Toward precision medicine and health: Opportunities and challenges in allergic diseases

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives:

1. To define features of precision medicine.
2. To recognize the potential benefits and current challenges in developing precision medicine–related strategies.
3. To identify ways in which elements of precision medicine are currently used to tailor treatment decisions or disease-monitoring strategies for specific allergic disorders.

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Precision medicine (also called personalized, stratified, or P4 medicine) can be defined as the tailoring of preventive measures and medical treatments to the characteristics of each patient to obtain the best clinical outcome for each person while ideally also enhancing the cost-effectiveness of such interventions for patients and society. Clearly, the best clinical outcome for allergic diseases is not to get them in the first place. To emphasize the importance of disease prevention, a critical component of precision medicine can be referred to as precision health, which is defined herein as the use of all available information pertaining to specific subjects (including family history, individual genetic and other biometric information, and exposures to risk factors for developing or exacerbating disease), as well as features of their environments, to sustain and enhance health and prevent the development of disease. In this article I will provide a personal perspective on how the precision health–precision medicine approach can be applied to the related goals of preventing the development of allergic disorders and providing the most effective diagnosis, disease monitoring, and care for those with these prevalent diseases. I will also mention some of the existing and potential challenges to achieving these ambitious goals. (J Allergy Clin Immunol 2016;137:1289-300.)

Key words: Allergy, asthma, atopic dermatitis, exposome, gene-environment interactions, metabolome, microbiome, personalized medicine, pharmacogenomics, stratified medicine

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The idea that treatments for individual patients should be tailored to the specific disease characteristics of that patient is not a new concept in the practice of clinical allergy/allergology. This notion arguably had its scientific foundation with Noon's and Freeman's description of a protocol to immunize patients afflicted with grass pollen–induced allergic rhinitis with an extract of grass pollen to reduce their clinical reactivity to that specific allergen.[1-3] Indeed, accurate diagnosis is foundational to the selection of optimal treatment in all areas of medicine.

Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
LEAP: Learning Early About Peanut
OIT: Oral immunotherapy
SIT: Allergen-specific immunotherapy
SPT: Skin prick test
Treg: Regulatory T

Accordingly, first identifying the allergen or allergens and other factors that drive disease in individual allergic patients before attempting to define the most appropriate management and treatment for those patients represents one of the best examples of the critical importance of this general principle.

However, even the first step, identifying the clinically important offending allergen or allergens, has its challenges. It is well known that whether one attempts to detect allergen-specific serum IgE or uses skin prick tests (SPTs) to measure reactivity to particular allergens, a positive result does not prove that the identified allergen-specific IgE is disease causing in that patient.[4] Put differently, although, by definition, allergen-specific IgE is necessary for the development of an IgE-dependent allergic disorder, it is not sufficient. For example, in the case of food allergies, the diagnostic gold standard is the double-blind, placebo-controlled food challenge (DBPCFC).[5] Although substantially more expensive than an SPT, the DBPCFC can definitively answer the following clinically important question: Will this particular allergen, when taken orally, induce significant signs and symptoms of allergic disease in that patient? Similarly, the development of recombinant allergens,[6] together with new methods that permit one simultaneously to assess small amounts of patients' blood for levels of IgE antibodies reactive with any of a large number of different allergen proteins,[7-9] has ushered in an era in which the definition of the offending allergen or allergens in individual patients can become increasingly detailed and precise.

Yet the need to personalize or stratify the management of patients with allergic disorders clearly extends far beyond simply identifying the offending allergen or allergens. Long gone are the days when it was adequate to know only that a patient had "asthma" or even "atopic asthma" to decide on the optimal course of treatment for the asthmatic patient, particularly for those with the most severe forms of the disorder.[10] Not only have several subtypes, phenotypes, or endotypes of asthma now been reported,[11-15] but the effort to define clinically important subtypes of asthma (beyond assessing only disease severity) is a work in progress, with large studies underway in several countries. This work should help to improve our understanding of the relative importance of various allergic mechanisms in patients with different subtypes of asthma and might provide additional evidence that in some patients asthma can develop essentially independently of IgE. Efforts also need to be continued to understand better the heterogeneity of the wheezing disorders observed early in life and what factors can determine whether these are or are not followed by the development of asthma.[16-18] Progress in this and related areas will be critical to the success of attempts to devise individualized approaches to classify current disease, assess the risk of subsequent development of asthma, and prevent or modify the development or progression of disease.

Similar work to identify clinically important subtypes of diseases is in progress in many areas of medicine. Indeed, the US National Research Council recently produced a monograph outlining how recent advances in the power (together with striking reductions in the cost) of the analytic and computational tools available to produce huge amounts of biomedical data and, as importantly, to mine such data for biological and clinical meaning might be exploited to generate a comprehensive "new taxonomy of disease."[19] This report also argued that if the specific elements comprising this new taxonomy of disease could be appropriately validated with respect to their clinical utility (eg, by showing that such new classifications of disease would improve our ability to predict disease development, render accurate prognoses, and/or select the most effective management and treatment options in individual subjects), then this new taxonomy of disease would help to foster marked improvements in health outcomes for both individual patients and populations while also potentially reducing the total cost of medical care.[19]

Easier said than done! For example, the identification of subtypes of asthma based on combinations of genetic, gene expression, phenotypic, and clinical criteria is really only the first step toward establishing the clinical relevance and clinical utility of such proposed new entities (see Berry et al[20] and Potaczek et al[21] in this issue of the *Journal*). There are many relevant questions to ask. What criteria should be used and by which official organizations to decide whether a proposed new subtype of asthma should now be generally accepted for the purposes of diagnosis and treatment of individual asthmatic patients and thereby included officially in a new taxonomy of asthma and allergic diseases?[22] What criteria should be used to decide whether a particular newly introduced targeted treatment (eg, biologics directed at particular cytokines or their receptors, which are often used in conjunction with biomarkers that are thought to identify those patients with a subtype of disease that is more likely to benefit from such treatments) is clinically useful and therefore should become the standard of care? What evidence is sufficient to conclude that a new targeted approach to prevention or treatment of allergic diseases is cost-effective (and what agency or groups will be entrusted to make such decisions)?[23] Finally, at what point and based on what evidence should payers (whether they are private insurance companies or national health care systems) decide that a targeted treatment for a newly recognized subtype of allergic disease merits coverage in that health plan?

These are key questions that need to be answered before knowledge identifying new subtypes of disease, defining new tests to detect such disease subtypes, and characterizing genetically determined variation in individual responses to therapeutics (ie, pharmacogenomics) can be translated effectively into clinical practice. Although therapeutic interventions can rapidly produce benefit in those afflicted with a disease, it might take many years to demonstrate the effectiveness of attempts to prevent or postpone the development or modify the manifestations of disease in susceptible subjects. In this article I will provide a personal perspective on the promises and challenges of taking advantage of the special biological features of allergic diseases to use a personalized medicine and health approach for improving the health of persons who have or are at risk of allergic disorders.
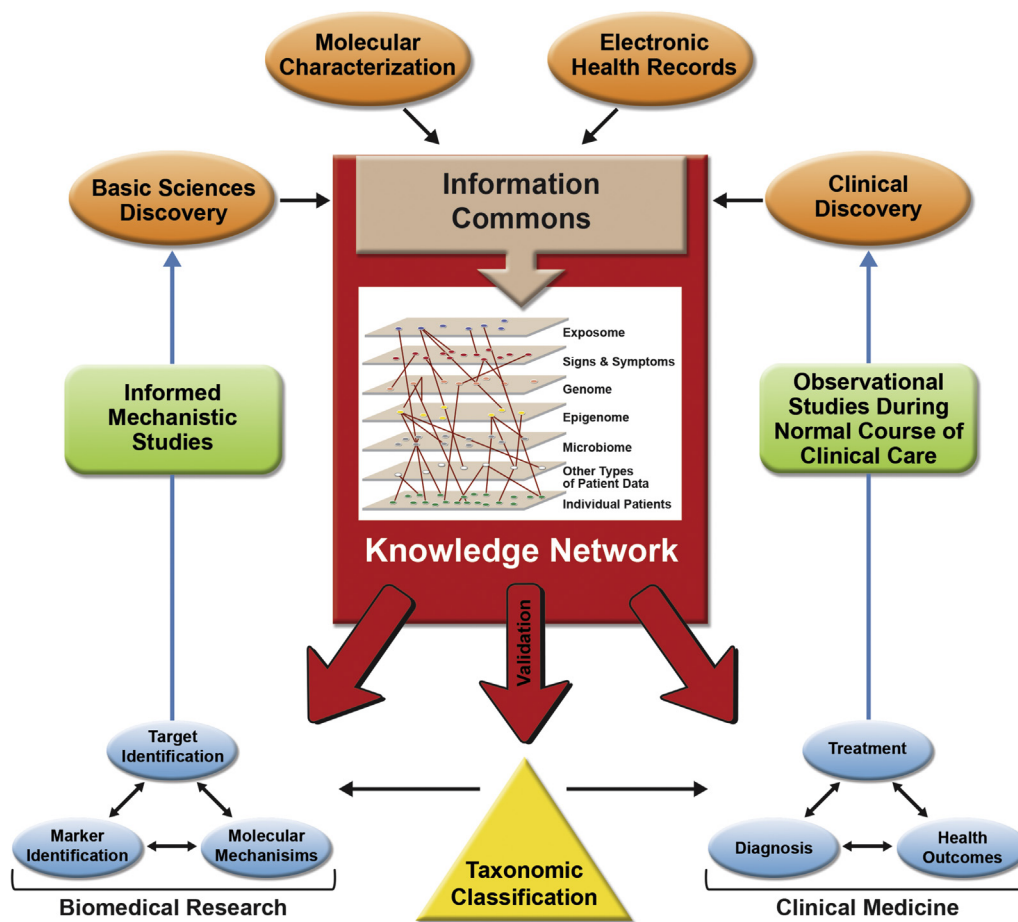
FIG 1. Building a biomedical knowledge network for basic discovery and improved health. The proposed information commons contains current health and disease information about individual patients that is continuously updated by new data (including those from observational studies) generated during the normal course of health care. Validated findings emerging from the knowledge network, such as those that define new diseases or subtypes of diseases that are clinically relevant (eg, which have implications for patient prognosis, disease monitoring, or therapy), would be incorporated into a new taxonomy to improve diagnosis (ie, disease classification), health and disease monitoring, and treatment. The extent to which other information in the knowledge network needs various types of validation before its widespread use will vary. For example, certain biomedical research projects might require raw data contained in the information commons, whereas findings in the knowledge network (eg, regarding the efficacy and safety of a new therapeutic agent) might require extensive replication before being used to change the standard of care in clinical medicine. This is Fig 3-1 from Desmond-Hellman et al,[19] which is reproduced in slightly modified form with permission of the National Academy of Sciences USA.

GENERAL PRINCIPLES OF PRECISION MEDICINE AND HEALTH

One piece of evidence indicating that a concept has become mainstream is when it is widely used to sell products directly to physicians and consumers. For years, various commercial enterprises have been offering to sell individuals an analysis of their "genomes" (these analyses typically are not based on sequencing the full genome but on analyzing thousands of single nucleotide polymorphisms in individual genes) to trace their ancestry or, initially at least, even to permit them to assess their risk of specific diseases. Sometimes called "recreational genomics," such testing has become popular enough to have generated both substantial revenues for test vendors and, in the United States, the intense interest of regulatory agencies, such as the US Food and Drug Administration, who are concerned with the possibility that consumers would be at risk if they were to use

some of the results of such analyses to guide important medical decisions.[24]

Whatever one thinks of the merits of these commercial ventures, the impetus to be counted among those who are using genetic information to improve health outcomes or quality of life for their patients is now pervasive in health care as well. In the United States it is now common to hear radio announcements or see television advertisements that inform patients that particular health care practices, hospitals, or health systems are using your own "genes," "genetics," or "genome" to personalize and (as stated or implied) thereby improve the effectiveness of your care. Obviously, many such claims markedly simplify and in some cases exaggerate or distort reality. The effort to find information demonstrably beneficial to health and the treatment of disease by mining increasingly vast amounts of genomic and other "omics" data, as well as data on demographic

characteristics, environmental exposures (ie, the so-called exposome), and responses to various therapeutic interventions, will be complex, ongoing, and of very long duration. The National Research Council report "Toward precision medicine, building a knowledge network for biomedical research and a new taxonomy of disease,"[19] came to several conclusions and made a number of recommendations regarding what the committee decided to call precision medicine (which was meant to encompass disease prediction and prevention, as well as disease classification, treatment, and monitoring). Although these conclusions and recommendations were crafted to apply to biomedical research and clinical care generally, they also can be used to guide approaches for improving care in individual medical subspecialties, including allergology/clinical allergy.

To illustrate this point, let us consider the general scheme envisioned for the creation of a knowledge network of disease, as shown in a figure from the National Research Council's "Toward precision medicine" report (Fig 1).[19] The data used to create such a proposed knowledge network (ie, the "information commons") would be comprised of detailed information about the characteristics of multiple individual subjects and their environments. This information then could be mined by using sophisticated bioinformatics and computational tools to identify combinations of genetic and environmental factors that can contribute to the development, exacerbation, or even spontaneous resolution of asthma, eczema, food allergy, or other allergic disorders and to assess the effectiveness of interventions to prevent, ameliorate, or cure such disorders.

Clearly all of the information to be entered into such a database (the information commons) would have to be collected in a way that is in accord with the privacy rules and other policies and laws that apply in jurisdictions where the subjects live. For example, in the United States a proposal is now under consideration to revise the regulations concerning the ethical conduct of research involving human subjects in such a way as to require the consent of the subject for the use of all biospecimens in research, irrespective of whether these specimens are deidentified.[25] Many concerns have been raised during the open comment period for this proposed change regarding the potentially serious unintended negative consequences for biomedical research should the provisions be implemented without substantial modification. However, should such a change in the common rule be enacted, then all subjects or their legal guardians would be required to provide consent in advance for any potential use of blood, sputum, bronchoalveolar lavage, or airway biopsy specimens to search for genetic, epigenetic, proteomic, or metabolomic findings that could be used to understand or subclassify disease pathology or to identify potential new therapeutic targets. Because the power of such information commons is inextricably dependent on the quality and amount of patient-specific data contained therein and the ability to use these data for diverse research projects, exploiting such an approach might be most practical in those countries with single, universal health care systems that are enabled by electronic health records with suitable functionality and that also have effective means (eg, laws, policies, and consenting mechanisms) of ensuring the appropriate agreement of subjects to participate in these efforts by permitting the use of their genetic and other biometric, medical, demographic, and social information for such research.

Sophisticated data mining in such information commons (eg, to find those constellations of genetic and environmental factors that

are likely to predispose to the development of various allergic disorders or to prevent them) will contribute to the development of the knowledge network that can inform disease classification and, in turn, guide targeted treatment and other forms of individualized patient management. What is envisioned is a dynamic system for producing and continuously revising/updating the classification of disease and for the development of novel clinical diagnostics and treatments while also supporting basic science. However, for such knowledge to be prudently applied in the clinical setting, it is critical that this information be clinically validated. Clinical validation can be defined as obtaining compelling objective evidence indicating that the information in fact has clinical utility. For example, with respect to a new diagnostic test or biomarker, clinical utility can be defined as the ability of such a diagnostic or screening test to prevent or ameliorate adverse health outcomes, such as morbidity, disability, or mortality, through adoption of efficacious preventive measures or treatments based on test results (modified after Khoury[26]). As discussed immediately below, there is evidence that such approaches already have been working in the field of allergology/clinical allergy. Finally, one important topic was not directly incorporated into the scheme illustrated in Fig 1: What will all this cost, and who will pay? More on that below.

ALLERGIC DISORDERS: A UNIQUE OPPORTUNITY FOR THE DEVELOPMENT OF PRECISION MEDICINE AND PRECISION HEALTH

In the asthma field several recent studies have provided data indicating that proper selection of patients based on their clinical characteristics, including certain readily measurable features of their disorder (these can be called, generically, biomarkers), can identify subsets of patients more likely to respond favorably to biologics that impair the functioning of pathways implicated in the development of airway pathology in such subjects (for a recent review, see Berry et al[20]). In such cases the personalization or stratification of the individual patient's care, at least with respect to which biologics to prescribe, is not based on which specific allergens might contribute to the development or progression of their signs and symptoms but on proper targeting of final common pathway elements that are thought to be activated in tissues regardless of the specific inciting allergens. In principle, care in this setting can be personalized based on the use of biometric tests (sometimes called companion diagnostic tests) to identify patients who are more likely to benefit from a particular targeted therapeutic.

Although this is an active area of research, there are already data indicating that patients whose asthma is associated with increased levels of biomarkers of a T_H2 phenotype,[12,27] including periostin,[28,29] and high blood eosinophil counts[30] will benefit more from therapy targeting elements of the T_H2 response (eg, IL-4, IL-5, IL-13, and/or their receptors) than will patients with low levels of such biomarkers.[31-36] However, recent data indicate that such biomarkers might be more useful in some patient subpopulations than others. For example, in patients with childhood asthma, blood periostin levels might not be a useful biomarker of disease,[37,38] which is in contrast to assessment of levels of both exhaled nitric oxide and blood eosinophil counts, which is helpful in identifying children with the highest asthma morbidity.[38] Similarly, therapy designed to target eosinophils and their activities might show benefit primarily in those subjects whose asthma

subtype includes the presence of high eosinophil counts, and the presence of high eosinophil counts in the blood can be used to select patients likely to respond favorably to such treatment.[30,39-43]

However, even when such biologics or conventional pharmaceutical agents, such as corticosteroids or drugs targeting specific mediators derived from effector cells, ameliorate clinically significant manifestations of disease, they are not curative. It is here, in being able to alter the cause of the disease, that there are special opportunities in patients with allergic disorders. There are also attractive prospects for crafting increasingly personalized treatment and management plans. These opportunities can be divided into: (1) prevention, (2) management/treatment, and (3) cure. In each of these areas, there is evidence that care can be tailored to the particular characteristics of individual subjects.

PREVENTION
Preventing disease development

There is strong evidence that hereditary factors contribute to the propensity to allergic diseases.[44-46] Therefore an effective way to reduce the incidence of allergic diseases in your children would be to select your spouse carefully, avoiding candidates who have a strong family history of allergic disorders. Such approaches already are being taken, along with adoption, to avoid the transmission of severe hereditary disorders that are based on the deleterious effects of single affected genes. However, many might think that this is not a very practical or appealing approach to take for reducing the development of allergic disease.

What other, more practical measures can be taken to prevent the development of allergic disorders? The exciting results of the recently published Learning Early About Peanut (LEAP) study showed that the introduction of peanut products into the diets of atopic children at high risk of peanut allergy resulted in a marked reduction in the development of that potentially life-threatening disorder in comparison with the outcome in atopic children who were randomized to the peanut avoidance group.[47] As noted in an article providing interim guidance based on consensus among the American Academy of Allergy, Asthma & Immunology; American Academy of Pediatrics; American College of Allergy, Asthma & Immunology; Australasian Society of Clinical Immunology and Allergy; Canadian Society of Allergy and Clinical Immunology; European Academy of Allergy and Clinical Immunology; Israel Association of Allergy and Clinical Immunology; Japanese Society for Allergology; Society for Pediatric Dermatology; and World Allergy Organization (which will be followed up by more formal documents from the National Institute of Allergy and Infectious Diseases–sponsored Working Group and the European Academy of Allergy and Clinical Immunology),[48] this seminal LEAP study supports the potential benefits of early (rather than delayed) introduction of peanut into the diet of such at-risk infants. However, without further studies, this finding cannot be generalized to what would happen if the same approach were to be taken with nonatopic children or children with other food allergies.

Having said that, it now will be important to determine (1) whether and to what extent the introduction of foods containing known allergens into the diet of infants and children can represent a general strategy to prevent the development of such allergies, (2) whether this approach works only for a subset of food allergens or only in certain subsets of subjects (eg, those with abnormalities of skin barrier function), and, if the latter is true, (3) whether genetic or other biometric tests would permit better identification of subjects who are more or less likely to respond to such preventative measures than would a simple family history combined with currently available tests, such as SPTs and IgE measurements. Ideally, adding such new and better predictive tests to the current selection criteria would permit this type of preventative measure to be used in those who are most likely to respond favorably.

In principle, another approach to prevention would be to alter human microbiomes in ways that reduce the incidence of allergic disorders. Studies of a model of food allergy in gnotobiotic mice suggest that the transfer of a Clostridia-containing microbiota to germ-free mice can protect against the development of food allergies in the recipient animals.[49] In human subjects a comparison of fecal samples obtained from small numbers of healthy control subjects and infants with cow's milk allergy before and after treatment with extensively hydrolyzed casein formula with or without supplementation with *Lactobacillus rhamnosus* GG suggest that extensively hydrolyzed casein formula plus *Lactobacillus rhamnosus* GG might help promote tolerance in infants with cow's milk allergy in part through effects on the strain-level bacterial community structure in the infant's gut.[50] Recent work indicates that at least some of the ability of exposure to pet dogs[51,52] (and cats[51]) to reduce the incidence of allergic sensitization[51] and allergic diseases[52] that has been suggested by epidemiologic[51] and longitudinal[52] studies might be attributable to alterations in the subjects' microbiomes that reflect the introduction of environmental bacteria into the home by pets that are permitted to spend time outdoors.[53] In wild-type mice this protective effect can be transferred by a single bacterial species, *Lactobacillus johnsonii*.[53]

Such studies, together with epidemiologic analyses comparing the incidence of allergic disease in ethnically similar farming populations in which farming families do or do not live in close proximity to their livestock suggest that one of the major mechanisms underlying these diverse observations is that microbiomes that promote health and help to suppress the development of allergic diseases are shaped importantly by close interactions with environmental microbial populations and their products, especially those derived from livestock and companion animals.[54,55] Moreover, recent evidence from studies in mice suggests that the development of oral tolerance to food antigens can be regulated by the influence of both microbiome-induced and dietary antigen–induced populations of peripheral regulatory T (Treg) cells, which develop outside of the thymus from conventional T cells.[56] Recent studies in a general population–derived birth cohort provided evidence that infants at risk of food allergy can display a hyperresponsive innate immune response at birth that, together with mucosally derived TGF-β, might both promote nonclassic differentiation of T_H2 lymphocytes and impair the function of natural Treg cells.[57] It will be of interest to assess whether these interesting findings can be confirmed in other populations, as well as to investigate how such processes can be influenced by different effects of microbiomes, the timing of introduction of various food allergens, or both.

Clearly it would be impractical to advise families at risk of allergic diseases to reduce the likelihood of that by taking up farming or living with livestock, and some families might not be willing or able to acquire a dog or two. Therefore interest is now

focused on how microbiomes can be manipulated therapeutically, including through dietary changes, to move from disease-promoting dysbiotic microbiomes to those that are more conducive to health.[58,59] However, there are many challenges to instituting a microbiome management plan that can be individualized based on the characteristics of the particular subject. These include but are not limited to the following.

1. Identifying how best to assess and measure the health or dysbiosis of native microbiomes and to monitor the success of attempts to alter them (eg, which microbiomes should be measured [eg, the gut, skin, airway, or all of the above] and which aspects of the microbiome should be measured [eg, only the species composition or also their metabolic products]). In what ways should such measurements be made and how frequently to assess whether interventions are achieving the desired effects?

2. Given that current evidence suggests that human microbiomes tend to be stable once established early in life,[60] can relatively transient alterations in the microbiome have clinical benefit, and if such effects are limited or transient, can other safe and cost-effective strategies be developed to induce and maintain stable healthful alterations in key microbiomes? Notably, a recent comprehensive review concluded that, apart from the use of hydrolyzed formulas in high-risk infants to reduce the incidence of atopic dermatitis, there was not enough evidence to recommend other dietary modifications, including probiotics or other microbial products.[61]

3. Can we succeed in effectively limiting the inappropriate medical or agricultural use of antibiotics, which can profoundly alter microbiomes, with multiple potential adverse effects, including development of obesity and metabolic abnormalities?[60]

Proving the clinical utility of attempts to alter microbiomes and their products to prevent, manage, or treat allergic disorders will require well-conducted, randomized, placebo-controlled longitudinal studies of sufficient size and duration to permit assessment of long-term effects of such interventions on the development and severity of allergic diseases. Only time will tell whether such efforts will identify microbiome-targeted approaches to reduce the occurrence or severity of allergic disorders that are sufficiently successful, practical, and cost-effective to result in such interventions becoming the standard of care. However, it is likely that success might depend on developing accurate, precise, and inexpensive ways of assessing and monitoring over time the key features of individual microbiomes and their metabolic products.

Finally, there has been considerable interest in the possible role of a deficiency in vitamin D (which has a spectrum of potential effects on the immune system, lung development, and the microbiome) in influencing the development of asthma and other allergic disorders.[62,63] If vitamin D deficiency (whether related to decreased dietary intake of vitamin D, reduced sunlight exposure related to a more sedentary lifestyle, or both) indeed contributes to the development of allergic disorders, then supplementation of the diets of pregnant women or children with vitamin D would represent an inexpensive way of modifying such disease risk. Two recently published randomized trials of vitamin D_3 (cholecalciferol) dietary supplementation during pregnancy did not demonstrate a statistically significant benefit in reducing the risk of asthma or persistent wheezing in the offspring.[64,65] However, on the basis of the findings obtained (including not statistically significant reductions in the primary end points in the treatment vs control groups of 16% vs 20%[64] and 24% vs 30%,[65] respectively), each group of investigators concluded that the studies might have been underpowered. It is possible that larger studies with longer periods of follow-up, perhaps testing higher doses of vitamin D_3, earlier onset of treatment during pregnancy, and/or adding postnatal dietary supplementation with vitamin D_3, together with the identification of biometric data that can be used to select those most likely to benefit from such dietary supplementation, might reveal a statistically significant benefit of this simple and inexpensive approach to reduce the burden of allergic disorders.

Preventing exacerbation of existing disease

Patients with allergic disorders long have been advised to avoid exposure to those allergens that induce signs and symptoms of their disease. However, there are other opportunities for personalizing the care of allergic subjects, depending on the nature of their allergic disease. For example, it is known that much of the morbidity and cost of care for asthmatic patients are related to exacerbations of the disease induced by respiratory tract infections, particularly those with rhinoviruses.[66] Can more effective methods be devised to reduce the occurrence or severity of such infections in asthmatic patients? If effective vaccines could be developed against any of the offending viruses (a big if), then these could be offered, particularly to children with or at risk of asthma.

In the case of food allergies, it is clear that individual subjects can vary in the amount of offending allergen required to induce a clinical reaction.[67,68] In principle, the care of such patients might eventually be improved by combining better food labeling to describe the amounts of allergens actually present with appropriately cautious testing of patients to establish their individual thresholds of clinical responsiveness to their offending food allergens because these thresholds can vary by orders of magnitude in individual subjects.[67,68] However, because the levels of food allergen exposure required to induce clinical reactions can be lower in subjects with viral infections, during exercise, after alcohol consumption, or for reasons that might not be entirely clear,[67,69,70] it will be challenging to develop an approach to advise patients how to make safe use of information about their food allergen thresholds that is based on determining such thresholds under baseline conditions. Allergen thresholds also can change because of the natural evolution of the disorder, such as in children who outgrow their allergies, and it will be helpful to have better approaches for determining when it is safe for such subjects to stop avoiding allergens to which they are no longer clinically reactive.

MANAGEMENT/TREATMENT
Avoidance

Although the scrupulous avoidance of offending allergens is a mainstay of the management of allergic disorders,[71] as noted above, this approach can be personalized, at least in principle, by using appropriate testing to carefully establish which allergens must be avoided and by defining the threshold amounts of such allergens individual subjects can ingest without triggering clinical signs and symptoms. Because various factors can alter one's threshold for

TABLE I. Principles of precision medicine for allergic disorders*

Characterize the disease: Identify the disease and, if applicable, the subtype of allergic disorder; precisely define the offending allergen proteins.

Profile the patient: Characterize patient genotype and phenotype (and in some cases microbiomes); assess the patient's likelihood to respond to pharmacologic or biological agents, SIT, or other forms of management.

Select optimal management: Based on the subject's subtype of disease, offending allergens, genetic and phenotypic characteristics, and an evidence-based assessment of her or his likelihood to respond to various treatment/management options.

Monitor disease and response to management: Perform appropriate biometric monitoring during treatment (eg, with pharmacologic or biological agents or with SIT) to assess, for example, 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 refined and improved (Fig 1).
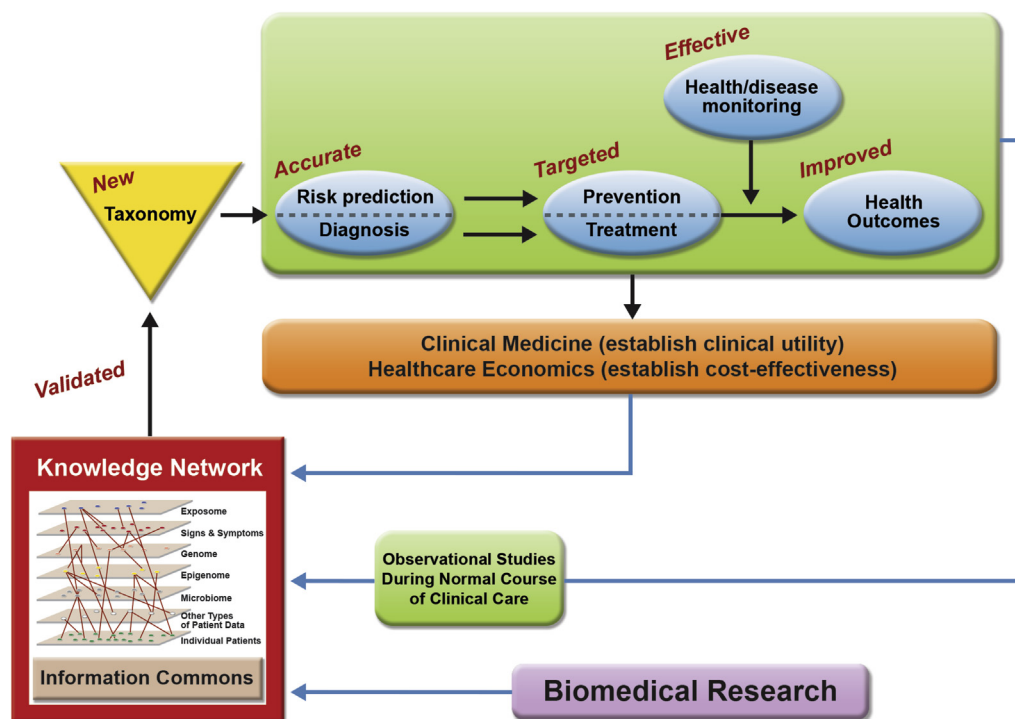

FIG 2. An iterative process to enable increasingly individualized approaches for improving health outcomes in subjects with or at risk of developing allergic disorders. Ongoing analyses of diverse data in the information commons can both generate new knowledge to refine our taxonomic classification of allergic disorders (and asthma) and enable development of new approaches to assess and monitor the risk of disease, disease severity, and responses to interventions to prevent or treat disease in individual subjects. By using validated approaches in these areas (ie, those proved to have clinical utility), health outcomes can be improved in individual subjects and populations. The extent to which such validated approaches actually will be adopted clinically is likely to be influenced by their cost-effectiveness. This is a modified version of Fig 1-3 from Desmond-Hellman et al,[19] which is reproduced with permission of the National Academy of Sciences USA.

clinically reacting to an offending allergen, including infections, exercise, and alcohol consumption,[67,70,71] careful education of patients, their guardians, or both would be required for them to be aware of when the subject might be at risk, even when exposed to amounts of the offending allergen that are substantially less than their usual threshold at baseline.

Pharmacotherapy and treatment with therapeutic antibodies

There are many reviews on these topics, and in principle, it is generally accepted that therapeutic agents should be used when there is a favorable balance between their benefits and potential risks. In the case of small-molecule drugs, examples from other fields suggest that pharmacogenetic data can help predict both the benefit and toxicity of particular drugs in individual patients.[72] Although promising work is being done to identify genetic criteria on which to base selection of pharmacologic and biological agents for treatment of subjects with asthma and other allergic disorders,[73] more studies are needed before such approaches can be put into routine clinical practice.

CURE

Allergen-specific immunotherapy has shown considerable success in modifying underlying disease in certain settings,

TABLE II. Some examples of implementing P4 medicine in patients with selected allergic disorders*

Disorder	Prediction	Prevention	Personalization	Participation
Asthma	Improve ability to predict risk for asthma in those with early-life wheezing disorders†; improved biometric testing to identify clinically significant subtypes of asthma†; develop better approaches for defining those gene-environment interactions most critical for driving development of disease and develop algorithms to use such data in clinical practice†	Identify potentially modifiable developmental or environmental factors (eg, that influence airway mucosal functions, microbiome composition, exposure to viral respiratory tract infections) and devise approaches to alter them to prevent disease development, progression, or exacerbation†	Selection of the most appropriate targeted therapies based on individual biometric characteristics†; precise selection of those who are likely to benefit from SIT, allergens to use for SIT, and most effective approaches to induce SIT based on individual biometric data†; selection of the most appropriate monitoring tests to use in each subject to assess response to treatment and to detect possible adverse effects of treatment†	Selection (eg, based on the subject's biometric data, environment, personal preferences and health plan, and risk-benefit analysis of various options) of standard or targeted pharmacotherapy, treatment with biological agents, and/or SIT†; develop improved methods for effectively advising subjects and guardians to adopt healthful life practices (eg, exercise, proper nutrition, and pet ownership) once these have been shown to have benefits in preventing disease or disease progression/exacerbation†
Food allergy	DBPCFC (standard); improved biometric assessment (eg, with basophil activation tests, analysis of T- and B-cell populations, and characterization of antibody repertoires) to identify those most at risk for a severe reaction†	Early introduction of peanut (and perhaps other food allergens) into the diets of defined populations of at-risk subjects†; develop approaches to favor the establishment/maintenance of healthful microbiomes that reduce risk of disease development†	Biometric testing to assess which subjects would benefit from early dietary introduction of various allergenic foods and/or alteration of their microbiomes†; selection of specific allergens to use for SIT in those with multiple food allergies and selection of sequential vs simultaneous SIT to these allergens†; disease-monitoring tests (eg, of T- and B-lymphocyte and basophil populations and levels of other types of biomarkers) to assess the magnitude and duration of responsiveness to SIT†	Selection (eg, based on risk-benefit analysis and subject's personal preferences) of SIT vs allergen avoidance and epinephrine autoinjector (or both); improve methods for effectively advising subjects and guardians to adopt various measures (eg, improved compliance with management/treatment plans, increased exercise, proper nutrition, and pet ownership) once these have been shown to have benefits in treating disease or in preventing disease development or progression/exacerbation†; engaging patients and their families and advocacy groups in efforts to improve options for disease prevention, treatment, and management and in efforts to improve public understanding of and public policies related to food allergies
Venom-induced anaphylaxis	Develop tests to identify those with venom-specific IgE who are most at risk for venom-induced anaphylaxis†	SIT of those who have had an episode to prevent future episodes (current); develop effective "preventative SIT" approaches for those at risk of the disorder (eg, beekeepers)†	Component-resolved testing to identify specific offending allergenic proteins and to select optimum allergens to use for SIT†; modify standard SIT (or newly devised SIT approaches) based on individual biometric data to enhance the efficacy and duration of SIT†	Selection of preventive vs therapeutic SIT vs allergen avoidance and epinephrine autoinjector (or both); improve the effectiveness of approaches to convince patients and their families of the importance of complying with management plans†

*P4 medicine is defined as predictive, preventive, personalized, and participatory. Some of the examples given are already part of clinical practice (eg, DBPCFC), whereas others (marked with daggers [†]) would need to be developed further and/or validated in appropriate large studies before becoming standard of care. Examples such as those provided in the table also could be given for allergic rhinitis, atopic dermatitis, and other disorders.

notably in the setting of allergic rhinitis,[74-76] and a number of promising approaches for developing novel immunotherapy vaccines are under investigation.[77] Although determining whether successfully treated patients are truly cured of their disease depends on how one defines cure, many patients can experience long-term relief of symptoms, and their state of clinical nonreactivity to the offending allergens can persist for long periods of time, particularly in those treated for 3 years or more.[75] Yet some patients derive more benefit than others from allergen-specific immunotherapy (SIT). What if the outcome of instituting

various forms of SIT in particular patients could be predicted in advance of treatment, thereby saving the future nonresponders (and their health care system) the trouble, expense, and risk of undergoing what would be an essentially futile course of therapy? As noted above, pharmacogenetic evidence indicates that individual responsiveness to a growing number of drugs can be predicted based on genetic tests.[72] By contrast, to my knowledge, no such predictive tests have yet been shown to have clinical utility in predicting responses of individual patients to SIT. Thus, as noted by Akdis and Akdis,[76] "The general use of disease endotypes for allergies and asthma and correct selection of the responder patient population with defined biomarkers remain essential unmet needs in the clinical settings."

DISEASE MONITORING IN ALLERGIC DISORDERS

If one unmet need in clinical allergy/allergology is to identify approaches that can accurately predict responsiveness to SIT, another is to develop disease-monitoring tests that can assess the extent to which such SIT is working in patients undergoing treatment. In the case of food allergies, initial studies indicate that some patients treated with oral immunotherapy (OIT) can achieve sustained clinical nonreactivity to a maintenance dose of the offending allergen, whereas others do not.[78-81] Can we devise tests to identify those subjects who are responding favorably to such OIT? In one small phase 1 single-site study, 4 of the 7 subjects with peanut allergy who achieved sustained unresponsiveness to peanut (based on passing a DBPCFC at 3 months after discontinuation of OIT) had regained reactivity to peanut 3 months later, whereas the 3 other patients continued to exhibit a more persistent pattern of nonreactivity.[79] That study suggested that persistent demethylation of the forkhead box protein 3 *(FOXP3)* gene in Treg cells might help to identify this subtype of patients who can maintain longer-term clinical nonreactivity to peanut, even in the absence of regularly consuming maintenance doses of peanut.[79] Another study of a small number of subjects suggests that successful OIT in patients with peanut allergy might be associated with expansion of a population of allergen-specific CD4^{+} T cells that develop an anergic T_H2 T-cell phenotype, cells that were largely absent in both pretreatment participants and healthy control subjects.[82] Although these studies are encouraging, they need extension to larger numbers of subjects and confirmation in multiple test sites. Moreover, in addition to T-cell analyses, promising recent work indicates that *in vitro* tests of blood basophil phenotype and function might have value for discriminating between peanut-sensitized children who are allergic versus those who are tolerant to peanut.[83]

TOWARD PRECISION MEDICINE AND HEALTH IN THE FIELD OF ALLERGY

Providing the best possible personalized care for patients with allergic diseases and helping those at risk to avoid such disorders will be ongoing long-term efforts. However, it is possible to think now about general approaches for achieving those goals and to consider some broad principles for practicing precision medicine in the field of allergy (Table I). Notably, each of the topics listed in Table I has its own set of challenges.

For example, there is much current interest in defining subtypes of asthma, but less has been done to define clinically

important subtypes of other allergic disorders. Whether it will be possible to define subtypes of patients with atopic dermatitis, allergic rhinitis, or food allergies who might benefit from more personalized management plans remains to be determined. In the area of patient profiling, one ideally would be able to use a limited number of reasonably inexpensive tests to predict responses to various forms of treatment rather than to rely on comprehensive analyses of the subject's entire genome, metabolome, and microbiome, for example. The same point can be made with respect to what type of testing might be needed for effective disease monitoring and assessment of treatment responses.

The last point in Table I, selecting the most cost-effective management approach for that patient, might represent one of the biggest challenges to address. The potential cost of personalized or precision medicine has been much discussed,[23,84] and the costs to individual patients and health systems will vary by country and, in countries with private health care options, based on one's type of health insurance. Moreover, assessing the cost-effectiveness of an intervention should ideally consider all of the costs and benefits of the decision, including placing values on such important outcomes as long-term wellness and enhanced quality of life, as well as on the avoidance of time lost to school or work and reductions in long-term economic productivity.

Although the measures summarized in Table I pertain to those who already have allergic disorders, in principle one also can propose a similar general approach for preventing the development of allergic diseases in those at risk to do so: (1) *assess and quantify individual risk* for allergic disorders or to experience their exacerbation; (2) *assess the environment* to identify and quantify factors that might promote disease development or exacerbation (eg, progression in the allergic/atopic march) in that person; (3) *modify risk factors* in the subject (eg, by using approaches to increase skin health and barrier function in subjects at risk of atopic dermatitis[85] and environment (eg, acquire a few dogs)[51,53]; (4) *monitor the subject and environment* to assess the effectiveness of interventions and the durability of favorable changes; and (5) *improve the effectiveness of communication between patients and caregivers* to increase understanding of the disease prevention process and the rationale to comply with preventative measures or interventions.

Certain general approaches need to be applied both to efforts to individualize the diagnosis and management of allergic disorders and to attempts to prevent the occurrence of these diseases in those at risk. These include (1) improve basic scientific understanding of how gene-environment interactions (including gene-environment interactions in one's microbiome) contribute to the development and exacerbation or amelioration of allergic disorders; (2) better define the features of the disorders that result in the most important clinical manifestations of these conditions (this might help to define approaches to treat or prevent the development of these key features of the disorders, even if one cannot yet prevent the occurrence of the disease itself); and (3) improve the ability to measure the clinical effectiveness of these measures and their overall cost to the patient, the health care system, and society (Fig 2).[19]

Finally, Hood and colleagues[86,87] have emphasized the importance of involving patients, their guardians, or both meaningfully in making decisions about their health care. This participatory aspect of medicine constitutes the fourth

"P" of P4 medicine (ie, predictive, preventive, personalized, and participatory medicine). Table II provides some examples of how the various components of P4 medicine might be applied to improve disease prevention and treatment of selected allergic disorders.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

It is difficult to imagine a more promising and exciting time in the history of clinical allergy/allergology. There can be no doubt that we face a big challenge, in that the factors which have contributed to the striking increase in the prevalence of allergic diseases since the late 19th century are probably both diverse in their nature and complex in their interactions.[88] The good news is that there has been a marked increase in the power of new scientific and bioinformatics tools that can be used to generate and search vast amounts of experimental, clinical, genetic, phenotypic, environmental, and demographic data to yield new knowledge about the origins, natural history, and manifestations of allergic disorders. In principle, such methods also can be used to monitor and accurately measure the beneficial (and potentially harmful) effects and the net clinical utility of interventions designed to prevent, ameliorate, or cure these diseases. The broader use of such approaches should enable us to provide increasingly personalized precision approaches to reduce the development and morbidity of allergic diseases in individual subjects and populations.

For example, it might be possible to devise approaches using biometric and other data (including data about one's personal environment) to identify more accurately those children who would most benefit from the early introduction of peanut (and perhaps other potentially allergenic foods) into their diet, to better predict which patients with asthma will or will not respond favorably to treatment with expensive biologics, and to assess the likely effectiveness of diverse interventions, including modifications of one's environment, designed to prevent, delay, or ameliorate the development of allergic diseases in individual subjects. It might also be possible to define constellations of biometric and other individual characteristics that could change the trial-and-failure approach currently often used to move from first- to second- to third-line therapeutic approaches to one in which the caregiver, in consultation with the patient (and/or her or his guardians), can more quickly select a treatment with a high probability of success for that person. Such precision care approaches not only will permit health care resources to be used in a more cost-effective manner but, more importantly, would result in improved satisfaction of patients and their families with their management and treatment, along with producing favorable social and economic effects by improving attendance and performance in school or at work. If we can overcome the not insignificant impediments to establishing such new approaches, then we will be able to offer a much brighter future to those subjects at risk of allergic diseases and to those patients who already have them.

What do we know?

- Allergic diseases provide unique opportunities for precision medicine and health.
- Progress is being made in defining clinically relevant subtypes of allergic disorders, particularly asthma.
- Optimal treatments for different subtypes of allergic disorders can vary.
- Some subtypes of allergic disorders can be identified by biomarkers of disease.
- Based on the LEAP study, it might be possible to reduce the development of peanut allergies in certain at-risk subjects by appropriate early dietary peanut exposure.
- Progress is being made in defining useful approaches for disease monitoring to define disease severity and responses to treatment, including SIT.

What is still unknown?

- Can we devise and personalize clinically useful and cost-effective measures to prevent the development or progression of allergic disorders in at-risk subjects across the spectrum of allergic disorders?
- To what extent will such preventative approaches include both developmentally appropriate exposure to relevant allergens (either at mucosal surfaces, such as in the diet, or as vaccines) and/or modifications of individual microbiomes?
- Can we prospectively identify subjects likely to respond favorably or to have toxicity to individual treatments or management plans for allergic disorders?
- Can we fashion disease-monitoring approaches in patients with allergic diseases that are both clinically useful and cost-effective?
- Can we succeed in global efforts to pool patient-specific data across institutions and among different countries to build the most comprehensive information commons to enable basic and clinical research?
- Can we develop effective mechanisms to forge an international consensus on the classification, diagnosis, monitoring, and prevention and treatment of allergic disorders, including the development of improved clinical trial processes to prove the safety and efficacy of new targeted therapies?

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