7.4 Stratified medicine and pharmacogenomics

See Background Paper 7.4 (BP7_4Stratified.pdf)

Stratified medicine is a rapidly developing field that is likely to have an important impact on clinical practice in the coming decades. Personalized medicine has been defined as ‘a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention’. However the term ‘stratified medicine’ is more accurate than the still popular term ‘personalized medicine’. The term ‘stratified medicine’ reflects the realistic effects of medicines at population level, while the term ‘personalized medicine’ reflects the possibly overambitious promise of individualized unique drug targeting and development. The population approach aligns with the public health approach of this cross-cutting chapter and with the overall aim of the Priority Medicines Report.

Figure 7.4.1: The concept of stratified medicine.

Historically, human disease has been treated on a ‘one-size-fits-all’ basis. One medicine should suit all patients, and the choice of a medicine has been guided by evidence-based information, professional guidelines and a ‘trial-and-error’ approach. Without applying the concept of stratified medicine, a particular treatment is targeted to the whole patient group, without being able to predict the treatment response in patients. When a patient does not respond adequately to a prescribed medicine or shows substantial adverse drug reactions, the dosage can be adjusted or the medicine may be replaced by another medicine. The availability of genomic and non-genomic biomarkers and other characteristics may enable physicians to increasingly target
treatment specifically to sub-populations of patients who are more likely to benefit from a particular treatment or less likely to develop adverse drug reactions (see Figure 7.4.1). In this way, the benefit-risk profile of the medicine can be assessed per population stratum, and unnecessary (in case of non-response) or harmful (in case of toxic effects) use of medicines may be prevented. In this sense the other cross-cutting themes in this chapter (children, women and the elderly) are also examples of stratified medicine.

Pharmacogenomics study the influence of genomic variation on treatment response. Two successful pharmacogenomics examples include HLA-B*5701 genotyping and the risk of hypersensitivity to the antiretroviral treatment abacavir and HER2 testing in breast tumour biopsies and clinical response to the antineoplastic agent trastuzumab.

The first example illustrates the importance of stratified medicine for the safer use of existing medicines. Abacavir was approved in the late 1990s by regulatory authorities. It was well tolerated in the majority of patients, but caused a life-threatening hypersensitivity reaction in a small group of patients (5% to 8%). From 2001 onwards, there was increasing evidence for the relation between a genetic variation in the HLA-B*5701 gene and the risk of hypersensitivity to abacavir. Sales of abacavir-containing medicines subsequently declined. A shift took place after the development of a genetic test that was shown to be valid across patient populations (different regions and genetic ancestry) and have a very high negative predictive value, and the development of a skin patch test to immunologically confirm the genetic test. HLA-B*5701 testing was rapidly adopted by HIV practitioners and the test was incorporated in clinical guidelines. Genetic testing of HLA-B*5701 kept abacavir on the market because it is now possible to target the drug to a patient population with almost no risk for developing the severe hypersensitivity reaction.

The second example is related to medicines effectiveness. Trastuzumab is used to block human epidermal growth factor receptor 2 (HER2). This protein is encoded by the ERBB2 gene and the gene is overexpressed in approximately 15% to 30% of patients with breast cancer. Only patients with high levels of HER2 are likely to respond to trastuzumab. Regulatory agencies have approved trastuzumab for the treatment of HER2 overexpressing breast cancer (and in other HER2-overexpressing carcinoma) and HER2 testing has been imbedded in clinical guidelines. The classic example of trastuzumab and HER2 highlights the potential of stratified medicine in the targeted use of expensive medicines, thus ensuring that (public) expenditures are not wasted on ineffective pharmaceutical care.

Despite these and similar examples, clinical implementation of stratified medicine has been limited. However, it holds promise for better and safer use of existing medicines in all settings, as well as for the identification of new medicines, drug targets and the development of innovative diagnostic tools. Science is shifting from monogenic (assessing one single gene, e.g. many orphan diseases) to polygenic (assessing multiple genes at the same time, e.g. many chronic diseases such as diabetes mellitus, cancer and depression) diseases and approaches. Pharmacogenomics is only one of the many
–omics technologies that have emerged. All of these technologies (e.g. transcriptomics, proteomics and metabolomics) hold promise, to a greater or lesser extent, to improve the prediction of the incidence and course of disease, phenotyping of disease and prediction of drug response. This chapter focuses mainly on the role of pharmacogenomics in stratified medicine as this particular field has been most successfully translated into clinical practice in comparison to the other -omics fields. Although technologies develop rapidly and collaborations emerge, there remain major gaps related to the development, translation and implementation of this new knowledge.

Currently, stratified medicine mainly focuses on the development of new medicines, drug targets and diagnostics. This is also reflected in the guidelines of the different regulatory agencies on the use of pharmacogenetic methodologies in assessing drug pharmacokinetics, which primarily concentrate on medicines that are currently under development. In addition, pharmaceutical companies may be less interested in assessing stratified medicine post-approval, due to pricing inflexibility and possible loss of market share. Several genomics initiatives are emerging in low-resource settings, but stratified medicine approaches are still rare and should be encouraged. In countries where resources are limited, stratified medicine could be very successful in ensuring that limited health care resources are used as efficiently as possible. In addition, efforts should be made to stimulate the use of stratified medicine in vulnerable groups. Research should be funded to allow biomarker-based prescribing during pregnancy and childhood.

It should be acknowledged that a large part of variability in treatment response cannot be explained by genomic variations. Patient characteristics (such as age, gender, severity of disease), gene-environment interactions, patient compliance, and also epigenomic regulation and protein modification may also play an important role and should not be underestimated. Therefore, the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters should be stimulated.

Several scientific limitations currently hamper efforts to exploit the full potential of stratified medicine. For example, the lack of standardization of response outcomes, including adverse drug reactions complicates the comparability of studies. Successful replication is generally low, and there is as yet no global or European pharmacogenomic database with a thorough inventory of available knowledge and biological specimens. A European catalogue of pharmacogenomic datasets and a harmonization programme should therefore be established. To validate pharmacogenomic findings, there is a need for replication studies in different cohorts and for harmonization of outcome measures. An electronic platform that will enable data sharing is therefore essential. Finally, a funded EU research network could function as a partner for the European Union in identifying opportunities in research, strengthening collaborations within Europe, contributing to standardization processes, and organizing educational and scientific conferences.
Ideally, medicines and diagnostics should be developed simultaneously and stratification of patients should be taken into account during the drug development process, market authorization and reimbursement procedures. However, in the EU introducing stratification prior to registration has been complicated due to the different regulatory frameworks for diagnostics and therapeutics. The EC recently submitted a proposal for a new regulation to replace the current Directive 98/79/EC on in vitro medical devices, which includes clinical genetic tests. However, other regulatory guidelines and reimbursement procedures might need to be adapted. There is a need to align regulatory processes between different regulatory agencies, but also on the evidence required to assess clinical utility. A randomized clinical trial might not always be feasible because of ethical reasons, lack of resources or small populations. Clear guidelines are needed to assess when a randomized clinical trial is necessary in order to test a stratified medicine approach. Furthermore, an adaptive trial design, which enables the researcher to implement prior knowledge to optimize the remainder of the trial might be a cheaper and faster alternative to test observational findings. Assessment of the added clinical value of a test or a marker calls for the development of a framework in which clinical utility and cost-effectiveness are assessed and compared to current clinical practice.

There is a need for a well-organized technology infrastructure, professional training and an internationally aligned ethical, legal and regulatory framework. At present, only a low proportion of health care providers have received training in stratified medicine and pharmacogenomics. They should be better prepared for clinical decision making by having adequate knowledge about the medicines for which patients should be tested and how test outcomes should be interpreted and acted upon. Patients and the public need to be informed about stratified medicine in order to understand the possibilities and limitations of this approach. The new genomic era brings with it new ethical and social issues such as genomic data sharing, consent, ownership and liability. These issues should be further studied in order to guide the implementation of stratified medicine in global health.

In summary, this chapter recommends investments in the following areas to further strengthen research in and knowledge of stratified medicine and pharmacogenomics:

- Stimulate pharmacogenomic approaches to existing drugs, with a particular emphasis on the use of stratified medicine approaches for vulnerable groups.
- Stimulate the use of multi-dimensional analyses in which biomarkers generated from different technologies are combined with clinical parameters.
- Establish a European research network and establish a European catalogue of pharmacogenomic datasets with a harmonization programme.
- Adapt regulatory guidelines and pricing and reimbursement procedures. For pricing and reimbursement, develop a framework in which clinical utility and the cost-effectiveness of new approaches are assessed and compared to current clinical practice (clinical added value) and, where needed, refined.
- Develop and evaluate harmonized training and education programmes, not only for researchers, but also for clinical specialists, pharmacists and the public.
Investigate the ethical, legal, economic and social implications of stratified medicine.

References


