This is a modified version of Table 1 in [4], reproduced with permission of the American Academy of Allergy, Asthma, and Immunology.

Table 2

Needs for advancing precision medicine for allergic disorders and asthma.

Identify biological factors contributing to development of allergy/asthma	• More detailed understanding of genotype-phenotype relationships, and interactions with environmental exposures • Barrier state differences (affecting skin, respiratory and GI systems, etc.), and how these contribute to allergy development • Mechanistic effects of early vs. later allergen exposure (via skin, airways or ingestion, etc.) • Mechanisms of other protective vs. pro-allergy environmental factors (pets? farm animals?)
Identify pathogenic immune system features	• Which IgE antibodies actually contribute to allergy/asthma? • What T cell phenotypes and cytokine profiles contribute to allergy/asthma? • What basophil/mast cell populations and/or states contribute to allergy/asthma? • Interactions between mast cells/basophils and IgE/IgG4/other immunoglobulin isotypes • Epithelial and other cell type contributions to allergy/asthma • Determine which key features of the disease process in the affected tissues can effectively be "monitored" (e.g., to assess treatment outcomes) via the analysis of cell populations and other analytes in the blood.
Identify correlates and mechanisms of immunotherapy efficacy	• Differences between temporary desensitization and sustained unresponsiveness/tolerance • Antibody-mediated protection/desensitization (IgG4, and others?) • Are there potential T cell mechanisms of tolerance, beyond influences on antibodies? • Changes in basophil/mast cell sensitivity • Basis for "natural" desensitization or tolerance • Key biomarkers for predicting side effects of treatments
Identify new therapeutic strategies	• Modifications of current approaches (e.g., speed of updosing, multi-allergen therapies in food allergy IT) • New potential targets for biologics/other mechanistic-based therapies • Combination therapies (e.g., multiple biologics, biologics plus IT, small molecule drugs plus other treatments) • Companion diagnostics
Evaluate cost-effectiveness of new therapeutic strategies	• Evidence-based evaluation of the clinical utility of new treatment strategies • Measurement of disease and treatment costs – Cost to the patient – Cost to the health care system – Cost to society