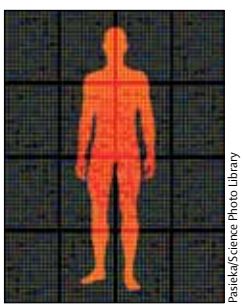
14tlrm0291_Chung
THELANCETRM-D-14-00291R1
S2213-2600(14)70188-2
Embargo:

Targeted omics and systems medicine: personalising care



Pasieka/Science Photo Library

Lancet Respir Med 2014

Published Online
September 17, 2014
http://dx.doi.org/10.1016/
S2213-2600(14)70188-2

A key problem in the management of respiratory diseases is that subsets of patients do not respond to available treatments. Ideally, clinicians should have access to diagnostic markers to personalise drugs for patients with respiratory diseases before starting treatment. Although such markers do not exist in clinical settings,[1] some markers for personalised medicine could reach the clinic in the near future. For example, in asthma, biomarkers such as airway eosinophilia, high exhaled nitric oxide,[2] and transcriptional signatures from bronchial brushings might potentially stratify patients for available and novel biological drugs.[3] However, high-throughput (omics technologies) studies of patients with seasonal allergic rhinitis show the complexity of identification of biomarkers for treatment response.[4] Thousands of genes change expression in nasal fluids, nasal fluid cells, nasal mucosa, and allergen-challenged blood T cells in patients with seasonal allergic rhinitis compared with controls.[4] The involvement of different cell types and external triggers suggests that similar numbers of genes might change in expression in airways diseases such as asthma and chronic obstructive pulmonary disease (COPD). This complexity indicates that single biomarkers might not suffice to stratify accurately patients for personalised medicine.[5] Instead, a change of scale to omics-based diagnostics might be needed. Diagnostic kits that measure transcriptional signatures are now used to stratify patients with breast cancer.[6] But will this technique be achievable in the respiratory clinic? Achievement of this goal can be broken into three parts—one, measurement and validation of human genes, gene products, and metabolites on a genome-wide scale; two, extraction of parts of the genome-wide data with potential diagnostic value, ideally based on functional understanding or so-called targeted omics; and third, such biomarkers being clinically useful at a reasonable cost.

Omics technologies allow analyses of most types of potentially relevant molecules, such as genes, transcripts, or proteins on a genome-wide scale. These have been reviewed recently,[7] leading to stringent criteria for the clinical use and validation of omics. The potential of targeted omics has already been shown in breast cancer. However, the selection of potential biomarkers for targeted omics is a formidable challenge because of the large number of genes, gene products, and metabolites identified. Systems medicine is an emerging discipline that aims to find novel diagnostic markers and therapeutic targets by combining omics with bioinformatics, as well as functional and clinical studies.[8] One important principle for how to understand and prioritise potential biomarkers is to map genes or gene products on the corresponding proteins in protein-interaction networks. The most relevant genes or gene products tend to co-localise and form highly interconnected modules in such networks. Such modules can be further analysed to detect pathways and individual genes that might represent diagnostic or therapeutic candidates.[5] Investigators showed translational feasibility of module-based analysis in a study of seasonal allergic rhinitis.[9] The study spanned from a genome-wide analysis of gene expression to high-throughput knockdowns of candidate genes, and diagnostic and therapeutic studies in an animal model of allergy and samples from patients. An important limitation was that it was based on only mRNA and protein expression. Studies of allergic rhinitis and asthma have shown the importance of other genomic layers, such as genetic variants, DNA methylation, and non-coding RNAs.[10,11] These layers only partially correlate, and given the complexity of respiratory diseases, combinations of targeted omics analyses from different layers might be needed for personalisation.

To bring such analyses to the clinic, many challenges would need to be addressed—first, clinical research is needed to determine and validate what targeted omics analyses are needed for diagnosis. Recent studies of asthma and seasonal allergic rhinitis support the feasibility of targeted transcriptomics to stratify patients for treatment response.[12] However, larger studies that include other omics analyses are needed. Second, laboratory technology for targeted omics must be developed in clinical settings. An initial solution could be that commercial providers of omics-based diagnostics do the analyses, as in the case of breast cancer. Third, software is needed for diagnostic classification based on the omics data. In the simplest case, patients could be stratified into high-risk and low-risk groups, again as in breast cancer. However, user-friendly software that can potentially be customised to allow clinicians to make diagnostic classifications in any disease based on

functional understanding of underlying mechanisms has already been used in a study of seasonal allergic rhinitis.

Such software can also include routine clinical data in the classification.[13] Fourth, clinical implementation would also need solutions for large-scale training of health professionals. Such problems are currently addressed by a multidisciplinary consortium initiated by the European Commission called Coordinating Action Systems Medicine across Europe. Fifth, analysis of the cost-effectiveness of targeted omics for personalised medicine should be initiated. Ineffective drugs in the USA alone cost about US$350 billion every year.[8] A recent study indicated that targeted omics in breast cancer could be cost-effective at a treatment threshold of £20 000.[6] This threshold is close to the costs of biological drugs such as anti-IgE used for treating severe asthma, which can exceed £12 000–15 000 per patient per year. Such costs are a substantial challenge to modern health care. Thus, in respiratory diseases, clinical implementation of targeted omics could be valuable to stratify patients—eg, patients with asthma for treatment with biological drugs. Finally, a dedicated effort in that direction would need multidisciplinary collaborations that include health-care professionals and academic leaders, patient representatives, experts in genomics and bioinformatics, and participants from pharmaceutical and biotechnological industries. Preliminary results from projects funded by the Innovative Medicines Initiative and European Union, such as U-BIOPRED[14] and MULTIMOD,[12] provides support that these collaborations could potentially result in clinical implementation of treatment stratification with biological drugs in asthma in specialised centres within 5 years. This roll-out could pave the way for similar projects in other respiratory diseases, as well as for less expensive drugs. Eventually, this technique could lead to a more general implementation, including in primary care. Such a development would be more likely if some forms of targeted omics are less complex than those suggested above. In support, a recent study showed that analysis of only ten lipids in peripheral blood could predict Alzheimer's disease with a high degree of accuracy.[15] It is also of note that the costs of omics are rapidly decreasing. For example, the sequencing of one human genome cost $100 million in 2001, now it costs only $1000.

Increased understanding of the mechanisms by which patients do or do not respond to treatments could lead to the development of new drugs for non-responders. If the above problems can be resolved, then it is likely that multiple novel therapeutic options will be used to treat respiratory diseases and that diagnostics will personalise those options in the foreseeable future.

For **Coordinating Action Systems Medicine across Europe** see https://www.casym.eu

*Joint senior authors

*Huan Zhang, Mika Gustafsson, Colm Nestor, *Kian Fan Chung, *Mikael Benson*

Centre for Individualised Medicine, Department of Pediatrics, Faculty of Medicine, Linköping University, Linköping, Sweden (HZ, MG, CN, MB); Experimental Studies, National Heart and Lung Institute, Imperial College London and NIHR Respiratory Biomedical Research Unit at the Royal Brompton NHS Foundation Trust and Imperial College London, London, UK (KFC); and Allergy Centre (MB) and Sweden Children's Clinic (MB), Linköping University Hospital, Linköping, Sweden

f.chung@imperial.ac.uk or mikael.benson@liu.se

MB is a co-leader of the European-Union-funded Coordinating Action Systems Medicine (CASyM) and MULTIMOD projects to implement systems medicine in clinical research and practice towards personalised medicine. HZ, MG, and CN have received funding from CASyM. KFC is a co-leader of the Innovative Medicines Initiative (IMI)-funded U-BIOPRED project, a public-private partnership, for an integrated systems biology approach to severe asthma.

1 Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43:** 343–73.

2 Chung KF. New treatments for severe treatment-resistant asthma: targeting the right patient. *Lancet Respir Med* 2013; **1:** 639–52.

3 Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; **368:** 2455–66.

4 Nestor CE, Barrenäs F, Wang H, et al. DNA methylation changes separate allergic patients from healthy controls and may reflect altered CD4+ T-cell population structure. *PLoS Genet* 2014; **10:** e1004059.

5 Barabási A-L, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011; **12:** 56–68.

6 Ward S, Scope A, Rafia R, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2013; **17:** 1–302.

7 McShane LM, Cavenagh MM, Lively TG, et al. Criteria for the use of omics-based predictors in clinical trials. *Nature* 2013; **502:** 317–20.

8 Clermont G, Auffray C, Moreau Y, et al. Bridging the gap between systems biology and medicine. *Genome Med* 2009; **1:** 88.

9 Bruhn S, Fang Y, Barrenäs F, et al. A generally applicable translational strategy identifies *S100A4* as a candidate gene in allergy. *Sci Transl Med* 2014; **6:** 218ra4–a4.

10 Zhang H, Nestor CE, Zhao S, et al. Profiling of human CD4+ T-cell subsets identifies the TH2-specific noncoding RNA *GATA3-AS1*. *J Allergy Clin Immunol* 2013; **132:** 1005–08.

11 Kabesch M. Epigenetics in asthma and allergy. *Curr Opin Allergy Clin Immunol* 2014; **14:** 62–68.

12 Gustafsson M, Edstrom M, Gawel D, et al. Integrated genomic and prospective clinical studies show the importance of modular pleiotropy for disease susceptibility, diagnosis and treatment. *Genome Med* 2014; **6:** 17.

13 Wang H, Gottfries J, Barrenäs F, Benson M. Identification of novel biomarkers in seasonal allergic rhinitis by combining proteomic, multivariate and pathway analysis. *PLoS One* 2011; **6:** e23563.

14 Auffray C, Adcock IM, Chung KF, Djukanovic R, Pison C, Sterk PJ. An integrative systems biology approach to understanding pulmonary diseases. *Chest* 2010; **137:** 1410–16.

15 Mapstone M, Cheema AK, Fiandaca MS, et al. Plasma phospholipids identify antecedent memory impairment in older adults. *Nat Med* 2014; **20:** 415–18.