Clinical reviews in allergy and immunology

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

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Date of Original Release: May 2016. Credit may be obtained for these courses until April 30, 2017.

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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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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: S. J. Galli declares that he has no relevant conflicts of interest.

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.

Recognition of Commercial Support: This CME activity has not received external commercial support.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

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*

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.

From the Departments of Pathology and Microbiology & Immunology, the Sean N. Parker Center for Allergy and Asthma Research, and the Stanford Center for Genomics and Personalized Medicine.

Supported by National Institutes of Health grants U19AI104209 and R01AR067145 and the Department of Pathology of Stanford University.

Received for publication February 3, 2016; revised March 14, 2016; accepted for publication March 14, 2016.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.03.006

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.