Personalised medicine: are we ready?

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A new series entitled "Personalised medicine in respiratory diseases" begins with a focus on asthma http://ow.ly/VGGE30eYTmT

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This issue of the *European Respiratory Review* (*ERR*) contains the first article of a new series entitled "Personalised medicine in respiratory diseases". The specific topic of this first article is personalised medicine for asthma [1], as in another recent article published in the *ERR* [2]. Is it really worth focusing that much on this new concept? The exponentially growing number of articles on personalised medicine in PubMed suggests that the answer is yes: there was one citation referring to "personalised medicine" in 1990, eight in 2000, 482 in 2010, and 1851 in 2016! Before going further, let us note as a preamble that the terms "personalised", "individualised", "precision" and "P4" (predictive, preventive, personalised and participatory; to be discussed later in this editorial) medicine are often used interchangeably (and this list is not exhaustive), although some authors have suggested differences between them. For instance, it has been proposed that "precision" refers mostly to improvements in the taxonomy of diseases and patients' stratification, and thus is more a component of personalisation than of prevention, prediction and participation [3]. To avoid this debate, we will restrict ourselves to the term "personalised medicine" here. Of note, stratified medicine is based on groups (strata) rather than individuals. Thus, it represents a step towards personalisation but is not synonymous to it. The main targets of personalised medicine are chronic noncommunicable diseases, which now represent the leading causes of death, handicap and health-related direct or indirect costs in the world [4]. The purpose of this editorial is to introduce the topic of personalised medicine, discuss how it can be illustrated in the asthma field based on the article by Chung [1], and introduce future articles of this series.

General comments on personalised medicine

What is personalised medicine? Is it really something new? The first, instinctive answer is that "personalised medicine means providing the right care to the right person at the right moment", which has been a fundamental principle in medicine since some humans began treating others [5]. But, although old in its principles, the concept is trapped in a never-ending modernisation process that sometimes makes it difficult to fully capture it [6]. Deciphering diseases has been a first step towards personalising care, aiming at answering the question "what is this patient suffering from?" This process began several centuries ago and is certainly not completed, as illustrated, for example, by debates surrounding the links, differences and overlaps between asthma and chronic obstructive pulmonary disease (COPD) [7]. Elucidating underlying biological mechanisms is the immediate correlate of a disease's identification,

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hopefully leading to the development of effective treatments. However, in the last century it appeared that one single disease seldom equals one single mechanism: as in nature in general, there is huge complexity in the human body, which is made not only of juxtaposed components but also of multiple interactions at all levels, from organ systems down to molecular networks. Complexity is increased by external influences that make it futile to consider individuals outside their environment. Altogether, an organism cannot be summarised as the sum of its parts.

The last century saw an exponential increase in our understanding of health and disease, clinical phenotypes [8, 9], biological endotypes and targeted biologics, as illustrated in the field of asthma and allergic diseases [10] although not yet for COPD, the other most frequent chronic bronchial disease [11]. But the end of this road is not yet visible on the horizon: the size of what we still need to learn is probably much larger than our current knowledge. Yet, the power of available tools has increased at a huge speed over a limited period. Human beings made this, but also need to adapt their thinking so that they can manage the enormous amount of information that they are able to gather: collecting data through various types of measurements is one thing, being able to analyse it and understand what is happening and how it can be modulated is another. In addition, static measurements ("omics") are certainly not sufficient to understand the underlying dynamics of interactions that occur with varying time and spatial scales: at some point modelling tools are required since relations are mostly nonlinear, making straight inferences hazardous. Addressing this complexity is what systems or networks biology and medicine try to do, using bioinformatic tools and knowledge engineering to transform data into understanding and ultimately gain the ability to modulate individual target mechanisms to treat each patient more effectively, which is one fundamental goal of personalised medicine [12–14].

However, most authors agree that systems biology is only one of many components required to achieve personalised medicine, which is part of a larger concept called "P4 medicine" (predictive, preventive, personalised and participatory). P4 medicine was introduced about 15 years ago following the whole human genome sequencing [15], which highlighted that identifying all human genes was not enough to understand the whole human functioning: regulatory networks from the molecular to the environmental levels also need to be accounted for. Importantly, a person is not restricted to his/her biological components and interactions: so-called "human factors" also intervene as drivers or modulators of health and disease. In other words, personalised medicine is not restricted to pharmacogenomics or other biological approaches and should not be opposed to them: from our perspective, it should remain intimately connected with patient-centred care.

The most striking example is how health-to-disease states can be influenced by behaviours such as nutrition, smoking or physical activity. As a result, a continuum of health stages has been proposed recently, going from apparent health (stage A, reinforced by healthy behaviours, *e.g.* regular physical activity) to the appearance of clinical and/or biological signs of disease (stage B, *e.g.* increased body mass or, in the respiratory field, decreased lung function), followed by disease symptoms (stage C, *e.g.* dyspnoea on exercise), and ending with the disease's diagnosis (stage D). This has led to proposal of a continuum of interventions categorised based on their level in healthcare systems: from global or country based (level I) to community based (level II), then at individual and family unit levels (level III), ending with physiological systems-specific interventions (level IV). For now, level IV interventions target mostly subjects belonging to C and D health stages. Progress in P4 medicine should lead to application of level IV approaches to earlier health stages. Again, behaviours will play an important role, since they comprise adherence to healthcare interventions, including not only curative therapies but also preventive policies. In this context, accounting for patients' concerns, life circumstances, perspectives and preferences is necessary [16]. In the end, the challenge is to integrate systems biology and "personomics" or "humanomics", which underlines the need for closely interacting and open-minded multidisciplinary approaches [16, 17].

Importantly, the scope of personalised medicine goes far beyond the clinical effectiveness of care at the individual level: it also has economical and ethical implications. Because of the Maastricht Treaty, all governments in the Eurozone are currently struggling to reduce public debt and maintain annual budget deficit below 3% of the GDP (gross domestic product). One of the major consequences of this forced sparing is a reduction in the healthcare expense. Personalised medicine can certainly help in building such a strategy without compromising the health status of the population. Better targeting of efficient treatments to the right patients means not only that new and costly treatments should be reserved for the patients that substantially benefit from these treatments, but also that indication of previous blockbusters might be reconsidered.

Asthma as an illustration of progress towards personalised medicine

As illustrated in the article in this issue of the *ERR* by Chung [1], asthma is certainly a shining example of a chronic disease for which the concept of phenotype has progressed the most over the last 20 years. This

is partly due to the emergence of the technique of induced sputum, which has enabled the investigation of airway inflammation in large cohorts of patients with asthma. It has become apparent that asthma, which is defined by the combination of chronic, or sometimes recurrent, respiratory symptoms associated with variable airflow limitation, actually exhibits several types of airway inflammation. In particular it has been proposed that asthma may be divided into several phenotypes based on the type of granulocytes infiltrating the airways. It has become popular to distinguish eosinophilic from neutrophilic and paucigranulocytic asthma. It soon appeared that this cellular classification was supported by different molecular pathways. Eosinophilic asthma shows molecular upregulation of so-called T-helper cell type 2 (Th2) pathways, while upregulation of local innate immunity was found to be prominent in neutrophilic asthma [18]. The U-BIOPRED study, which used a sophisticated unbiased statistical approach and in-depth molecular and gene analysis of sputum from cohorts of moderate to severe asthma patients, has confirmed the heterogeneity of molecular pathways in different clinical and physiological phenotypes of asthma [19].

However, dealing with asthma phenotypes is only interesting when it can help predict disease evolution and choose or adjust treatment. So far it is without any doubt in severe eosinophilic asthma that personalised medicine has been the most successful. In this regard, phenotyping based on high blood eosinophilic count has proved to be essential to predict good clinical response to anti-interleukin-5 (>300–500 eosinophils·μL^{-1}) and anti-IgE (>260 eosinophils·μL^{-1}), in asthmatics uncontrolled by moderate to high doses of inhaled corticosteroids (ICS) combined with long-acting β-agonists [20]. Therefore, the best biomarker to use biologics in severe T2 asthma is rather simple (blood cell count) and somewhat contrasts with the great deal of sophisticated research that has been needed to establish the role of IgE and interleukin-5 in severe asthma and to characterise T2 asthma. Outside T2 asthma, high sputum neutrophil count in severe asthmatics has been suggested to predict good biologic response to macrolides in a small pilot study [5]; however, a recent large prospective trial primarily looking at exacerbations and quality of life did not find significant differences in the efficacy of azithromycin on exacerbations between patients with *versus* without higher sputum eosinophils [21]. One interesting finding from the U-BIOPRED study is the identification by transcriptomics of a cluster with heavy airway neutrophilic inflammation, proteasome activation and tumour necrosis factor (TNF)-α expression, a cluster named TAC2 (transcriptome-associated cluster 2). This observation could reopen the way for anti-TNF-α treatment in severe asthma, a field which was closed based on the lack of convincing effect of golimumab (a monoclonal TNF-α-blocking antibody) on a cohort of severe asthmatics who were however not selected on the basis of their airway inflammatory profile [20]. Knowing that at least 50% of severe asthmatics are eosinophilic asthmatics [18] and that sputum cells from eosinophilic asthmatics produce less TNF-α than those of their noneosinophilic counterparts [22], it is conceivable that the effect of anti-TNF-α treatment would have been better if the study had selected noneosinophilic and neutrophilic asthmatics in particular. Clearly the selection process of patients for biologics must include biomarkers of the pathway supposed to be targeted by the drug.

As appropriately pointed out by Chung [1], personalised medicine in asthma should not be restricted to the severe spectrum of the disease and it is really time to also apply the principle to patients with mild to moderate disease. In this respect, without wishing to obscure the major therapeutic advance brought by ICS in asthma [23], there is compelling evidence showing that noneosinophilic asthmatics, defined as those having <2–3% eosinophils in their sputum cell count, respond poorly to ICS [2]. Yet guidelines still recommend starting with ICS in all asthmatics with persistent symptoms, irrespective of their inflammatory status, with the potential to upgrade ICS in uncontrolled but unresponsive asthmatics, thereby transforming otherwise mild to moderate asthmatics into "fake" severe asthmatics. An impediment to applying personalised medicine for ICS usage in routine practice is the difficulty in performing induced sputum. Therefore, great efforts have been made to validate biomarkers that can ascertain the presence of eosinophils in the airways [24]. Demarche *et al.* [25] have recently shown that combining exhaled nitric oxide fraction with blood eosinophil counts and total serum IgE could strongly predict or rule out a sputum eosinophil count ⩾3% in around 60% of a large asthmatic population, leaving however 40% of patients with uncertain eosinophilic status. We therefore urgently need large prospective long-term trials to clarify whether ICS are useful or not in noneosinophilic asthma. If the answer were to be that ICS are useless (or even detrimental), this should lead to a revision of guidelines that could potentially bring cost savings by sparing unnecessary prescription. As aforementioned, personalised medicine is not only about stepping up treatment with costly drugs in difficult disease but might also be sparing long-term treatment with inefficient drugs in patients with mild to moderate disease.

Upcoming articles from the personalised respiratory medicine series in the *ERR*

As illustrated here for asthma, all fields of respiratory medicine are concerned by the vast concept of personalised medicine, for multiple reasons owing more to systems biology or to humanomics, depending

on the considered condition. Thus, choices had to be made regarding the diseases or groups of diseases that needed to be addressed in this series. In addition to this first article on asthma [1], articles are planned for this series on the topics of personalised medicine in COPD, bronchiectasis including cystic fibrosis, lung cancer [26], interstitial lung disease, pulmonary vascular disorders, sleep disorders [27] and pulmonary rehabilitation. An additional article will develop the concept and reality of personalised medicine in the respiratory field. At the end of this series, readers should be convinced that this approach to medicine holds huge promises, some of which have already been made realities.

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