



Will precision medicine be available for all patients in the near future?

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Purpose of review

Evidence-based medicine and guidelines directing the diagnosis and treatment of patients are changing. General recommendations are moving towards an individual focus, where technology evolution allows identification of specific patterns and where 'one size fits all' no longer has a place.

Recent findings

Emerging innovations on health technology include useful tools for individualizing patients' specific conditions and follow-up. There are several preventive initiatives that aim to reduce allergic disease development, but they have no generalizable and definitive results as yet. Both omics and molecular diagnosis have provided the basis for differentiating clusters of patients, both allowing prediction of severity and also indicating appropriate management. Here we discuss examples contributing to some specific conditions we are now facing.

Summary

Precision medicine encompasses a personalized care of the patient, the prediction of a successful treatment, the potential prevention of a disease and its progression when present and the important active participation of the patient in the planning and guidance of the approach and management. Technology and medical innovations like omics and molecular diagnosis help for discriminating specific phenotypes/endotypes and the correct individualized interventions. The great challenge for implementing precision medicine will be the possibility of providing those advances to everyone at affordable costs.

Conclusion

Technology and innovations in medicine are aimed to help all patients globally, providing evidence for particular conditions that need to be personally considered, involving the patient's decision while treating, predicting and preventing disease. Our aim should be to have precision medicine available everywhere at any time.

Keywords

affordability, patient participation, precision medicine, prediction, prevention

INTRODUCTION

Precision medicine is the natural evolution of the patient's guided management whereas guidelines and evidence-based medicine have made a huge contribution over previous decades.

Protocol consensus for many conditions has provided a homogenization of treatment for the most frequent conditions in health services. However, the 'one size fits all' concept in specific diseases like asthma has generated many questions by physicians who deal with patients presenting with several individual expressions (phenotypes), whereas science has provided their particular pathogenic explanations (endotypes). Additionally, patients request effective solutions on their specific conditions, no matter what science states should be done for a certain disease.

Precision medicine is not just an intention to take care of individualized patients; it includes consideration of genetic background, prediction of future risks and envisioning of preventive measures accordingly, with mutual agreement and active participation of patients in decisions [1].

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Curr Opin Allergy Clin Immunol 2019, 19:75–80

DOI:10.1097/ACI.0000000000000491

KEY POINTS

- Molecular diagnosis and omics contribute to differentiation of phenotypes and endotypes, resulting in individual characterization for proper management.
- Precision medicine involves personalized care, prediction of treatment outcomes, potential prevention and active participation in treatment: the four 'Ps.'
- Availability and affordability of emerging and existing technologies at all latitudes and populations is a great challenge.

WHAT DOES PRECISION MEDICINE ENCOMPASS?

The four pillars of precision medicine are the four 'Ps' described as follows: personalized attention to the patient; prediction of a successful treatment; prevention of disease development and patient participation in the management of disease [2,3] (Fig. 1).

Personalized attention to the patient

Allergic and chronic respiratory diseases affect up to 40% of general population in some regions of the

world [4,5] and on follow-up of affected patients, there is a tendency to further increases in sensitization and the consequent clinical manifestations [6[¶]]. The great variety of possibilities within allergic diseases generates the need to evaluate several conditions for each patient, even at different times. Such evaluations demand extra time from the physician [7].

E-health is an emerging tool to provide better follow-up of patients, with the opportunity of having practical information on exposure and exacerbations, as well as therapeutic behaviours and control of disease. MASK-rhinitis is an example of a successful and simple system centred on the patient. It has been devised to obtain real time and patient reported status, as well as a clinical decision support system based on a widely known guideline in allergic rhinitis (ARIA guideline) [8]. More than 4000 patients reported daily symptoms with their mobile technology, showing remarkable intra-individual variability and unexpected severity of allergic multimorbidity [9]. Patients can provide their individual recordings to a physician, and then a personal map of evolution, and consequent intervention is possible from this technology.

However, on the other side, a systematic review and meta-analysis concluded that telemedicine

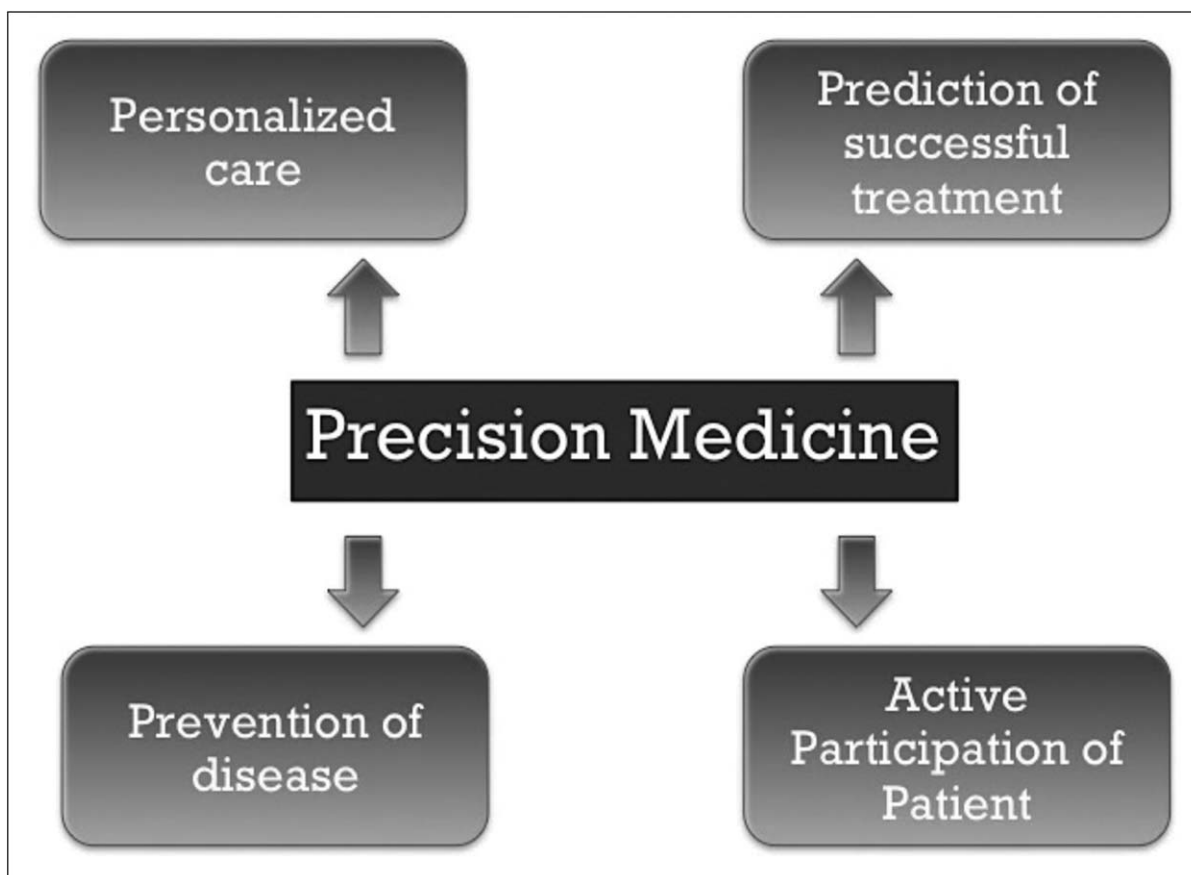


FIGURE 1. The four 'Ps' are the components of precision medicine.

cannot result in better outcomes on asthma scores; some possibilities such as those described in the previous paragraph must be considered, and might make a difference [10].

Prediction of a successful treatment

The several clinical expressions (phenotypes) of asthma have been explained by various immune inflammatory pathogeneses (endotypes). In asthma, Th2 lymphocyte inflammation was initially identified as the major responsible response until the initiating role of mast cells, epithelium and type 2 Innate Lymphoid Cells (ILC2) were recognized in attracting, recruiting and activating eosinophils. Then, a T2 type was considered a more appropriate term [3,4,11] (Fig. 2).

Why was this description so important for the clinical setting? The reason is because it has led to the revolution of asthma control by the introduction of anti-inflammatory treatment with inhaled corticosteroids. This control reduced mortality as

the most outstanding outcome, but also reduced exacerbations and significantly improved quality of life [12,13[■]].

Despite the benefits for many, nonresponders have been recognized [14[■],15,16] and the explanation has been provided by phenotypes/endotypes with specific biomarkers. The characterization of biomarkers is based on biological systems involving transcriptomics, proteomics, genomics and metabolomics in representative samples of patients, in order to potentially generalize the findings. The analysis and description of each of these are beyond the scope of the present report; however, it is noteworthy to mention that MeDALL started integrative analysis on transcriptomics, epigenetics and biological markers related to clinical expression of allergic diseases (including asthma), clarifying their role in both diagnosis and predictions [17]. The term 'Personomics' has been proposed, indicating that all the aspects (clinical, emotional, psychological, functional, phenotypical, endotypical, etc.) should be considered about the 'person/patient' as a complete entity [18[■]].

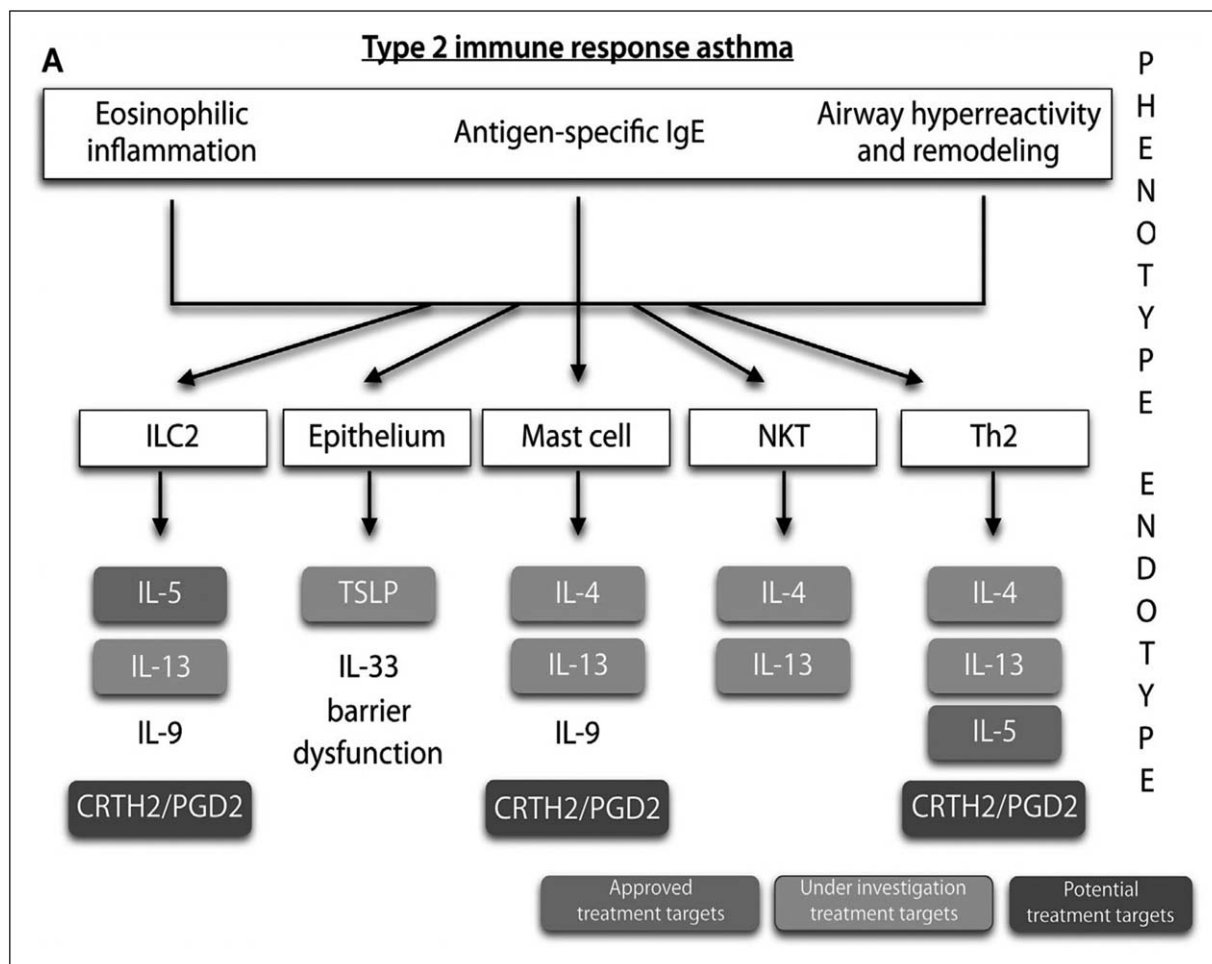


FIGURE 2. Phenotype and endotype characteristics of type 2 immunopathogenesis in asthma (T2 asthma). Data from Ref. [11].

In parallel to those advances, it must be mentioned that molecular-based allergy diagnosis is a novel system, which identifies the allergen sensitization pattern (in-vitro specific IgE) of a patient at a molecular level, using highly purified natural or recombinant allergen components. The major benefit of molecular-based allergy is its accuracy, identifying genuine cross reactivity of sensitization in multisensitive patients, not only predicting severity of exposure according to the pattern of molecular positivity but also identifying those patients with the most favorable chances of success with allergen-specific immunotherapy [19].

A nice example of molecular-based allergy usefulness is the peanut allergy frame described by Burk *et al.* [20]: Ara h 2-specific IgE detection has emerged as a great candidate for diagnosing peanut allergy, and those patients monosensitized to Ara h 8 may be clinically tolerant. It also provides regional sensitization patterns, with Ara h 1, 2, and 3 likely to be major allergens in the United States whereas Ara h 9 sensitization predominates in the Mediterranean. A successful therapeutic response to immunotherapy can be predicted for patients positive to Ara h 2- and whole peanut-specific IgE.

Several contributions from molecular-based allergy with clinical correlation are available. Another example for food allergy is the identification of molecular components involved in children with cow milk allergy, where having significant specific IgE towards α -lactalbumin, β -lactoglobulin and casein before oral immunotherapy intervention was associated with lower maintenance dose reached, while developing IgG4 to those mentioned molecular components was predictive of a successful intervention in desensitization [21].

Hymenoptera venom allergy can potentially be life-threatening because of IgE-mediated anaphylactic reactions. In one-third to half of allergic patients, there is a considerable overlap of sensitization to both honeybee and yellow jacket venom. Molecular-based allergy showed the allergenic relevance of Api m2 in contrast to Ves v2, with a significant carbohydrate reactivity and questionable role in clinical expression [22]. Recently, a new single test procedure has been developed, able to identify IgE against 282 different extracts or molecular components [23].

In general, IgE against cross-reactive carbohydrate determinants (CCDs) were considered as clinically irrelevant but molecular-based allergy elucidated the cause of another life-threatening situation in an anaphylactic reaction to cetuximab, where antiglycan IgE to the therapeutic monoclonal was identified [24].

Prevention of disease development

Primary prevention is still developing, and nowadays one of the hot topics has been the investigation of the alteration of the composition and timing of microbial load and the relation to increased risk of allergic diseases in offspring, suggesting that probiotics, prebiotics and synbiotics administration both in pregnancy and early in life could alter this progression [25²⁶].

Another hot topic is the prevention of food allergy. When favourable tolerance to peanut with early introduction was observed, encouraging messages about this tendency were disseminated and benefit suggested not just for peanuts. However, in order to be supported by evidence as generalizable, population-based studies are still needed [26²⁷].

From primary to secondary prevention, significant attention has been taken to the atopic march. Both food allergy and atopic eczema are considered the starters of the classic atopic march; nonetheless, this is being questioned [28–30]. Cohort studies provide several clusters where multimorbidity emerges as the most frequent phenotype instead of an inexorable progression from one condition to another. In this context, it seems that just the most severe eczema could influence the later development of asthma [31].

Prevention of disease progression should consider avoiding new sensitizations but particularly the underlying inflammatory mechanism. Therapeutic interventions for preventing asthma incidence in children with atopic eczema have failed [32].

Another nonpharmacologic therapeutic intervention with allergen immunotherapy has been investigated, searching for prevention of new sensitization and for alteration of the progression from allergic rhinitis to asthma as well. Both situations are still a matter of debate as no robust evidence completely supports these preventive outcomes at this time [33–35].

Also tertiary prevention should be kept in mind, when losing control of symptoms and the inflammatory process, may lead to an irreversible damage of the target organ. In allergic rhinitis, a clear clinical correlation with allergen sensitization provides a potential preventive capability on the progression to asthma from allergen-specific immunotherapy [36,37].

The role of molecular-based allergy as a preventive tool on potential near-fatal situations like anaphylaxis has been described earlier, such as food and venom allergy.

Patient participation in the management of disease

It is always considered that patients should have an active role in discussion of diagnosis and treatment. Even more, not only the voice of patients must be

heard on this interaction but also representative organizations of patients should participate on any plan of preventive interventions [3,4,38].

Physicians should look for partnership with their patients and educate on the preventive and interventional treatment, with the aim of obtaining an agreement for action [36].

In this regard, the voice of children is seldom considered in daily practice., Their assent for interventional clinical trials is obtained but there is a lack of a standardized instrument for obtaining children's consent, particularly in developing regions [39].

MAJOR COMMENTS ON PRECISION MEDICINE

Increasing knowledge and dissemination of precision medicine is needed to improve the predictability of clinical outcomes, avoiding inappropriate interventions and therapeutic adverse events, optimizing healthcare resources while improving quality of life and patients' cooperation and participation [40,41].

Precision medicine will probably deviate the course of the era of general guidelines and the concept of 'one size fits all,' without losing evidence-based support. Interest in the omics, to provide explanations of intrinsic mechanisms underlying phenotypes/endotypes and with focus on specific interventional strategies, will undoubtedly improve outcomes.

CONCLUSION: WILL PRECISION MEDICINE BE AVAILABLE FOR ALL PATIENTS IN NEAR FUTURE?

In developing countries, general medicine (not just the allergoimmunology field) is facing changes like telemedicine and innovative technical support progressively. It is expected that World Wide Web connectivity will facilitate some of these initiatives to enable access and allow them to be implemented everywhere.

However, use of omics in many regions (like genomics), are usually not available, and more studies on these population is desirable. Nowadays, data obtained from developing countries mostly come from multicentre clinical trials, with analysis of samples performed at central labs in Europe or United States.

A survey of more than a hundred allergologists from all over the world about molecular allergy diagnosis (authors request for specific purposes), found that it is available for three out of four respondents, and is reported to be covered by a

National Health System in 35%, by private insurers in 25% and in the rest by patients themselves.

Could the scarcity of technology and the few resources to afford it in developing countries be compensated with more time dedicated to patients' assistance? It seems to be the opposite, because lean salaries result in less time per patient and the pressure to assist many patients on a fixed salary.

Therefore, the chance to provide medical advances at affordable prices seems to be a real challenge for providing precision medicine to everyone.

Acknowledgements

We would like to thank all colleagues helping on local molecular diagnosis information. Special thanks to Prof. S. Tarlo for a magnificent revision and edition.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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