

Executive Summary

Pharmacogenetics offers new ways of understanding how drugs work and how this affects both the safety and efficacy of drugs in individuals. The potential opportunities are considerable. In drug development, pharmacogenetics shows great potential for improving the efficiency of the drug discovery process, particularly for identifying and validating new drug targets. It is expected to improve the translation of early-stage projects into medicines that meet public health needs. In clinical care, pharmacogenetics may enable doctors to prescribe more effective interventions and improve their use of evidence-based medicine. It can help identify those individuals most likely to benefit from a therapy, thereby optimising treatment strategies for both common and complex disorders. It may also enable preventive interventions.

This book examines the present use and future challenges facing pharmacogenetics at different stages in the health innovation cycle, including its uptake in the clinic. The report draws on debates held under the auspices of the OECD's Working Party on Biotechnology (WPB) which were initiated at an OECD workshop entitled "An International Perspective on Pharmacogenetics: the Intersections between Innovation, Regulation and Health Delivery", held in Rome, Italy, in 2005. The report reviews the evidence to date as to the impact of pharmacogenetics on decision making and efficiency in pharmaceutical R&D and in clinical care. Finally, it identifies policies governments need to put in place in order to facilitate the uptake of this approach to R&D and clinical care and to maximise its benefits.

The value of pharmacogenetics is heavily dependent on the identification of useful "biomarkers". Biomarkers are indicators that mark the presence of a potential gene-drug interaction or that measure response to therapeutic activity. Genetic biomarkers – which identify genetic variations in patient populations – are emerging as one of the most effective means of improving the efficiency of the drug discovery process. They can be used in clinical trials to stratify patients who respond to a new potential medicine appropriately, adversely or not at all. In clinical practice, genetic biomarkers can be developed into diagnostic tests to measure the potential efficacy or toxicity of a particular therapy. For medicines that eventually are brought to market for a genotype-specific population, these tests may be necessary to define which patients will benefit from the treatment and which will not. Pharmacogenetics is already being employed in a small number of cases to

optimise treatment strategies for common and complex disorders of public health relevance.

The use of pharmacogenetics is progressing rapidly. Its impacts are evident in three areas: *i*) basic research; *ii*) drug discovery and development; and *iii*) management of health care. But while research in pharmacogenetics is proceeding apace, by early 2009 only a few pharmacogenetics-based diagnostics were on the market. In fact, six years after the initial sequencing of the human genome, fewer than a dozen new pharmacogenetic products are commercially available. A number of scientific, regulatory and economic challenges need to be overcome if pharmacogenetics is to be taken up more widely by health-care systems.

The report concludes that governments have a role to play in creating an “enabling” environment for the uptake of pharmacogenetics. Six key messages aim to guide elaboration of public policy and co-ordinated international action.

1. Building infrastructures for large-scale association studies is necessary to identify and validate the biomarkers that underpin the use of pharmacogenetics.

Much work must be done to identify a biomarker, carry out studies to verify its association with relevant health outcomes or therapy-related effects, and validate its use as a diagnostic tool for clinical practice. Identifying and ultimately validating biomarkers requires integrating genetic and genomic data with phenotypic data. This can be both difficult and expensive because it requires accessing and integrating different types of data at multi-scale levels (from the molecular to the clinical) and in different formats.

Moreover, association studies usually involve clinical studies with a large number of patients, often from a variety of population groups. To carry out large-scale association studies, appropriate frameworks, systems and methodologies must be established.

Governments may be able to facilitate this process by helping to build the required research infrastructure. They might:

- encourage the formation of multidisciplinary international networks that can facilitate access to the necessary data sources and increase the efficiency of pharmacogenetic research.
- encourage agreements relating to the availability of raw data and the sharing of data.

- support the creation and utilisation of large-scale human biobanks and genetic research databases (HBGRDs).
- consider the formation of public-private partnerships to carry out association studies.
- foster the development of systems to manage knowledge and intellectual property so as to support open innovation platforms for pharmacogenetics.

2. Applying pharmacogenetics to established medicines will yield public health benefits but will require public as well as private support and collaboration in order to run the necessary prospective studies.

Frequently, adverse drug reactions are observed only once medicines have been on the market for some time and many thousands of patients have been exposed. The incentives for pharmaceutical or devices companies to apply pharmacogenetics to established medicines (particularly those that are off-patent) are weak, even though substantial benefits would accrue to patients and society as a whole in the form of reduced adverse drug reactions.

Applying pharmacogenetics to existing and common drugs requires major prospective studies to identify relevant genetic markers for patient stratification. Such prospective studies would allow regulatory authorities to determine whether it is necessary to modify the labelling of specific established medicines in order to improve clinical practice and patient health. However, as the cost of such trials may be very high, the application of pharmacogenetics to established medicines becomes an issue of public policy.

3. Pharmacogenetics has the potential to transform the drug development process, but incentives to adopt this technology may need to be strengthened.

Pharmacogenetics can be used to reduce the size, duration and cost of clinical trials. However, the adoption of pharmacogenetics will pose economic and organisational challenges for industry as it may entail substantial reforms both of the drug discovery process and of the business models for pharmaceutical and diagnostic firms. For the pharmaceutical industry, to the extent that pharmacogenetics reduces the size of the population for any given drug, it puts pressure on the blockbuster business model. For the devices and diagnostic industries, uncertainties include how to capture value from assays, and from challenges relating to co-developing and co-marketing assays and therapeutics.

Drug and device development has occurred independently until now. In pharmacogenetics, drugs and diagnostics could be co-developed and co-marketed: the need to co-ordinate and synchronise development may encourage pharmaceutical companies to partner with device companies or seek to develop their own in-house expertise.

The economic incentives to invest in the development of biomarkers are influenced by signals that flow from the broader health-care system. Within current pricing and reimbursement mechanisms, the lack of recognition of the value of testing represents a disincentive for the devices industry to develop new, genetics-based assays. Policies can help make the uptake of pharmacogenetics more attractive. Clear signals from governmental and regulatory bodies about how this technology will be priced and reimbursed, recognition of the added value of diagnostic tests for the health system as a whole, and mechanisms for capturing and protecting the intellectual property inherent in diagnostic tests might improve the incentives for investment.

4. Co-ordination and dialogue with regulatory authorities are critical to strengthening investments in the development of pharmacogenetic products by industry.

Regulation of the combined use (co-development) of a therapeutic with a diagnostic is evolving across OECD countries. There is concern that pharmacogenetics will make an already complex approval process for pharmaceuticals even more complicated. Clarity about how regulation will deal with the co-development issue is therefore necessary, in terms both of the data requirements for approval and of how reimbursement systems will react to, and value, the co-marketing of co-developed products.

When evaluating new pharmacogenetic drugs and associated tests, decision makers will want to balance benefits and needs and find evidence of value for money. The use of pharmacogenetic testing for the prescription of new drugs may make them more expensive. However, the costs of inappropriate prescribing or the results of the adverse reactions that will be prevented/reduced may more than offset the added costs of the pharmacogenetic tests, resulting in increased clinical value to the patient and prescriber.

To reduce uncertainties, innovators, regulators and end users may need to engage in dialogue to clarify how the approval process and subsequent reimbursement/coverage decisions might proceed for pharmacogenetic products. OECD countries may, for example, want to consider the options of conditional market approvals, through the use of post-market pharmacovigilance, and risk-sharing mechanisms for pharmacogenetic products. The development of common methodologies or approaches to policies, coupled

with efforts to close existing gaps in regulatory and technology assessment practices could also help improve incentives to innovate across the OECD.

5. The health and economic impacts of pharmacogenetics need to be better understood if the health-care system is to adopt this new technology.

As with any health-care innovation, introducing pharmacogenetic testing into health care will pose a number of challenges for health-care systems. Studies on the health economics of pharmacogenetics and on the cost-benefit ratio of pharmacogenetic testing and products could provide the evidence base necessary for their uptake. Presently there is a lack of data demonstrating the clinical utility and cost-effectiveness of many pharmacogenetic therapeutics and diagnostics, and no agreement over whose responsibility it is to develop such data.

Although existing health technology assessment models for evaluating new genetic tests and medicines are generally regarded as acceptable, this may not be the case in future if the numbers of pharmacogenetic products increases significantly. There is likely to be a need to develop new models and methodologies for the assessment of diagnostics and medicines which may eventually influence the pricing and reimbursement of such products.

6. Health-care providers will need to be educated about pharmacogenetic assays and treatment options, and they must have easy access to clinically useful information at the point of care in order to interpret these assays.

In health-care decision making, pharmacogenetics is contributing to better clinical care. It is improving our understanding of disease heterogeneity, reducing the uncertainties of responses associated with specific treatments, changing the risk-benefit ratio for treatments, and enhancing the ability to prescribe accurate dosage for medicines.

However, pharmacogenetic assays rarely provide simple, clear-cut results: the information generated is probabilistic rather than absolute. Before pharmacogenetic testing becomes a routine part of care, there needs to be more evidence to support the clinical utility of pharmacogenetic testing, information on pharmacogenetics and other relevant information need to be available at the point of care, and health-care providers need to be educated and trained to access and interpret these new sources of health data.