

Stratified Medicine in 2015 – Leeds Christmas Lecture

Professor Sir Munir Pirmohamed, NHS Chair of Pharmacogenetics, Professor of Medicine, Liverpool School of Medicine, and Director of the Wolfson Centre for Personalised Medicine, gave a Christmas lecture at the Faculty of Medicine and Health, University of Leeds, on stratified and precision medicine.

Stratified Medicine in 2015 – challenges and opportunities

Wednesday 9th December 2015, the Leeds Medical School Lecture Theatre, Level 7, Worsley Building at 5:00-6:00pm .

Here a few notes from attending this very instructive lecture:

From the **Academy of Medical Sciences**:

'Stratified medicine' is the grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques.

Stratified medicine leads to precision medicine (PM), here discussed with a focus on medicines and genomic profiles (pharmacogenomics – PGx).

After decades of discovery, inherited variations have been identified in approximately 20 genes that affect about 80 medications and are actionable in the clinic. [...]. Current efforts that focus on the processes required to appropriately act on pharmacogenomic variability in the clinic are moving away from discovery and towards implementation of an evidenced-based strategy for improving the use of medications, thereby providing a cornerstone for precision medicine.

RELLING, M. V. & EVANS, W. E. 2015. **Pharmacogenomics in the clinic**. *Nature*, 526, 343-350.

Challenges: The evidence

Among the challenges to PGx are research related challenges – what is the evidence (for drug approval, for recommendations in the clinic) and how to gather the evidence: there may be very small numbers of patients with the genetic profile of interest; there are new ways of gathering the evidence, rather than a trial – e.g. modelling; there are novel trial designs (e.g. umbrella trials, basket studies, adaptive trials); lack of skills among reviewers of applications for funding for these innovative designs.

See for example:

BIANKIN, A. V., PIANTADOSI, S. & HOLLINGSWORTH, S. J. 2015. **Patient-centric trials for therapeutic development in precision oncology**. *Nature*, 526, 361-370. 

Trials may uncover incidental findings – with ethical challenges. See for example:

AYUSO, C., MILLAN, J. M. & DAL-RE, R. 2015. **Management and return of incidental genomic findings in clinical trials**. *Pharmacogenomics J*, 15, 1-5.

Challenges: Costs and Funding

Most PGx research is in oncology; the high cost of medicines makes research in this area cost-effective. But there is a role for PGx for other much cheaper drugs – such as warfarin (the challenge – who will pay for research in these cheaper drugs).

Challenges: The data and the technology

Stratified Medicines needs ‘**deep patient phenotyping**’ in EHR. Big Data for each patient.

Challenges: companion diagnostics

...scientific, financial and regulatory barriers impede the development and adoption of companion diagnostics

MEADOWS, N. A., MORRISON, A., BRINDLEY, D. A., SCHUH, A. & BARKER, R. W. 2015. **An evaluation of regulatory and commercial barriers to stratified medicine development and adoption**. *Pharmacogenomics J*, 15, 6-12.

Opportunities: precise dosing

PM is not just the right drug, but the **right exposure** to the drug.

...there is chaos in warfarin dosing in primary care!

PGx for anticoagulation therapy can provide algorithms for precise dosing –

- Warfarin is the most commonly used oral anticoagulant for thrombotic disorders.
- Genotype-guided dosing of warfarin may have clinical utility.
- New oral anticoagulants have benefits, as well as drawbacks.
- Methods are needed for stratification between the new and established anticoagulants.

There have recently been significant advances in the field of oral anticoagulation, but these have also led to many controversies. Warfarin is still the commonest drug used for clotting disorders but its use is complicated owing to wide inter-individual variability in dose requirement and its narrow therapeutic index. Warfarin dose requirement can be influenced by both genetic and environmental factors. Two recent randomized controlled trials (RCTs) came to different conclusion regarding the utility of genotype-guided dosing; we critically explore the reasons for the differences. The new generation of oral anticoagulants have been demonstrated to be as efficacious as warfarin, but further work is needed to evaluate their safety in real clinical settings.

PIRMOHAMED, M., KAMALI, F., DALY, A. K. & WADELIUS, M. **Oral anticoagulation: a critique of recent advances and controversies.** Trends in Pharmacological Sciences, 36, 153-163.

Unexpected consequences

The most interesting part of the lecture for me: the case of the introduction of PGx decision support in HK. Alternative drugs were prescribed, following CDS guidance, but negative patients outcomes emerged out of the use of the alternative drug. Unfortunately I missed the details of this case and this is all I have in my notes.

December 19th, 2015 | [Medicines](#), [Personalised medicine](#), [Research](#) | [0 Comments](#)

