Asthma: personalized and precision medicine

Giorgio W. Canonica[a,b], *Matteo Ferrando*[c], *Ilaria Baiardini*[c], *Francesca Puggioni*[b], *Francesca Racca*[b], *Giovanni Passalacqua*[c], *and Enrico Heffler*[a,b]

Purpose of review
In this review, we herein describe the progress in management of severe asthma, evolving from a 'blockbuster approach' to a more personalized approach targeted to the utilization of endotype-driven therapies.

Recent findings
Severe asthma characterization in phenotypes and endotypes, by means of specific biomarkers, have led to the dichotomization of the concepts of 'personalized medicine' and 'precision medicine', which are often used as synonyms, but actually have conceptual differences in meaning. The recent contribute of the omic sciences (i.e. proteomics, transcriptomics, metabolomics, genomics, ...) has brought this initially theoretic evolution into a more concrete level.

Summary
This step-by-step transition would bring to a better approach to severe asthmatic patients as the personalization of their therapeutic strategy would bring to a better patient selection, a more precise endotype-driven treatment, and hopefully to better results in terms of reduction of exacerbation rates, symptoms, pulmonary function and quality of life.

Keywords
biological therapies, biomarkers, personalized medicine, precision medicine, severe asthma

INTRODUCTION

Personalization of management and treatment of each patient has been the physician goal since Hippocrates. In the last century, progression of research and industry leaded to great achievements, such as the discovery of molecules able to treat a relevant proportion of patients with a certain disease. In that context, we lived the era of the 'blockbusters' drugs [1].

What was already evident at that time was the following: a need for generic drugs, whose intent is to cover more patients in the developed countries and to extend the treatment to underdeveloped countries; a decrease of the so-called 'blockbuster approach' while developing a 'phenotype driven treatment'; and finally, considering the burden of treatment with branded biologics, we also envisaged the possible forthcoming of biosimilars in asthma and allergic diseases.

Nowadays, mainly because of the new biologic therapies, 'Personalized Medicine' and 'Precision Medicine' are commonly used as terms to indicate a more individualized approach to single patient treatment [2].

We previously reported that the two terms are used interchangeably [2], mainly in this area, but we should revise that view, seeing not a complete overlapping between Personalized and Precision Medicine.

'Precision medicine' is mainly targeting the endotype of the patient, that is the mechanism(s) of the disease of the individual patient [3]. Support to this definition of target patient is coming from several 'omic' sciences, such as proteomics, transcriptomics, metabolomics, genomics, and so forth, ... detecting biomarkers able to identify the molecular mechanisms of the patient''s disease and

[a]Department of Biomedical Sciences, Humanitas University, [b]Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milano and [c]Allergy and Respiratory Diseases, Policlinico San Martino-IST, University of Genova, Genova, Italy

Correspondence to Professor Giorgio W. Canonica, Personalized Medicine, Asthma and Allergy Clinic, Humanitas University and Research Hospital, Via Alessandro Manzoni 113, Rozzano, Milano, Italy.
Tel: +39 02 82247741; e-mail: giorgio_walter.canonica@hunimed.eu

Curr Opin Allergy Clin Immunol 2017, 17:000–000
DOI:10.1097/ACI.0000000000000416

KEY POINTS

- 'Personalized medicine' and 'precision medicine' are often used as synonyms but actually have slight meaning differences.
- Personalized–precision medicine would bring to better treatment strategies in dealing with severe asthmatic patients.
- Checking patient adherence to their therapies, the phenotypization and endotypization processes, the utilization of predictive biomarkers and the contribution of the omic sciences would be relevant in reaching this goal.

accordingly to lead to the choice of the correct and effective biologic drug [4].

Precision medicine is of key importance and it will lead to a new classification of the diseases on the basis of the molecular mechanisms [5].

'Personalized medicine' has a broader value and meaning. Of course, we can see precision medicine as a core moment of personalized medicine, but we should consider all the aspects related to the 'person' we have to treat [6]. In the context of omic sciences, FitzGerald recently proposed the term 'Humanomics', a very interesting concept, refocusing doctor's attention on patient's features [7,8▪]. In this context, we herein report also 'Personomics', indicating all the aspects (clinical, emotional, psychological, functional, phenotypical, endotypical, etc...) [9] we should consider, evaluate and investigate about the 'person/patient' we have to treat. Thus, the term 'omic sciences' is not just restricted to system biology but it is also encompassing other areas of knowledge and research [10]. (Fig. 2).

Nowadays the most challenging task is to transfer into the current clinical practice the principle(s) of personalized medicine. Recently an interesting approach to this has been envisaged by Pritchard and colleagues and a suitable proposal of how to reach this goal has been formulated [8▪,10]. Interestingly, National Institute for Health and Care Excellence (NICE) reports that the knowledge of the personal experience about a disease (made by values, needs, concerns, beliefs, expectations, ...) represents a fundamental step to achieve the best possible experience of care [11].

THE PATIENT: A CHANGING ROLE

Recently Hood and co-workers promoted 'P4 Medicine', where in addition to preventive, predictive and personalized medicines, participatory medicine has also been included [12▪]. This is giving a new and key role to the patient, whose 'participation' in context is not anymore limited to the obsolete ''patient/doctor'' interaction as such. P4 Medicine also means the active participation of the patients in the entire health process till an active involvement in clinical trials: an innovative approach.

In order to realize this, biomedical advances alone are insufficient: all those psychological aspects that make 'unique' each person, should be integrated with the clinical, biological and genetic data [13]. Gorini and Pravettoni [14] proposed a more complex approach, highlighting the opportunity to add a fifth 'P' (psycho-cognitive) to the P4 Medicine: thus, reaching both the biological and the psychosocial dimensions.

Agusti *et al.* [15] proposed a novel strategy for the management of airway diseases aimed to overtake the limits of the traditional diagnostic classification that tends to make 'stereotypical' the patient. They suggested a bottom-up approach (from endotypes to disease phenotypes) instead of a classical top-bottom approach (from symptoms to mechanisms). In this perspective, the identification of 'treatable traits' (those traits that are identifiable and treatable according the current knowledge) in each patient permits to apply a targeted strategy of disease management. This personalized approach takes into account physical, psychological and behavioral features.

INHALER DEVICES AND ADHERENCE TO TREATMENT

A key aspect to be considered, whenever treating patients with asthma, is the adherence to treatment [16▪]. Official recent data from the Italian Regulatory Authority reported adherence to treatment in obstructive pulmonary diseases, including asthma, as 13.8% of the expected (http://www.aifa.gov.it/content/luso-dei-farmaci-italia-rapporto-osmed-gennaio-settembre-2016; accessed 8th July 2017). On the other hand, adherence has been always indicated as a weak point in chronic disease management [17], with a dramatic economic impact on disease burden.

In asthma, a critical role is played by the inhaler devices, quite a few on the market [18] and it is a specific task of the specialist to know all the features on each inhaler and to choose the most appropriate one accordingly to the single patient characteristics. This key issue has been extensively described and discussed in the European Respiratory Society (ERS)–International Society for Aerosols in Medicine (ISAM) Task Force document published in 2011 [19]. Additionally, to the correct choice of the device, the prescriber should consider an

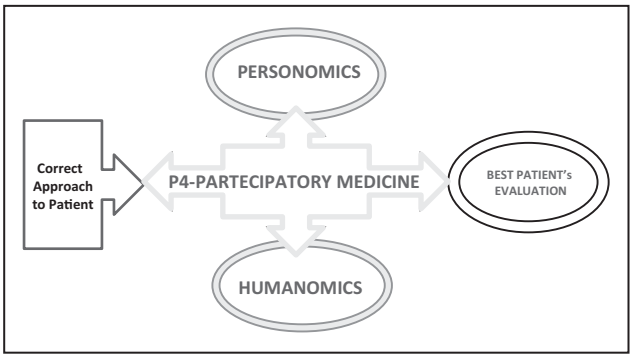

FIGURE 1. Steps forward to the best patient's evaluation.

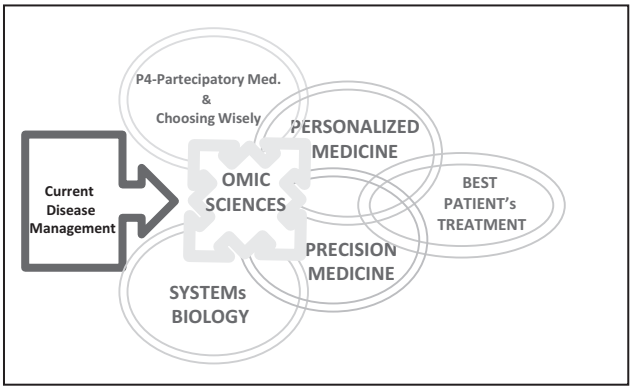

FIGURE 2. Steps forward to obtain the best patient's treatment.

educational training to the patient about the device use. In fact, Virchow *et al.* [20] reported a very low capability of the patients (about 21%) to use properly inhalers just after reading the written instructions, whereas a specific educational intervention can rise the correct use up to 52%. Being this the case, educational intervention is a key element for a correct treatment of asthma patients [21]. A specific education is also crucial whenever a switch of device is needed [22], as we should avoid multiple inhalers whose prescription is confusing the patient, with the risk of defective adherence [23▪]. The prescriber should also always properly educate the patient to new devices and check the inhalation patient's technique at each visit, as part of the correct asthma management [23▪,24].

Improvement of adherence has been the aim of several projects [25] involving different stakeholders and technologies. Recent useful approaches have been proposed such as using monitoring tools for inhalers that can be improve adherence [26].

These new technologies will certainly help both the patients and doctors to control adherence and they will also provide further interesting data about asthma management in general.

PRECISION MEDICINE AND PERSONALIZED MEDICINE IN ASTHMA

As already previously stated, the concepts of 'personalized medicine' and 'precision medicine' have been often considered as overlapping. We think that they are not interchangeable but strongly related and depending on each other, being 'Precision Medicine' essential to achieve the goal of personalizing the medical approach [Figs. 1 and 2]. According to the National Institution of Health (NIH) definition, Precision Medicine is 'an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person' (https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative; accessed 8 July 2017).

The precision medicine approach aims to find predictive parameters to more accurately choose which treatment or prevention strategy is more suitable for a particular disease in a specific group of patients. Therefore, precision medicine is the opposite of the so-called 'one-size-fits-all' approach, in which clinical decisions and therapeutical strategies are applied, without considering the possible individual [1]. Precision medicine implies the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease.

Two additional approaches are of great relevance in this context: 'choosing wisely' and 'slow medicine' [27], whose aims are the best for the patient while controlling sustainability of the process.

In order to identify subpopulation of patients ('phenotypes' [28▪▪]), the precision-medicine approach looks into the underlying mechanisms of different forms of each disease ('endotypes' [3]) by the use of surrogate measures that acts as biomarkers [29].

The ability to provide precision medicine to patients in routine clinical settings depends on the availability of easily assessable biomarkers, possibly with point-of-care technology [30▪▪], together with the knowledge bases on how correctly translate biomarkers result into a personalized clinical–therapeutical decision. Therefore, we should be aware that a personalized and precise approach, such as in severe asthma, will be managed by few well equipped reference centers in which high-level trained staff works [31,32].

The precision-medicine approach became a priority for clinicians and researchers when, in 2015, also the United States President Barack Obama

stated his intention to fund a 'Precision Medicine Initiative' 'to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments' (https://obamawhitehouse.archives.gov/node/333101; accessed 8 July 2017). Such an initiative has been confirmed early this year [33] by the NIH research investment in the next decade.

After the first biologic agent (omalizumab, 37) 10 years ago, recently new biologics have been approved for severe asthma: mepolizumab (a monoclonal antibody against IL-5) and reslizumab (another anti-IL monoclonal antibody). In the next few years, some more will come; benralizumab, an IL-5 receptor antagonist; dupilumab, an IL-4 receptor alpha antagonist, blocking both the IL-4 and IL-13 inflammatory pathways; tezepelumab an antithymic stromal lymphopoietin (TSLP) antibody, we are now at the beginning of a new era in the management of severe asthmatic patients: a 'Precision Medicine Era'. In fact, severe asthma patients necessarily must be clinically, functionally, inflammatorily and molecularly phenotyped in order to personalize the therapeutic approach.

FROM PHENOTYPES TO ENDOTYPES: A ROUNDTRIP

Asthma was previously viewed as a single disease characterized by chronic airway inflammation, bronchial hyperreactivity, airway obstruction and airway remodeling. More recently, this simplistic concept, ignoring the heterogeneity of the disease, became obsolete: nowadays, asthma is considered a multidimensional disease with different clinical, inflammatory, pathologic and physiologic involvements [28▪▪,29,30▪▪,31,32–35].

Mainly using cluster analysis-based approaches, several asthma phenotypes have been described so far [36▪▪]. The most common phenotypical classification of asthma highlights the type of inflammatory airway involvement, separated in four subgroups according to sputum eosinophilia or neutrophilia: an eosinophilic asthma generally (early-onset) well responsive to inhaled corticosteroids, a noneosinophilic but neutrophilic asthma generally with more severe disease and less sensitive to inhaled corticosteroids, a mixed eosinophilic–neutrophilic form with features of both the previously described forms and a paucygranular sputum pattern asthma whose existence is still highly debated [37,38]. Subsequently, a more complex way of dividing asthmatic patients in subgroups was developed according to the presence (Th2-high) or not (Th2-low) of assessable biomarkers of Th2-mediated airway inflammation [39,40]. The Th2-high phenotype includes mainly the classical allergic one and the late-onset, nonallergic but highly eosinophilic asthma (including the subgroup associated with acetylsalicylic-acid sensitivity); on the other hand, the Th2-low phenotypes are more diversified and less well defined. The existence of other phenotypes has been reported: asthma associated with obesity; a very late-onset asthma without eosinophilic inflammation mainly in women; cigarette smoker asthmatic patients with neutrophilic sputum and a paucygranular asthma phenotype with predominant airway hyperreactivity [41].

These phenotypic, cluster-analysis-based classifications helped clinicians and researchers to better understand that asthma is a multifaceted syndrome.

Additional consideration should be paid to comorbidities, which may negatively influence asthma control, severity and response to therapy (including response to biologics).

Comorbidity could be a real hallmark as it happens to chronic rhinosinusitis with nasal polyps (CRSwNP), which is present in the great majority of late-onset, highly eosinophilic, nonallergic asthma [42]. The presence of CRSwNP, in fact, being associated with more severe, steroid-dependant asthma [43], was seen to increase lower airway inflammation [44], and negatively correlate with asthma control [45]. Another example of relevant comorbidity associated with a specific phenotype of asthma is obesity: there is evidence that overweight and obese asthmatic patients tends to have a less eosinophilic and more neutrophilic airway inflammation with the consequence of a reduced corticosteroid sensitivity, and therefore, a more severe asthma [46]. Weight loss has been associated with restored asthma control and improved asthma-related quality of life [47].

Phenotypes describe characteristics of asthmatic patients but do not provide insights of the disease causes. Therefore, the term 'endotype' was proposed to indicate a subtype of a condition defined by a specific biologic mechanism [3]. Each endotype may account for one or more phenotype, and vice versa. The study of underlying mechanisms of asthma gave the opportunity to the researchers to identify more precise therapeutic targets [48]. In particular, some inflammatory pathways were identified as relevant in different severe asthma endotypes: a proportion of patients are characterized to have a 'classical' allergic asthma induced by the exposure to relevant (mainly perennial) allergens, resulting in an increased concentration of cytokines as IL-4, IL-5 and IL-13 and IgE production [49]; another relevant proportion of severe asthmatic patients, often associated with CRSwNP, blood and serum

eosinophilia, and generally without evidence of atopy, is characterized by an intense production of IL-5 and IL-13, which is responsible for the high levels of blood and tissue eosinophils [42]. This endotype seems to be because of the activation of a subset of inflammatory cells, with similar characteristics to Th2 but different in their trigger, called innate lymphoid cells of type 2 (ILC2) [49]. The hypothesis is that a still unknown agent (i.e. virus, bacterium, fungi, pollutants, cigarette smoking, occupational agents, ...) directly damage airway epithelium, inducing the activation of epithelial cells with the production of epithelial cytokines such as TSLP, IL-25 and IL-33, which act as potent activators of ILC2 [50]. 3) A smaller proportion of patients with severe asthma are characterized by a noneosinophilic, mainly neutrophilic airway inflammation, higher frequency of chronic–recurrent airway infections, higher prevalence of smokers or ex-smokers, and higher BMI [51]. In these patients, the TNFα [52] and IL-17 [53] inflammatory pathways are the most studied and more probably etiopathogenetically correlated underlying processes.

BIOMARKERS TO IDENTIFY ENDOTYPES AND PHENOTYPES

The definition of different endotypes and phenotypes implies the need of finding reliable and possibly easily assessable biomarkers that may guide the clinician in order to identify the right therapeutic target for each single endotype, and therefore, for each single patient.

An ideal biomarker should be suitable to identify the disease or a specific endotype/phenotype, and it should appear or disappear over the course of disease progression, and thus, be useful in determining the prognosis of a disease within an individual. Moreover, the ideal biomarker should change as a biomarker-driven therapy is started, adjusted or discontinued, and should be easily obtained with minimum discomfort or risk to the patient (https://www.fda.gov/ohrms/dockets/ac/01/briefing/3798b1_04_holt/tsld005.htm; accessed 8th July 2017).

In severe asthma, many possible biomarkers have been investigated but only few of them, so far, had at least one of the above-mentioned characteristics and can be easily used in clinical practice.

Briefly, the current most reliable biomarkers are: blood eosinophil count, sputum eosinophils and neutrophils, serum total IgE and exhaled nitric oxide (FE_{NO}) [29]. Among the other molecules that need more studies in order to be validated as biomarkers of severe asthma endotypes–phenotypes, serum periostin and dipeptidil-peptidase 4 (DPP4) seems those with the most promising profile [54,55], for a certain asthma endotype.

The severe allergic asthma phenotype is generally characterized by no or mild blood eosinophilia, high levels of FE_{NO}, and high levels of serum total IgE [49]. This endotype differs from the nonallergic, late-onset, eosinophilic refractory one because the latter is generally characterized by important blood and sputum eosinophilia despite high dose of inhaled and oral or just oral corticosteroid treatment; these patients generally have also high FE_{NO} but serum total IgE can be both normal or elevated but probably with a lower etiopathogenetical importance [42]. Among the eosinophilic refractory asthma patients, some probably have a high IL-5 expression whereas others may have a predominant IL-13-mediated and IL-14-mediated inflammation. Serum periostin has been proposed to identify patients responsive to anti-IL-13 monoclonal antibody treatment [56], but other subsequent studies reduced the enthusiasm on this biomarker [57]. More recently, DPP4 has been proposed to be able to distinguish those endotypes with a predominant IL-13-mediated and IL-4 mediated inflammation from those in which IL-5 is the main key player [55]; further studies are needed to confirm these first evidence.

Interestingly, blood eosinophil count, FE_{NO} and serum periostin seems to be able to predict sputum eosinophilia, with best results for blood eosinophils and serum periostin [57]. The combined evaluation of blood eosinophils and lymphocytes ratio and eosinophils and neutrophils ratio in a mathematical model (the so-called ELEN index [58]) seems to be more precise than blood eosinophil count alone to identify sputum eosinophilia.

This evident overlap between the biomarkers implies the need of using panels of biomarkers instead of single ones [59]: this approach will probably increase the precision in identifying endotypes for a more precise medicine approach to severe asthma management.

As mentioned before, two of the desired characteristics of a biomarker are the easiness and noninvasiveness of assessment; this is also part of the definition of point-of-care testing (POCT). Among the available severe asthma biomarkers, FE_{NO} is the one with all POCT characteristics, being performed in a noninvasive, very easy and rapid way, usually by using a portable device; these features give the opportunity to clinicians to assess the measure directly in their offices during the time of a visit [60▪]. We recently published the validation of a blood eosinophil count assessed by a portable, POCT and noninvasive device (the system is able to determine this information by analyzing a single drop of

blood collected with a finger prick) in a severe asthmatic setting [30▪▪]. Similar devices but for the assessment of serum total/free IgE [61] and periostin [62] are being developed and need a validation in a severe asthma setting. We believe that these POCT devices, if applied to the assessment of severe asthma biomarkers, could really accelerate the path leading to a precision medicine approach and clinical management of severe asthma.

BIOMARKER-TARGETED THERAPIES

Biomarkers, in addition to their role in defining phenotypes and endotypes may also have a predictive value for defining responders to each biological treatment.

As far as biomarkers useful to choose the right endotype-based treatment, serum IgE, blood eosinophils were the most studied ones.

Serum total IgE is in fact used for verification that the patient with severe allergic asthma is a suitable candidate for anti-IgE therapy (omalizumab) with total serum IgE levels between 30 and 1500 IU/ml [63].

As far as the available or closely available anti-cytokine strategies (i.e. anti-IL5, anti-IL4/IL-13, ...) the biomarker chosen to define the possibility to prescribe such treatments is peripheral blood count. Several different cutoffs in blood eosinophil measurements were chosen as minimum values for prescribing biologicals acting in the eosinophilic refractory forms of severe asthma: they range from a eosinophil count of 150/ml for dupilumab [64] (more recent data did not confirm eosinophils as predictive biomarker of response to dupilumab [64]) and mepolizumab (together with at least one historical report of more than 300/ml for the latter) [65] to 300/ml for benralizumab [66] to 400/ml for reslizumab trials [67].

Whenever considering predictive biomarkers of response to biological treatments, a proteomic approach showed that galectin-3 tissue levels were directly correlated with a good response, in terms of reduction of airway remodeling to omalizumab [68,69].

Post hoc analysis of clinical trials, showed that patients with high-serum periostin levels were those with the highest response to lebrikizumab (an anti-IL13 agent) in terms of lung function improvement [56]. Furthermore, as mentioned previously about POCT, high FE_{NO} levels, high-serum periostin and high-blood eosinophil levels positively correlate with improvement in terms of reduction in exacerbations in patients treated with omalizumab [70].

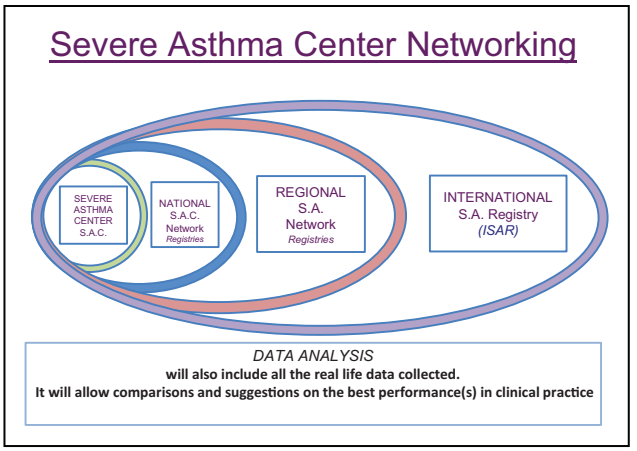

FIGURE 3. Severe Asthma Center Networking would ameliorate the exchange of data and information on severe asthmatic patients.

CONCLUSION

We should definitely put aside the concept of the 'one-size-fits-all' traditional approach [6].

In the last 10 years, only omalizumab was available, later followed by mepolizumab and hopefully by the other monoclonal antibodies previously described.

We will move from the availability of only one monoclonal antibody to a situation in which we will have to choose one monoclonal antibody among many: this implies the need of more selective biomarkers (or panels of them) in order to identify the right biological for each single patient, in a more personalized and precise medicine approach to the disease treatment.

The era of new 'Magic Bullits' to target molecular mechanisms of severe asthma [34] has come and it implies new expertises and professionalities, also because severe asthma precision medicine has a cost [71] and in this context, the leading role of the Severe Asthma Reference Centers is crucial [72▪]. The potential of networking among the severe asthma centers is of great relevance [73▪▪,74], as collecting data, big data, will provide real life and research evidences capable of driving the process to the best practice (Fig. 3).

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

G.W.C. has been member of advisory board, speaker, scientific meeting for GSK, Teva, Sanofi, Roche,

Novartis, Astra Zeneca. G.P. was consultant/speaker for ALK-Abellò, AstraZeneca, Lofarma, Novartis, Stallergenes-Greer.
Funding: this article has been partially supported by ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche) Genova.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Braido F, Holgate S, Canonica GW. From 'blockbusters' to 'biosimilars': an opportunity for patients, medical specialists and healthcare providers. Pulm Pharmacol Ther 2012; 25:483–486.
2. Canonica GW, Bachert C, Hellings P, *et al.* Allergen immunotherapy (AIT): a prototype of precision medicine. World Allergy Organ J 2015; 8:31.
3. Lötvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 2011; 127:355–360.
4. Benson M. Clinical implications of omics and systems medicine: focus on predictive and individualized treatment. J Intern Med 2016; 279:229–240.
5. De Ferrari L, Chiappori A, Bagnasco D, *et al.* Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma? Expert Rev Respir Med 2016; 10:29–38.
6. Ferrando M, Bagnasco D, Varricchi G, *et al.* Personalized medicine in allergy. Allergy Asthma Immunol Res 2017; 9:15–24.
7. FitzGerald JM, Boureslami I. The need for humanomics in the era of genomics and the challenge of chronic disease management. Chest 2014; 146:10–12.
8. ■ Pritchard DE, Moeckel F, Villa MS, *et al.* Strategies for integrating personalized medicine into healthcare practice. Per Med 2017; 14:141–152.

The article described the roadmap to be followed to reach personalized medicine from the current clinical practice.

9. Ziegelstein RC. Personomics. JAMA Intern Med 2015; 175:888–889.
10. Hellmann DB, Ziegelstein RC. Personomics: a new series in the Green Journal. Am J Med 2017; 130:622.
11. National Institute for Health and Care Excellence (NICE) - Clinical guideline [CG138]: Patient Experience in Adult NHS Services: Improving the Experience of Care for People Using Adult NHS Service. 2012. https://www.nice.org.uk/guidance/cg138 (accessed 8th July 2017).
12. ■ Auffray C, Charron D, Hood L. Predictive, preventive, personalized and participatory medicine: back to the future. Genome Med 2010; 2:57.

The P4 medicine, the concept of participatory medicine provides a new role for the patient and a new challenge for the physicians.

13. Horne R. The human dimension: putting the person into personalised medicine. New Bioeth 2017; 23:38–48.
14. Gorini A, Pravettoni G. P5 medicine: a plus for a personalized approach to oncology. Nat Rev Clin Oncol 2011; 8:444.
15. Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J 2016; 47:410–419.
16. ■ Braido F, Baiardini I, Blasi F, *et al.* Adherence to asthma treatments: 'we know, we intend, we advocate'. Curr Opin Allergy Clin Immunol 2015; 15:49–55.

An official manifesto on adherence in obstructive respiratory diseases.

17. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005; 353:487–497.
18. Braido F, Baiardini I, Sumberesi M, *et al.* Obstructive lung diseases and inhaler treatment: results from a national public pragmatic survey. Respir Res 2013; 14:94.
19. Laube BL, Janssens HM, de Jongh FH, *et al.* European Respiratory Society; International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J 2011; 37: 1308–1331.
20. Virchow JC, Crompton GK, Dal Negro R, *et al.* Importance of inhaler devices in the management of airway disease. Respir Med 2008; 102:10–19.
21. Canonica GW, Baena-Cagnani CE, Blaiss MS, *et al.,* GAPP Survey Working Group. Unmet needs in asthma: Global Asthma Physician and Patient (GAPP) Survey: global adult findings. Allergy 2007; 62:668–674.
22. Braido F, Lavorini F, Blasi F, *et al.* Switching treatments in COPD: implications for costs and treatment adherence. Int J Chron Obstruct Pulmon Dis 2015; 10:2601–2608.
23. ■ Lavorini F, Braido F, Baiardini I, *et al.* SIAAC-SIMER. Asthma and COPD: interchangeable use of inhalers. A document of Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC) & Italian Society of Respiratory Medicine (SIMeR). Pulm Pharmacol Ther 2015; 34:25–30.

An official document on how to avoid the negative impact of switching inhaler device.

24. Global Initiative for Asthma (GINA) - 2017 GINA Report, Global Strategy for Asthma Management and Prevention. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ (accessed 8 July 2017).
25. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. Cochrane Database Syst Rev 2017; 4: CD012226.
26. D'Amato M, Baiardini I, Solidoro P, Braido F. Adherence to treatment and monitoring tools: what's new? Minerva Med 2016; 107(1 Suppl 1):5–8.
27. Heffler E, Landi M, Quadrino S, *et al.* Choosing wisely in allergology: a slow medicine approach to the discipline promoted by the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC). Clin Mol Allergy 2015; 13:28.
28. ■■ Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012; 18:716–725.

A crucial article in the definition of asthma phenotypes.

29. Vijverberg SJ, Hilvering B, Raaijmakers JA, *et al.* Clinical utility of asthma biomarkers: from bench to bedside. Biologics 2013; 7:199–210.
30. ■■ Heffler E, Terranova G, Chessari C, *et al.* Point-of-care blood eosinophil count in a severe asthma clinic setting. Ann Allergy Asthma Immunol 2017; 119: 16–20.

An added value for monitoring asthma patients in clinical practice.

31. Senna G, Guerriero M, Paggiaro PL, *et al.* SANI-Severe Asthma Network in Italy: a way forward to monitor severe asthma. Clin Mol Allergy 2017; 15:9.
32. Heaney LG, Djukanovic R, Woodcock A, *et al.* Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). Thorax 2016; 71:187–189.
33. Hudson KL, Collins FS. The 21st century cures act – a view from the NIH. N Engl J Med 2017; 376:111–113.
34. Tarantini F, Baiardini I, Passalacqua G, *et al.* Asthma treatment: 'magic bullets which seek their own targets'. Allergy 2007; 62:605–610.
35. Holgate ST. Asthma: a simple concept but in reality a complex disease. Eur J Clin Invest 2011; 41:1339–1352.
36. ■■ Loza MJ, Djukanovic R, Chung KF, *et al.* ADEPT (Airways Disease Endotyping for Personalized Therapeutics) and U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome Consortium) investigators. Validated and longitudinally stable asthma phenotypes based on cluster analysis of the ADEPT study. Respir Res 2016; 17:165.

Data coming from one of the most relevant group/consortium investigating asthma endotypes and biomarkers.

37. Gibson PG. Inflammatory phenotypes in adult asthma: clinical applications. Clin Respir J 2009; 3:198–206.
38. Demarche S, Schleich F, Henket M, *et al.* Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory? BMC Pulm Med 2016; 16:46.
39. Woodruff PG, Modrek B, Choy DF, *et al.* T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med 2009; 180:388–395.
40. Seys SF, Grabowski M, Adriaensen W, *et al.* Sputum cytokine mapping reveals an 'IL-5, IL-17A, IL-25-high' pattern associated with poorly controlled asthma. Clin Exp Allergy 2013; 43:1009–1017.
41. Ray A, Oriss TB, Wenzel SE. Emerging molecular phenotypes of asthma. Am J Physiol Lung Cell Mol Physiol 2015; 308:L130–L140.
42. Amelink M, de Groot JC, de Nijs SB, *et al.* Severe adult-onset asthma: a distinct phenotype. J Allergy Clin Immunol 2013; 132:336–341.
43. Bresciani M, Paradis L, Des Roches A, *et al.* Rhinosinusitis in severe asthma. J Allergy Clin Immunol 2001; 107:73–80.
44. Guida G, Rolla G, Badiu I, *et al.* Determinants of exhaled nitric oxide in chronic rhinosinusitis. Chest 2010; 137:658–664.
45. Heffler E, Pizzimenti S, Badiu I, *et al.* Nasal nitric oxide is a marker of poor asthma control. J Breath Res 2013; 7:026009.
46. Umetsu DT. Mechanisms by which obesity impacts upon asthma. Thorax 2017; 72:174–177.
47. van Huisstede A, Rudolphus A, Castro Cabezas M, *et al.* Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. Thorax 2015; 70: 659–667.
48. Stokes JR, Casale TB. Characterization of asthma endotypes: implications for therapy. Ann Allergy Asthma Immunol 2016; 117:121–125.
49. Lee JH, Haselkorn T, Chipps BE, *et al.,* Tenor Study Group. Gender differences in IgE-mediated allergic asthma in the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study. J Asthma 2006; 43:179–184.
50. Boita M, Bucca C, Riva G, *et al.* Release of type 2 cytokines by epithelial cells of nasal polyps. J Immunol Res 2016; 2016:2643297.
51. Chung KF. Neutrophilic asthma: a distinct target for treatment? Lancet Respir Med 2016; 4:765–767.
52. Heffler E, Berry M, Pavord ID. Tumor necrosis factor-alpha: a promising therapeutic target for asthma? BioDrugs 2007; 21:345–349.
53. Busse WW, Holgate S, Kerwin E, *et al.* Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am J Respir Crit Care Med 2013; 188:1294–1302.
54. Izuhara K, Ohta S, Ono J. Using periostin as a biomarker in the treatment of asthma. Allergy Asthma Immunol Res 2016; 8:491–498.

55. Nieto-Fontarigo JJ, González-Barcala FJ, San José E, *et al.* CD26 and asthma: a comprehensive review. Clin Rev Allergy Immunol 2016. [Epub ahead of print]

56. Corren J, Lemanske RF, Hanania NA, *et al.* Lebrikizumab treatment in adults with asthma. N Engl J Med 2011; 365:1088–1098.

57. Wagener AH, de Nijs SB, Lutter R, *et al.* External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. Thorax 2015; 70:115–120.

58. Khatry DB, Gossage DL, Geba GP, *et al.* Discriminating sputum-eosinophilic asthma: accuracy of cutoffs in blood eosinophil measurements versus a composite index, ELEN. J Allergy Clin Immunol 2015; 136:812–814.e2.

59. Wadsworth S, Sin D, Dorscheid D. Clinical update on the use of biomarkers of airway inflammation in the management of asthma. J Asthma Allergy 2011; 4:77–86.

60. ■ Nair P, Zhang Q, Brennan JD. A perspective on point-of-care tests to detect eosinophilic bronchitis. J Asthma 2015; 52:254–261.
An added value for monitoring asthma patients in clinical practice.

61. Steiss JO, Schmidt A, Rudloff S. Monitoring of omalizumab therapy by measuring free IgE using a bedside immunoassay. Clin Lab 2015; 61:31–37.

62. Takai M, Ono J, Kamei A, *et al.* A novel, automated periostin assay; correlation with a commercial ELISA method and usability as an asthma biomarker [abstract]. Eur Respir J 2016; 48(suppl 60):OA1980.

63. Normansell R, Walker S, Milan SJ, *et al.* Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014; (1):CD003559.

64. Wenzel S, Ford L, Pearlman D, *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 2013; 368:2455–2466.

65. Ortega HG, Yancey SW, Mayer B, *et al.* Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med 2016; 4:549–556.

66. Castro M, Wenzel SE, Bleecker ER, *et al.* Benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014; 2:879–890.

67. Castro M, Zangrilli J, Wechsler ME, *et al.* Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015; 3:355–366.

68. Mauri P, Riccio AM, Rossi R, *et al.* Proteomics of bronchial biopsies: galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients. Immunol Lett 2014; 162(1 Pt A):2–10.

69. Riccio AM, Mauri P, De Ferrari L, *et al.* Galectin-3: an early predictive biomarker of modulation of airway remodeling in patients with severe asthma treated with omalizumab for 36 months. Clin Transl Allergy 2017; 7:6.

70. Hanania NA, Wenzel S, Rosén K, *et al.* Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013; 187:804–811.

71. Gibeon D, Heaney LG, Brightling CE, *et al.,* British Thoracic Society Difficult Asthma Network. Dedicated severe asthma services improve health-care use and quality of life. Chest 2015; 148:870–876.

72. ■ Green RH, Shaw D. Strict adherence rules to obtain monoclonal therapy might cost lives. Lancet Respir Med 2017; 5:678–679.
A recent update about the cost treatments and how to deal with this aspect.

73. ■■ Djukanović R, Bruselle G, Walker S, *et al.* The era of research collaborations: new models for working together. Eur Respir J 2017; 49:; pii: 1601848.
Networking is the basis of the new approach for comparing and collecting data.

74. Bulathsinhala L, Eleangovan N, Liam Heaney LG, *et al.* Development of the International Severe Asthma Registry (ISAR): a modified Delphi study (submitted).