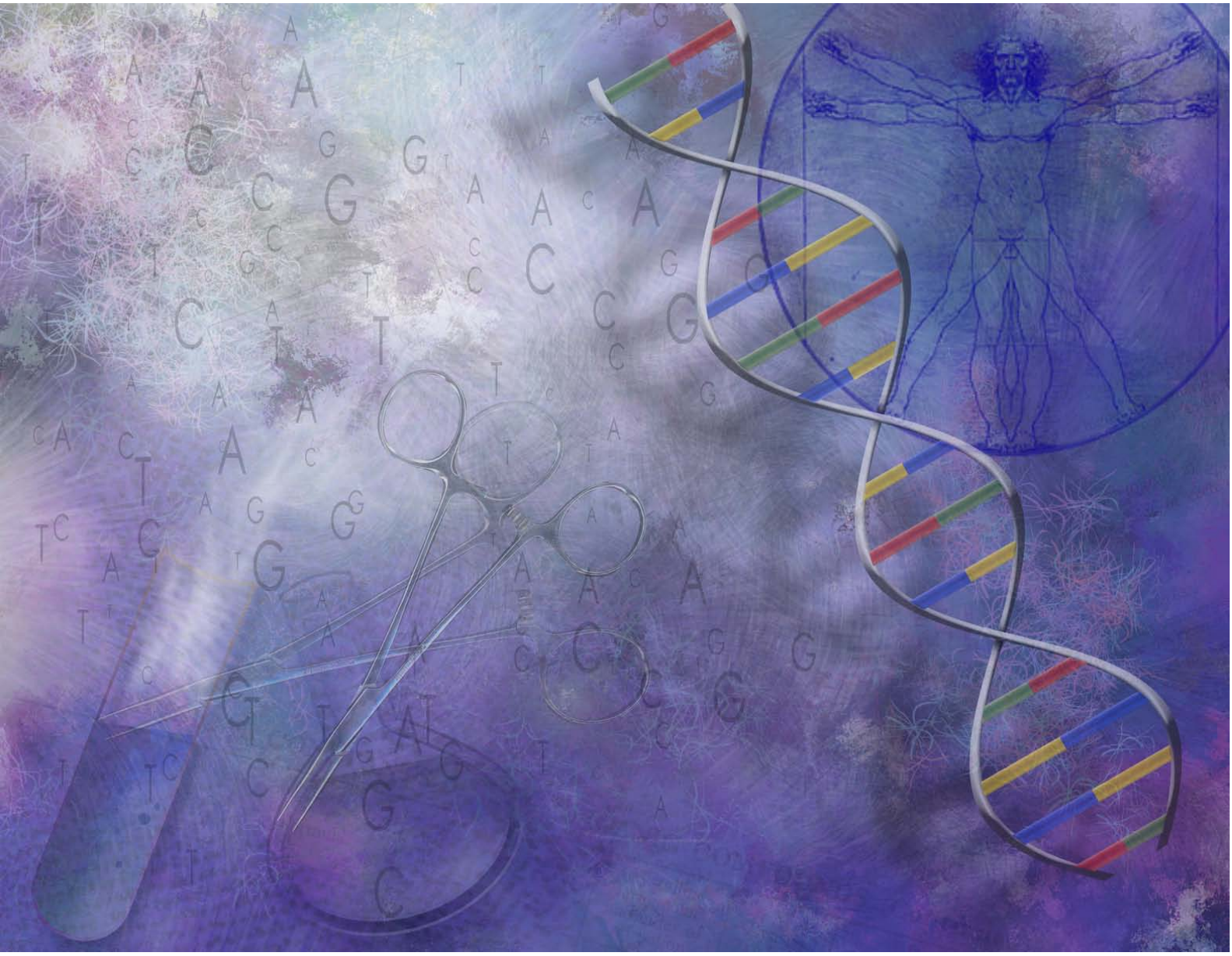
Policy Issues for the Development and Use of Biomarkers in Health



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Foreword

Application of biomarkers in the field of human health is improving our understanding of disease, and will provide new knowledge of disease mechanisms and processes providing a means for improved health management through the earlier diagnosis of disease and the delivery of more efficacious and safer therapies. This report examines the current economic, regulatory, and health care context in which biomarkers are being developed and identifies the barriers which may slow or block the uptake and diffusion of biomarker-based technologies in the clinical setting.

The report presents several policy options which could foster biomarker research, discovery, development, commercialisation and uptake in clinics. A number of scientific, economic, regulatory and governance challenges need to be addressed if biomarker applications are to be incorporated into clinical practice.

The report draws on discussions that took place at a workshop entitled, "Policy Issues for the Development and Use of Biomarkers in Health", held in Hinxton, United Kingdom in 2008 (under the auspices of the OECD Working Party on Biotechnology), as well as analytical work before and after: "Evidence Base and Knowledge Sharing", R. Zimmern and C. Wright, PHG Foundation (UK); "Formulation of the Basic Grounds for Health Industry Using Biomaker Database", J. Takahashi and N. Yumoto, AIST Tsukuba (Japan); "Clinical Evaluation of Biomarkers", R. Zimmern and C. Wright, PHG Foundation (UK); "Regulation and Policy", C. George, R. Zimmern and C. Wright, PHG Foundation (UK); "Industry Strategies and Biomarkers Business Models", A. A. Aslani, Araxes Associates (France); "Integration, Sharing and Access to Biomedical Data to Facilitate Decision Making in the Discovery and Validation of Biomarkers", D. Polverari, E. Molle and A. Malpertuy, Atragène (France); "Biomarkers: Impact on Biomedical Research and Health Care: Case Reports", W. Hempel, G. Sziraczky, L. Swalm and L. Takacs, Biosystem International (France) and Armus Corporation (United States); and "Emerging Biomarker-Based Companies and their Business Models", P. Coriat and M.-C. Le Goff, AEC Partners (France).

We are very grateful to all the consultants and experts who graciously contributed their time and knowledge to this project. We also would like to thank the delegates of the OECD Working Party on Biotechnology and the Task Force on Biomedicine and Health Innovation for their contributions and guidance.

The report was developed by Rachael Ritchie and Marie-Ange Baucher. Benedicte Callan managed the project and Stella Horsin provided critical administrative support.

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Executive summary

Biomarkers allow news ways of understanding disease processes and the ways in which medicines work to counteract disease. Within the practice of evidence-based medicine this knowledge can be used to improve disease diagnosis, to improve the safety and efficacy of existing medicines and to develop new medicines and targeted therapies. Novel molecular biomarkers have the potential to transform much of the current health care model, shifting the focus from a reactive 'one-size-fits-all' system to one that is more proactive and precise. In this new, proactive approach, disease or disease susceptibility may be diagnosed earlier, and disease may be controlled or possibly prevented before it starts; and when disease is detected, new biomarker-based diagnostics may be used to develop treatment strategies which are tailored to the characteristics of individual patients. Over the long term, the use of biomarkers may improve patient welfare by delivering better health outcomes.

Across OECD countries, and in every region in the world, health care costs are rising, and are projected to continue rising, as the population increases, people live longer and the prevalence of chronic and infectious diseases increases. Novel biomarkers, with their discovery and development accelerated following a decade of investment in genomics research, offer significant potential to improve health outcomes and reduce total health care costs in the long term. Given the high interest in and pace of research in biomarkers, and their critical role in delivering evidence-based medicine, OECD members and non-members are interested in how to translate these recent scientific advances into clinical practice.

This report describes the scientific, industrial, regulatory, and health care management system context in which biomarkers are being developed. It identifies some of the barriers which may impede biomarker research, discovery, development, commercialisation and, ultimately, uptake in clinics. It also focuses on the use of biomarkers in the health care system, as diagnostics and in medical tests, and explores the use of biomarkers for the development of improved medicines. It does not address the role of biomarkers upstream, as tools for basic research.

As governments develop the framework necessary to deliver on the promise of biomarkers and personalised medicine, they may wish to consider six key messages that emerge from this report:

1. Long-term investments in the development of sustainable initiatives and infrastructures, including public-private partnerships, are necessary to facilitate biomarker discovery and development.
2. There is a need for multi-stakeholder discussions about how to develop and populate an evidence base for molecular biomarker medical test evaluations. Regulatory agencies, health care payers, test manufacturers, physicians, and patients require evidence regarding the safety, efficacy, utility, and cost-effectiveness of novel tests to inform their decisions. However, generating, collecting, analysing and protecting such data and information, and making it available to different users is not straightforward.
3. Regulatory processes and reimbursement procedures must be adapted to the specificities of novel biomarker-based clinical tests, and harmonised across jurisdictions.
4. Business models are being developed within the private sector to support research, development and commercialisation of biomarker-based medical tests. However, in some instances market conditions may not be conducive to development of some biomarker-based products, and situations may arise in which policy intervention may be required to enable the development of biomarkers with a clear clinical value and proven clinical validity in the health care setting.
5. Integration of bioinformatics and genomic tools and other technologies, such as nanotechnology, will be needed in order to create new tools for the development of new biomarker-based diagnostics. Infrastructure, networks and other mechanisms that foster technology convergence should be supported and strengthened.

6. Networks and other mechanisms that facilitate communication of knowledge about biomarkers, advances in biomarker research, or evidence of their clinical utility should be supported and strengthened. Knowledge networks to improve communication between the medical community and patients are particularly important.

The following chapters provide an analysis of the factors which may affect the rate of biomarker discovery, development, commercialisation and clinical uptake in OECD member and non-member countries, and identify some areas where policy could make a difference. The ways in which policy may help accelerate the use of biomarkers in evidence-based medicine are summarised here:

Stimulating and supporting the organisation of large scale infrastructures – gathering the knowledge and data both from the research and industry communities – to foster the discovery and validation of novel molecular biomarkers.

- Stimulating the development of infrastructures capable of developing an evidence base for biomarker evaluation, particularly in determining if there is clinical evidence of their use.
- Monitoring the evolution of the industry help to ensure the benefits of biomarker-based products and services achieve clinical application.
- Adapting regulatory and reimbursement procedures so as to encourage the translation and penetration of biomarkers with proven clinical utility and health care value in the clinical setting.
- Enabling technology convergence by encouraging the integration of nanotechnology, bioinformatics and genomics and biomarker information in development of new diagnostics to encourage uptake and diffusion of biomarkers in the health care setting.
- Promoting education and communication within the health care system to familiarise health care providers and patients with the benefits of bio-marker based tests, and to facilitate uptake of these tests within the health care system.

Chapter 1

Biomarkers: An overview of the opportunities and challenges

Introduction

Biomarkers are objectively measurable indicators of biological states. Within the field of health care, biomarkers can improve our understanding of disease and can provide information on the presence of disease, or susceptibility to disease, in an individual, or predict or monitor patient response to therapeutic interventions. The use of novel molecular biomarkers within the practice of evidence-based medicine may improve diagnosis or treatment of disease, improving health outcomes and reducing the social and economic impact of disease.

Discovery of biomarkers is expanding at an unprecedented rate, as previous investments in genomic science are enabling improved understanding of disease mechanisms and individual patient responses to therapy. Such biomarkers are allowing early identification of disease, improved diagnoses, and safer and more efficacious treatments leading to better patient outcomes and efficient and effective public expenditure on health. Promising results from initial uses of biomarkers demonstrate that under the right conditions, their integration into evidence-based medicine may transform our approach to chronic disease and other serious diseases, changing the way disease is diagnosed and treated. Securing the right conditions for the uptake of biomarkers within health systems remains challenging, but achievable. Those countries which succeed in adopting biomarkers within their health systems stand to gain substantial improvements in the health of their citizens, and in the economic performance of their health care systems and supporting industries.

Governments of most OECD countries pay the majority of health care costs incurred by citizens. In 2010, health care spending rose faster than economic growth in all OECD countries (OECD, 2010).[1] Much of that health care spending was devoted to diseases where breakthroughs in diagnosis and treatment are elusive. Non-communicable, chronic diseases such as diabetes, cardiovascular diseases, chronic respiratory problems and cancer, are serious challenges to the health of aging populations, and to health care budgets.

Such diseases are no longer only the bane of high income countries. The incidence of chronic disease is also rising at an alarming rate in developing countries, many of which are also facing significant challenges to their health care systems from malnutrition and infectious disease. In 2005, the World Health Organisation estimated that 60% of global mortality was due to chronic disease and that 80% of this mortality occurred in low and middle income countries (WHO, 2005). The prevalence of chronic disease globally is expected to increase 17% in the next decade and it will constitute a leading cause of death in many developing countries (WHO, 2005). Biomarkers may provide a solution to the challenge posed by these and other diseases. Although originating and emerging from science, technology and development conducted in high income countries, clinical application of biomarkers may offer a revolution in global health equity, with benefits for disease management in developed and developing countries.

Reaping the benefits of biomarkers

Novel molecular biomarkers have the potential to transform the current health care model, shifting from a reactive 'one-size-fits-all' approach to one which is more proactive, and increasingly 'personalised'. In this new system, disease may be diagnosed, controlled or possibly prevented before it starts; and when disease is detected, treatment may be guided by information contained within a patient's genetic profile.

In what has been termed personalised medicine, practitioners will be able to supplement their current approach to treatment with new molecular information and biomarker-based tests to optimise treatment strategies for patients. This promising new approach to the practice of medicine, also called precision medicine or stratified medicine, seeks tailor treatments to the bio-characteristics of individual sub-groups of patients, to reduce side effects and to increase the efficacy of individual treatments. Integration of biomarker-based technologies into the health care system in this way offers many potential benefits:

- Improved diagnostics could lead to earlier detection and intervention of disease, potentially improving health outcomes, and minimizing the direct and indirect costs of disease and treatment.
- Increased safety and efficacy of therapies via the application of pharmacogenetics[2], may reduce adverse side effects and improve the efficacy of treatments.
- Increased numbers of safe effective treatments could become available as drug development costs and timelines are reduced through biomarker application in the area of pharmacogenetics.

In addition to delivering many positive outcomes for patients and health care systems, these changes may have positive economic consequences.

- Regulators and third-party payers may face less risk of adopting cost-ineffective drugs; less variation in patient response and fewer adverse effects will result in savings in the health care system as a whole.
- Developers of therapeutics may reduce financial risks and improve productivity: the cost of developing drugs is expected to decrease and biomarkers are expected to speed drug delivery and the safety and efficacy of those drugs.

While the promise of biomarkers is clear, significant challenges remain to be overcome to achieve widespread adoption of biomarkers within the practice of personalised medicine. The existing regulatory framework is not well adapted to the often complex biomarker-based diagnostic tests which are at the foundation of personalised medicine. There is a clear need for development of appropriate evidentiary standards and processes to facilitate evaluation and regulation of new diagnostics tools and to support appropriate integration and use of these tools within the health care system. Similarly the current reimbursement system in many countries is not well adapted to reflect the value of these tests in the health care setting, potentially detracting from development of new biomarker-based tools and limiting their adoption in the clinic. There is a need to develop clear and transparent regulatory and reimbursement procedures.

There are also industrial challenges to development and adoption of biomarker-based technologies. Industry needs to consider new business models to adapt to increasingly segmented markets arising from a health care system in which targeted therapies and early intervention replace the one-size-fits-all approach to health care. New business models may also need to include plans for diversification of existing firms or support for development of a new industry providing or developing new molecular diagnostics.

Despite the complexity of the landscape, biomarker discovery, development and application are progressing. Rapid progress is evident in the research and drug discovery sectors and in the diffusion of existing biomarkers within the clinical setting. This report will discuss the advances to date, and the challenges to broader uptake and diffusion of biomarkers within the health care system. The report also explores some of the socio-economic barriers to realising the promise of biomarkers, and examines some actions governments can take to remove those barriers.

The genomics revolution

Biomarkers have been in use for centuries and play a crucial role in the rise of evidence-based medicine: that is, the practice of medicine that seeks to integrate clinical expertise with the best available research evidence and patient values in clinical decision-making. The application of biomarkers to drug development and diagnostics has recently accelerated, thanks to advances in genomics research and associated technologies. Genomics research has improved our understanding of disease, allowing elucidation of the basis of individual differences in response to disease and drugs, and enabling tailoring of associated diagnostics, treatment and monitoring to the characteristics of individual patients. We now know that our individual susceptibility to disease, manifestation of disease, response to pathogens, drugs and environmental stimulus can be linked to various biomarkers. Understanding the molecular nature of disease has allowed development of many molecular biomarkers which can be used to study, monitor and evaluate these processes (see Box 1).

Box 1. Biomarker definitions

A biomarker is, according to the US National Institutes of Health, "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Biomarkers make take the form of cellular characteristics, metabolites (*e.g.* sugars, lipids and hormones), molecular variations, or physical features (*e.g.*, clinical symptoms) and are assessed accordingly, via measurement, annotation, documents, and images.

Increasingly, the discovery of novel biomarkers is closely associated with the advances in molecular biology techniques that can be accessed through analysis of DNA, RNA or proteins.

We can discriminate four main types of molecular biomarkers:

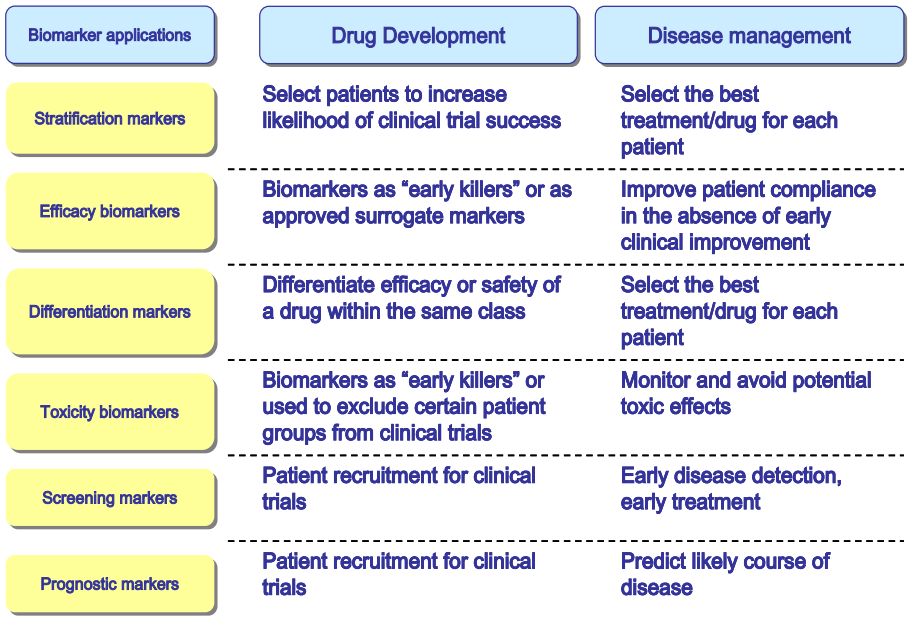
- Genomic biomarkers: based on the analysis of DNA (deoxyribonucleic acid) profiles, especially the analysis of SNPs (single nucleotide polymorphisms), i.e. identification of punctual variations in genomic DNA.
- Transcriptomic biomarkers: based on the analysis of RNA expression profiles.
- Proteomic biomarkers: based on the analysis of the protein profiles.
- Metabolomic biomarkers: based on the analysis of metabolites (metabolites are the intermediates and products of metabolism).

With the completion of the sequencing of the human genome in 2001, and other large scale international initiatives such as the International HapMap Project, we have gained new insights into common patterns of human DNA sequence variation. Concurrent advances in technologies such as DNA microarrays, mass spectrometry, functional genomic screens, antibody-based proteomics, and next-generation sequencing along with advances in computational bioinformatics, have facilitated identification of associations between genome differences among individuals and observations of individual variation in susceptibility to disease, and response to drugs. This suite of genomic technologies offers the key to understanding complex diseases such as cancer, and disorders such as dementia, leading to the development of information-rich diagnostics based on novel molecular biomarkers or biomarker panels. These diagnostics might not simply diagnose the disease but may provide information on the disease phase, its prognosis and can help identify treatment options. Through pharmacogenetics, novel molecular biomarkers arising from this work may help speed development and validation of new drugs and targeted therapies.

Application of biomarkers in evidence-based, personalised medicine

Personalised medicine evolves from traditional western medicine that defines broad categories of illness and attempts to 'type' the patient and to administer a treatment according to a standardised scale (Hempel, *et al.* 2008). The recent rapid advances in 'omics'[3] technologies are now making the goals of personalised medicine increasingly realisable. Indeed, advances in molecular biology and cell biology have provided us with an understanding of disease mechanisms at a molecular level, which can now be translated into diagnostic, prognostic, and therapeutic tools. Biomarkers in clinical use today are considered critical elements in evidence-based medicine, supported by a clear link to clinical evidence, and considered safe and effective by the medical community. Biomarkers can be utilised in either a standalone diagnostic test or as companion diagnostics, tests directly associated with the prescription of a therapy or treatment regime (also referred to as pharmacodiagnostic tests). Biomarkers are also increasingly used in a number of pharmacogenetic applications: from drug development, to characterisation of disease conditions and progression pathways, to characterisation of the effects of environmental exposures. According to their role in disease management and drug development, several types of biomarkers can be identified, from stratification markers used to select subpopulations of patients, to 'prognostic' markers which predict the likely course of disease (see Figure 1).

Figure 1. Biomarker types categorised by application and use in drug development and disease management



Source: Discussion paper, OECD Workshop on "Policy Issues for the Development and Use of Biomarkers in Health" 2008.

Diagnostics

Novel molecular biomarkers may be developed into simple diagnostic tests assaying one or two biomarkers, or more complex tests considering multiple biomarkers. Based on an improved understanding of disease states at the molecular level, such tests can provide faster, more accurate or information-rich diagnostics for many diseases. Biomarker-based tests can confirm a clinical diagnosis and may provide other information concerning prognosis, and best treatment options. These diagnostic tests may enable identification of disease (or disease susceptibility) in the early stages, before it can be diagnosed by other means, providing opportunities for prevention of disease progression or better disease management leading to better patient outcomes and a reduction in the direct and indirect costs of disease.

For example, mutations in the BRCA1 and BRCA2 tumour suppressor gene are associated with an increased risk of breast and ovarian cancer. Screening of these BRCA1 and BRCA2 biomarkers may be used to identify individuals at risk of breast or ovarian cancer, providing an opportunity for these individuals to manage their disease risk. In this particular case, the risk may be managed through proactive surveillance for signs of disease allowing early intervention, by chemoprevention to reduce the risk of developing cancer, prophylactic surgery of the at-risk tissue, or by reduction of other risk factors such as obesity and inactivity.

While the BCRA1/2 assay can be a very useful diagnostic tool for diagnosis for the majority of hereditary breast and ovarian tumours, mutations in these genes account for a very small number of all breast and ovarian cancers. Clearly many other genes and environmental or lifestyle factors contribute to these complex diseases. As our understanding of complex diseases grows, additional biomarkers are being identified and developed into new and improved diagnostic tools which analyse multiple biomarkers simultaneously to establish a complex molecular profile of a disease within a patient as well as information on the response of patients to given treatments. Such tests which combine the values of multiple variables to yield a single patient-specific result are called *in vitro diagnostic multivariate index assays* (IVDMIAs)[4].

The recently developed Oncotype DX (see Box 2) assay is a molecular diagnostic test which uses multiple biomarkers to provide information-rich diagnostics for breast cancer. By analysing a panel of 21 genes, Oncotype DX provides information on the type of breast cancer, information regarding likelihood of recurrence after ten years, and information on the utility of chemotherapy as a treatment option. Developed in the early stages of the 'omics' revolution, the Oncotype DX assay is a good example of an IVDMIA. Diagnostic tests incorporating multiple biomarkers are likely to be the key to diagnosis and management of complex or chronic diseases such as cancer, diabetes and high-blood

pressure. The complex tests may provide greater insights into the disease process or susceptibility to disease, and better opportunities for prevention or management of disease in advance of its progression to the chronic or acute phases which are more distressing for patients and typically more costly to manage.

To date, most of the biomarker-based diagnostics developed have been developed to guide drug delivery. These companion diagnostics may be used to identify patients likely to respond well to certain drugs or treatment options. These diagnostics are often used in conjunction with a specific drug. For example the Trofile™ assay is used to determine the trophism of the human immunodeficiency virus (HIV) and the likelihood a patient will respond well to prescription of Selzentry™.

Pharmacogenetics

Biomarkers facilitate improved understanding of disease processes, and patient variation in disease and response to disease treatments, helping the pharmaceutical and diagnostics industries evolve toward a business model that focuses on safer, more efficacious targeted treatments (OECD, 2009b). While biomarkers are important for the identification of potential targets for drug development and pre- and post-clinical research, their greatest utility may be in clinical trials. One of the major challenges in drug development is to find robust decision making tools to guide the progression of drug candidates through the different stages of clinical trials: a compound that fails in later phase trials represents a considerable financial loss. The use of biomarkers in various phases of drug development has helped identify patients most likely to respond well to a particular drug, improving overall efficacy of the drug, speeding the approval process. For example, in a Phase II clinical trial designed to evaluate myeloma patient response to Velcade, biomarker-based testing identified a 30-gene biomarker panel that predicted responders with 71% accuracy and non-responders with 84% accuracy (Claudio and Stewart, 2005). Moreover, in a Phase III clinical trial designed to evaluate CML (chronic myelogenous leukemia) patient response to Gleevec, biomarker-based testing was able to identify a 31-gene biomarker within the patient population that predicted clinical response with 94% accuracy (McLean, *et al.* 2004).

Box 2. The Oncotype® DX Assay

Oncotype DX, created by Genomic Health, appeared on the market in 2004. Oncotype DX is a validated genomic test which simultaneously analyses a panel of 21 genes within a tumour. These genes function as biomarkers of breast cancer. The statistical analysis of the level of expression of these 21 genes together allows the quantification of the likelihood of disease recurrence in women with early-stage breast cancer and assesses the likely benefit from certain types of chemotherapy. Oncotype DX is the first gene expression test that has been accepted as demonstrating the capacity to predict a patient's benefit from chemotherapy as well as the risk of recurrence.

Oncotype DX draws on a number of studies, performed by Genomic Health, that show its efficacy; this has greatly facilitated its approval by regulatory authorities. Oncotype DX was evaluated in numerous studies involving over 3 300 patients and a cost-effectiveness analysis was also performed. Thus, Genomic Health presented data on the validity of the test, its clinical utility and its cost-effectiveness when applied in clinical practice. Both economic and clinical evaluations were positive. Thanks to this type of evaluation, this complex test is now reimbursed by many health care payers in the United States even at its current list price of USD 3 820 (Lusky, 2008).

Thanks to the accuracy and relevance of the data collected, Oncotype DX was included in the 2007 American Society of Clinical Oncology (ASCO) Clinical Guidelines on the Use of Tumor Markers in Breast Cancer. Oncotype DX has also been included in the National Comprehensive Cancer Network (NCCN) 2008 Breast Cancer Treatment Guidelines.

Genomic Health total revenues increased from USD 0.1 million in 2003 to USD 27 million in 2006. The company's major contributor to the revenues during 2003-06 was the sales of Oncotype DX (Genomic Health, Inc., 2006).

Pharmacogenetic advances in personalised medicine have progressed well beyond the clinical trial stage and have led to development of effective personalised medicine approaches demonstrating the potential of biomarkers to transform medical practice and patient care (see Box 3). Herceptin® is one of the first examples of a personalised medicine arising from pharmacogenetics. It reached the market in 1998 with its companion diagnostic test Herceptest which analyses the expression of the human

epithelial growth factor receptor-2 protein (HER-2/neu). The development of this drug/test couple arose from the discovery that in 25-30% of breast cancers, HER-2 (Human Epidermal growth factor Receptor 2) is over-expressed and the patients who are part of this sub-population are particularly sensitive to the drug Herceptin®. Using biomarker-based testing to predict HER-2 over-expression as a means to stratify breast cancer patients eventually paved the way to a successful new drug application for Herceptin. Herceptin® is the first success story of a personalised medicine with sales of USD 747 million in 2005 (Hamilton, 2006). Since 2009, 37 personalised medicine drugs, treatment, and diagnostics have reached the market (Personalized Medicine Coalition, 2009).

Box 3. Pharmacogenetic tests: Herceptin / HER2 screening and Herceptin in breast cancer

Herceptin and HER2 were instrumental as early examples of predictive biomarkers in breast cancer and highlight the the potential of personalised medicine. Herceptin® is a therapy for women with metastatic breast cancer whose tumours express too much of a protein known as HER2. Approximately one in four women with breast cancer is positive for HER2, a consequence of the individual's genetic make-up. By using HER2 as a genetic biomarker to test all women diagnosed with breast cancer, it is possible to identify and treat those who will benefit from Herceptin®. This targeted use increases the observed effectiveness of Herceptin®. In effect, the percentage of women who will respond to the medicine is greatly enhanced within the targeted group, as compared to the percentage from the total population of women with breast cancer that would benefit. This approach can change the risk-benefit ratio for treatment: as the medicine is prescribed only to women who are likely to benefit, the number of patients who experience side effects (or experience no therapeutic effect) is significantly reduced. Herceptin® is the first success story of a personalised medicine with sales of USD 747 million in 2005. Since 2005, about 37 personalised drugs and their companion tests (also called pharmacogenetic tests) have reached the market.

Sources: Hamilton (2006), Issa (2007), Personalized Medicine Coalition (2009)

Pharmacogenetics can also be used to reduce toxicity or adverse side effects of drugs. It is estimated that many drugs do not work properly for a large proportion of patients. This may be due to the individual genetic make-up of those patients or differences in the way the drug is metabolised in those individuals. Adverse drug reactions are responsible for significant medical costs. In 2008, the US Centers for Disease Control and Prevention found that three drugs (insulin, digoxin and warfarin) were responsible for one in three emergency department visits related to medication among older adults. For warfarin alone, overdoses resulted in 40 000 visits to US emergency rooms at an annual cost of USD 2 billion.

Warfarin is used to reduce the risk of death, heart attack or stroke after a patient has a heart attack. It is also used to treat and prevent venous thrombosis (blood clots) and pulmonary embolism associated with atrial fibrillation or heart valve replacement surgery. Dosing of warfarin is difficult as the effective dose may vary depending on the patient. Pharmacogenetics has shown that the doses on which people are eventually stabilised are related to genetic profiles. Variation in two genes (VKORC1 and CYP2C9) account for 30-50% of individual variation in response to warfarin among patients. As the relationship between these biomarkers and clinical outcomes of warfarin become known, these biomarkers may be used to guide warfarin treatment significantly reducing costs associated with adverse drug reactions (Epstein, 2010).

Within the field of personalised medicine novel molecular biomarkers seem poised to help improve health care, allowing early intervention of disease, reducing the likelihood of adverse drug reactions and improving efficacy of drug treatments.

Towards a new health care paradigm: opportunities and challenges

Across OECD countries health care costs are rising – growing at a rate of ~4% annually over the last decade, now equating to almost 9% of GDP – due in large part to an aging population and the increasing use of expensive technologies such as magnetic resonance imaging (MRI) and computed tomography (CT) scans. Despite this expenditure, health care across the OECD remains in need of improvement. In Norway over 12% of hospitalised patients experience adverse events, 70% of which were preventable and over half of which lead to disability; and in England it is estimated that better primary care could have avoided over 40%, or nearly 1.7 million hospital emergency admissions.[5] Health care costs in the developing world are also rising and governments around the world are challenged with balancing their citizens' expectations of the best possible health care with the government's need to manage costs.[2] In particular, governments are focused on finding alternatives to the rising cost of pharmaceuticals, and the prevention of chronic disease. The use of biomarkers in

diagnostics and pharmacogenetics is changing the way disease is diagnosed and the manner by which it may be treated and may offer a solution to these issues.

The pharmaceutical context

Pharmaceuticals are an essential component in the prevention and management of disease in all OECD countries and have resulted in significant gains in patient care. Many deadly and disabling diseases can be effectively treated with pharmaceuticals, and drugs have contributed significantly to increased longevity of populations in the OECD countries. Over the last ten years however, the drug discovery and development process has become increasingly lengthy and expensive. Highly publicised withdrawals like that of Vioxx have further compounded the problem (Editorial, 2004; Rubin, 2004). The time for drug development, from target identification to clinical application, takes on average 12 years, and costs from USD 350 million to USD 1 billion (Di Masi, *et al.* 2003). Much of the expenditure is linked to poor target identification and validation, and to the failure (attrition) of compounds late in the development process. As industry necessarily focuses its efforts on more difficult disease targets, including those associated with complex diseases such as cancer, diabetes and asthma, costs and attrition seem sure to increase.

The diminishing productivity of the pharmaceutical sector has promoted a re-evaluation of the drug discovery process, with many actors seeking ways to increase the efficiency of the innovation process and to ensure continued emergence of effective new medical products. Incorporation of pharmacogenetics into the drug discovery and development process has the potential to improve its efficiency and reduce the costs of drug development and delivery. Biomarkers may *i)* speed identification of drug targets; *ii)* reduce the costs of attrition of compounds during the drug development process by incorporating biomarkers in the preclinical and clinical trial phases; *iii)* reduce the size, cost and duration of clinical trials; and *iv)* reduce the likelihood of adverse drug reactions.

The clinical context

The clinical application of biomarkers has already made significant contributions to the practice of evidence-based medicine. This is best illustrated by the number of diagnostic and pharmacogenetics-based tests currently available to help further inform clinicians' decision-making process. These tests can *i)* help in diagnosis of latent or subclinical disease; *ii)* help identify responders and non responders to a treatment; *iii)* aid in establishing appropriate dosages for responders; and *iv)* identify the likelihood of adverse drug reactions or toxicity, possibly excluding some patients from treatment.

The potential impact of biomarker-based tests in the clinical setting is substantial, especially when one considers them in the context of chronic diseases. Chronic diseases such as diabetes, cancer, chronic respiratory disorders, and dementia represent a significant and increasing socio-economic burden. For example, dementia affects 35.6 million people worldwide and the direct (medical and social care) and indirect (unpaid care giving by families and friends) costs of dementia are estimated at USD 604 billion annually, accounting for ~1% of the world's GDP. Within an aging and growing population, the number of people with dementia is projected to double by 2030 (65.7 million worldwide) and is estimated to triple by 2050 (115.4 million) (Wimo, 2010).

These chronic diseases have complex etiologies, which are not yet well understood, typically including a combination of genetic and non-genetic (life style and environmental) components. Once established, these diseases often become progressive and in later stages are more difficult and costly to treat. Early detection using biomarkers may provide a means for early intervention prior to disease onset, significantly reducing health care costs and safeguarding patient wellness. For example, there are ~300 million people worldwide living with diabetes, and it is estimated that the number of latent diabetes sufferers and people at risk of diabetes is double that number. Left untreated, diabetes is a chronic, progressive condition, with patients typically developing complications including vascular difficulties, kidney disease, blindness, and neuropathy. People with diabetes have a two- to fourfold increased risk of developing cardiovascular disease, peripheral vascular disease, and stroke, and these complications account for 65% of mortality from diabetes. It is believed that early detection and intervention is the key to primary prevention of the long-term complications of diabetes which are so costly to health care systems. Indeed it is estimated that 80% of diabetes may be prevented. With health care expenditures projected to rise to USD 490 million by 2030, biomarker-enabled early diagnosis could result in very large cost reductions for health care systems.

Challenges to implementation

The uptake and diffusion of biomarkers within a new health care paradigm may be transformative and will change the way disease is identified and managed. However the translation of biomarkers into clinical practice faces several challenges which will need to be addressed before personalised medicine becomes a reality:

1. *The identification of molecular biomarkers of clinical utility*. Genomic and related technologies and tools are generating data faster than it can be analysed and translated for use in the clinical setting. Indeed, the search for novel molecular biomarkers is a highly complex and expensive undertaking, and often beyond the capacity of any one actor. Despite the development and organisation of large-scale infrastructures established to gather and share knowledge to foster biomarker discovery and validation, progress is still slow and not as effective or efficient as it could be. Chapter 2 provides an overview of some existing knowledge sharing infrastructure and identifies ways in which this infrastructures could be strengthened to accelerate biomarker discovery and development.
2. *Proving the clinical validity and utility of biomarker-based tests*. Uptake of biomarker-based tests in the clinical setting will require evidence of the biomarker's clinical validity and utility. This is important not just to help inform physicians' decision-making process within the practice of evidence-based medicine, but also in order to achieve regulatory approval and appropriate reimbursement for the test. However, amassing the data necessary to show clinical validity and utility may be a time consuming and expensive process, which is further complicated by the lack of standards. There are also questions regarding how to share this data among those who need it, how to protect it, and how it should be analysed. Chapter 2 describes the potential of an evidence base to demonstrate the clinical validity and utility of biomarker-based tests.
3. *Poorly suited regulatory and reimbursement systems*. In most OECD countries, regulatory and reimbursement procedures are not well adapted to deal with this new wave of molecular biomarker-based diagnostic tests. Current regulatory systems were developed around simple diagnostic tests and are not well suited to novel biomarker-based diagnostics producing complex data requiring significant analysis and interpretation. Moreover, current reimbursement processes do not necessarily reflect the complexities of the testing, nor its value within the health care system. Poorly adapted regulatory and reimbursement systems can present a barrier to diffusion of these technologies in the clinical setting and may act as a disincentive to further biomarker discovery and development. At present, the procedures for seeking approval and/or reimbursement are still under development. Chapter 3 describes the way in which reimbursement and reimbursement systems are adapting, and need to adapt, to ensure uptake of biomarker-based tests in the clinical setting.
4. *Changing the practice of evidence-based medicine in the clinic*. There can be reluctance in the medical community with regard to uptake or use of novel clinical tests. Physicians need to understand the information provided by the test and know how to integrate it into their decision making process. Patients need to know how they can benefit from novel tests, and to understand the implications of new information the tests can provide. For biomarker-based tests, like other genetic testing, there are a number of privacy issues which need to be addressed. In addition, adoption of tests in the clinical setting will be a reflection of how easily they can be incorporated into the physicians' existing procedures. Chapter 4 looks at how dissemination of knowledge to physicians and patients can facilitate integration of novel molecular biomarker-based tests in clinics. It then considers other factors which may help integration of these tests in the clinical setting.
5. *Lack of appropriate business models*. Successful innovation requires that there be viable business models to advance the innovations into the market place. The same is true for delivery of biomarker-based innovations in the health care setting. Novel molecular biomarkers seem poised to revitalise a relatively flat diagnostic industry, or depending how you look at it, spawn a whole new industry. However there is a pressing need to identify viable business models to encourage development and commercialisation of biomarker-based diagnostic tests. Chapter 5 presents some existing models and some challenges and opportunities to development of new business models for the diagnostic industry. It also looks at the way in which biomarkers are challenging existing business models in the pharmaceutical industry, and the way in which this industry may respond to the challenges and opportunities provided by novel molecular biomarkers.

This report goes into greater depth for each of the above-mentioned challenges to the translation of biomarkers into clinical practice. It presents some of the solutions that have been proposed in different OECD countries and describes the key points that require attention from governments.

Chapter 2

Managing biomarker knowledge: generation and sharing

Translation of a biomarker into a clinically relevant and useful biomarker-based diagnostic test requires generation, analysis and sharing of considerable amounts of data and knowledge. Population studies must be performed to confirm the association of a biomarker with a particular disease state. Proof of this association and other information must be shared with other actors in order to gain regulatory approval for the biomarker-based test and its application in the clinical setting. Generation and analysis of this information is often logistically difficult, time-consuming, expensive, and is typically beyond the resources of any one actor. Further, it does not always achieve the desired result. Several initiatives have attempted to overcome the hurdles associated with generating and sharing the vast amount of data necessary for biomarker development. These initiatives have focussed principally on the precompetitive stage of biomarker development. Yet work remains to be done to address two significant challenges linked to the management of biomarker knowledge that must be addressed in order to ensure the broader delivery of biomarker-based tests and products in the health care system.

The first challenge concerns the difficulty of identifying appropriate biomarkers for specific disease states or biological processes. Genomics projects have provided a vast number of potential biomarkers. The challenge lies in distinguishing within this very large body of data those biomarkers relevant and useful to different clinical applications. Prioritisation and validation of relevant candidate biomarkers typically requires large scale association studies, in turn requiring access to large numbers of appropriate patient samples. Data generating, data sharing and association studies all need appropriate financial support and technical and management infrastructure. A number of major initiatives have been developed by both public and private entities to respond to these needs. The first part of this chapter provides a review of some of the knowledge sharing infrastructures which have been developed. This is followed by a description of ways in which this infrastructure could be augmented to improve generation and sharing of knowledge and accelerate biomarker discovery and development.

The second challenge concerns the creation of infrastructures for the development of what has been called an 'evidence base' for the clinical evaluation of biomarker-based tests and products. Evidence of the clinical validity and clinical utility of novel biomarker-based tests for clinical practice is increasingly seen as a key to development within the field of personalised medicine. Regulatory approval and professional acceptance of biomarker-based tests in evidence-based medical practice require evidence of clinical utility and validity. The challenge lies in understanding which data are required in such an 'evidence base'; how to obtain and share this data; and how to create the necessary and appropriate supports for its analysis. Information security and patients rights are clearly important features in this discussion. These challenges and possible solutions are discussed in the second part of this chapter.

A new wave of networking infrastructures

The discovery of novel molecular biomarkers and the delivery of personalised medicine are becoming priorities in government-supported health programmes. The discovery, development and regulatory approval process of novel biomarker-based tests is complex, time consuming and expensive. For these reasons, biomarker development is increasingly facilitated by the development of infrastructures to enable collaboration and knowledge sharing between a number of actors. Much of this infrastructure has been developed to facilitate large-scale genome association studies which often require resources beyond the reach of any individual partner.

Since 2005/06 a host of public-private initiatives and consortia have been launched in to which governments have invested significant resources. Many groups, initiatives and consortia, combine the efforts of industry, the research community, governments and other actors within the health care system. A number of entirely private initiatives are also emerging (see Box 4). Infrastructure developed to date allows sharing or pooling of patient samples, data, downstream analysis, or pooling clinical trial data.

The diverse memberships of these consortia take many forms, consider different types of data or knowledge, and occupy various points on the continuum from biomarker discovery–development–clinical validation. Biobanks, such as the UK Biobank (see Box 4), the Estonian Gene Bank, and the CartaGene initiative in Quebec seek to create the infrastructure to facilitate large association studies necessary for gene discovery. These initiatives are often government-led and typically provide

researchers access to population samples or data in return for inclusion of the results of their analysis back into the database. These initiatives require considerable ethical oversight to ensure that the data, often collected from volunteers, is appropriately protected and that knowledge generated is appropriately disseminated or developed.

Some initiatives take a targeted approach to biomarker discovery. The Treat 1000 initiative, a collaboration between CollabRx, a San Francisco-based personalised cancer research services firm, and Alacris Pharmaceuticals, is focused on the identification of biomarkers associated with cancer. By creating a database containing genomic sequencing data from 1000 individuals with cancer, it enables researchers to identify biomarkers associated with cancer which can be used for diagnosis and to aid drug development.

Box 4. Collaborative mechanisms, knowledge networks and consortia for biomarkers

Numerous collaborative mechanisms, knowledge networks and consortia have emerged in order to help biomarker discovery and delivery in clinics. Examples include:

- UK Biobank: The UK Biobank is a large long-term study being undertaken in the United Kingdom (UK) that was established in 2007 to investigate the contributions of genetic predisposition and environmental exposure (including lifestyle, medications, diet, etc.) to the development of disease. The study includes 500 000 individuals' ages 40-69 collected over a number of years. Detailed lifestyle, medical history and nutritional habits, and basic vital statistics such as weight, height and blood pressure will be collected for inclusion in the database and in addition to blood and urine samples which will be archived for later study. During the study, all disease events, drug prescriptions and deaths will be integrated into the study from the UK National Health Service. Once established research can apply to use the (anonymised) database, for example comparing a sample of participants who developed a particular disease, such as cancer, heart disease, diabetes or Alzheimer's disease, with a sample of those that did not in an attempt to measure the benefits, risk contribution and interaction of specific genes, lifestyles and medications.
- **The Biomarkers Consortium**: The Biomarkers Consortium is a major public-private biomedical research partnership lead by the Foundation for the National Institutes of Health (FNIH) which aims to facilitate the discovery, development, qualification and regulatory acceptance of the candidate biomarkers. The Consortium has strategically focused on high-impact areas of biomarker development and validation in four areas of research: cancer, inflammation and immunity, metabolic disorders and neurosciences. To date the launched projects aim, for example, to determine the value of FDG-PET imaging in non-Hodgkin's lymphoma to predict tumour response to treatment; to determine the utility of adiponectin as a biomarker of glycaemic efficiency; and determine the value of PET/CT as a predictive marker of tumour response and patient by a prospective validation in non small cell lung cancer in Phase II study. To give an example of the funds allocated for these projects, in the case of the lung cancer and lymphoma project, to date USD 6.46 million has been raised from the private sector (Amgen, AstraZeneca, BMS, Genentech, GSK, J&J, Merck, Pfizer, Wyeth) to support the project; USD 3.75 million came from the NIH.
- **CollabRx**: CollabRx is a commerce NetPortofolio company (privately held) which builds "virtual biotechs to help slash the time, cost, and risk of developing new therapies", and provides tools to patient groups and virtual biotechs to accelerate the development of treatments for diseases that don't attract major pharmaceutical company research funding. This web-based collaborative research platform gives different types of participants in a research ecosystem (*e.g.* genomic and proteomic profiling, combinatorial drug screening, mouse) access to all the data, knowledge and resources they need to function as a team. Scientific advisory board members can use the system to prioritise research opportunities in a funder's portfolio. Project managers can co-ordinate and track all activities and foundations can monitor progress and allocate resources in real time. A specific service in this initiative has been dedicated to personalised medicine delivery for cancer patients. Working on behalf of a limited set of cancer patients and their physicians, CollabRx is developing CollabRx ONE. This project aims to identify specific mechanisms of carcinogenesis based on a patient's tumour samples and to provide hypotheses for compounds that target those mechanisms.
- **Treat 1000**: Treat 1000 is a joint project of CollabRx and Alacris Pharmaceuticals to add full-genome sequencing to the CollabRx ONE offering. By sequencing 1 000 genomes of cancer sufferers, Treat 1000 aims to provide potentially life-saving information about individual cancers, but also to create a compendium of cancer genome information that will inform future research and treatment.
- **ENCePP E-register of Studies**: The E-Register is a joint initiative of the European Medicines Agency (EMA) and the European network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) seeks to increase the available information on the utilisation, safety and effectiveness of medicines used in clinical practice. The electronic register is a publicly accessible resource for the consultation of pharmacoepidemiological and pharmacovigilance studies conducted by academic centres and other research organisations. Participation in the database is voluntary, but those submitting studies may apply for special status of 'ÉNCePP Studies' This database provides a means to monitor medicines once they have been approved for use in the European Union and facilitates post-authorisation studies.

Other initiatives such as The Biomarker Consortium (TBC), launched by the National Institutes of Health (NIH) in the United States, aim to facilitate the discovery, development, qualification and regulatory acceptance of candidate biomarkers. The consortium is a major public-private biomedical research partnership that includes government agencies, industry, patient advocacy and other non-profit private sector organisations. The Consortium has strategically focused on support for pre-competitive research in high-impact areas of biomarker development and validation: cancer, inflammation and immunity, metabolic disorders and neurosciences. The Consortium has launched several projects in these areas, and helps concentrate and stimulate efforts and acts as a "hub" for biomarker data and knowledge exchange. It aims to provide robust analyses to regulators to help them during the biomarker approval process, and it also acts as a "grant provider" stimulating the submission of concept protocols by researchers. The consortium promotes "open" pre-competitive research and development for novel biomarkers by making TBC project results publicly available.

Knowledge sharing infrastructure for accelerated biomarker development and clinical application

Networking infrastructures developed to date take many forms and perform many functions to pool, generate, share or analyse data across the complete biomarker discovery-development-validation continuum (see OECD, 2011). These collaborative initiatives go far beyond what any one stakeholder could do alone and have proven utility in biomarker discovery and development. However, most initiatives operate relatively independently of the others, according to initiative-specific protocols and standards. Increased collaboration between consortia may, under the right conditions, further accelerate biomarker development and should be considered by relevant stakeholders. Harmonisation of guidelines for large scale association studies and development of appropriate intellectual property treatment strategies need to be considered and will likely underpin the success of greater collaborative efforts[6].

Indeed, as biomarker-based tests move into the clinical setting, the importance of considering and including data from additional initiatives and countries is becoming clear. The majority of consortia and networks developed so far have centred on development of biomarkers in, and for, Caucasian populations. This has not been by design, but rather it has been a function of the location of researchers leading these efforts and the source of financing for these consortia. This inadvertent bias, however, is likely to restrict the clinical application of these biomarkers in some populations, particularly those in developing countries. In order to ensure wide-spread and equitable clinical application of biomarkers it will be necessary to investigate biomarkers in the context of other populations and to expand existing infrastructure to include researchers and populations from underrepresented countries.

Fortunately there is good reason to believe that more biomarker discovery and development will expand beyond Western populations. China now accounts for 30% of the worlds R&D expenditures and in 2010 Brazil, China, Indian and South Africa will produce half as many PhD's as the 34 countries in the OECD. Diffusion of money and research within existing and new initiatives will no doubt stimulate further such work. In addition, a number of countries and non-profit groups like the Pharmacogenetics for Every Nation Initiative (PGENI) have initiated population based studies which can be further shared within these infrastructures.

The development of an evidence base for evaluation of biomarkers

Proving the relevance and amassing the evidence necessary for translating a molecular biomarker into a clinical tool can be difficult. One needs to prove, among other things, the clinical validity and clinical utility (see Box 5) of a biomarker if it is to be used in clinical practice. The challenge, as previously mentioned, is to determine, first, which data are required to perform these studies, second, how to obtain, share and pool these data together, and finally, how to create the necessary and adequate support to analyse them.

Box 5. Biomarker clinical evaluation: Definitions

The ACCE Model Project (an initiative of the CDC's Office of Public Health Genomics, OPHG) developed the first publicly-available analytical process for evaluating scientific data on emerging genetic tests. The ACCE Model Process identified four main criteria for evaluating a genetic test:

- **Clinical validity** describes the accuracy with which a test predicts a particular clinical outcome; when a test is used diagnostically, clinical validity measures the association of the test with the disorder; when used predictively it measures the probability that a positive test will result in the appearance of the disorder within a stated time period.
- **Clinical utility** is the likelihood that using the test result will lead to an improved health outcome; to evaluate this, the important information is about the effectiveness of the interventions available for people who test positive and the consequences for people with false positive or false negative results.
- **Analytical validity,** a component of clinical validity, describes how accurately and reliably the test measures the genotype of interest.
- **Ethical, legal and social implications (ELSI)** refer to other implications which may arise in the context of using the test and cross cut across the clinical validity and clinical utility criteria.

Source: Centers for Disease Control and Prevention (n.d.)

The need for an evidence base

Among OECD member countries there is currently significant variation in the scrutiny of biomarker-based tests both before and after their entry into the market. Unlike the extensive requirements for clinical trials of new therapeutics, the standards for novel biomarker-based tests often have minimal evidence of clinical performance or lack a robust evaluation process. Yet due to the variety and complexity of biomarker-based tests, evaluation of those tests may be significantly more complex than drug evaluation. This lack of standard practices discourages innovation on the part of biomarker developers. It may also discourage uptake in clinical practice or lead to inappropriate adoption of biomarkers by primary care providers. Consumers may also be negatively affected, as direct-to-consumer tests may represent unnecessary health costs.

As a growing number of biomarkers of increasing complexity are discovered, all actors need a robust basis for effective evaluation, development and implementation of biomarker-based clinical tests. Adequately robust evidence for an acceptable biomarker-based test should demonstrate: *i)* the utility of the test in clinical decision making; *ii)* that there is a benefit to using the test, and that it improves health care outcomes; *iii)* the potential cost of delivering the test; *iv)* the economic benefits that will be gained; *v)* where these benefits will be achieved within the health care organisation, and beyond; and *vi)* what operational changes are required in order to deliver these benefits. Much of this information may be collected as part of a country's Health Technology Assessment (HTA) programme as it would for any new health technology. Collecting data on the clinical utility and clinical validity of biomarkers will, however, require generation and assessment of additional data.

The data required for such analysis might include data similar to clinical trial data collected for drugs and would constitute an evidence base. For molecular biomarkers, the evidence base may also contain genetic information, disease and other biological or clinical data, for one or more populations and appropriate control populations. It may also contain information on natural genetic mutation, null alleles and other genetic variations. Analysis may include calculations to prove the association with disease, and then other calculations to describe the associated relative risk. Much of this data may be generated in early stages of biomarker research and development. Yet there remain many questions as to what data should be included, how to obtain and later share this data, and how to create the necessary supports and audits of the data and its analysis.

Consistency and transparency in the way biomarkers are assessed and validated would assist health service professionals, providers and patients in their decision making, and would also provide much needed clarity for commercial organisations and academic researchers who wish to ensure that their innovations are developed efficiently and used effectively. Generating an authoritative evidence base of all biomarkers used in medical testing, with clear and transparent standards would significantly

improve the situation. There are a number of steps required to ensure adequate evaluation: *i)* identification or creation of a set of standards to which biomarker evaluation and performance should adhere; *ii)* development of protocols for generating and analysing data for evaluation; and *iii)* generation and assessment of relevant biomarker data. It will be important to engage relevant stakeholder in developing a minimum set of standards for information associated with a given biomarker.

The ENCePP E-Register of Studies, a joint initiative of the European Medicines Agency (EMA) and the European network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) may provide a useful model of the sort of evidence base required for collection and analysis of data on biomarker utility (see Box 5). These databases include information on the utilisation, safety and effectiveness of medicines used in clinical practice. The databases include positive and negative study results and enable promotion of the exchange of information within the scientific community and prevent unnecessary duplication of research.

The CDC's (Centers for Disease Control and Prevention) ACCE Model Process discussed above (see Box 5) may also provide a useful model. The ACCE Model Process is composed of 44 targeting questions that address the disorder, testing and clinical scenarios as well as analytic and clinical validity, clinical utility and associated ethical, legal and social issues.

The clinical and regulatory context for development of an evidence-base

Application of biomarker-based tests in the clinical setting will require among other things generation of data demonstrating clinical utility and clinical validity of each test. Regulators need to know that the test is relevant and 'fit for purpose', and that the data used to make decisions is sound. Similarly, physicians and primary care providers need to know the clinical value and utility of the test to patients in the practice of evidence based medicine. It will be important to develop consistent and transparent processes by which this data can be developed and shared among relevant stakeholders.

Beyond the technical or scientific aspects of development of an evidence base, a number of governance issues remain to be addressed. It is currently unclear whose responsibility it should be to set up, resource and promote knowledge sharing and access to biomarker data, clearly numerous stakeholders will need to be involved, and ultimately governments may be required to oversee and co-ordinate the process. Although there are several national and international bodies involved in test evaluation, their coverage is not based on a consistent set of evidence and each has its own specific remit and perspective, making it difficult to make evidence-based decisions or comparisons between tests. None of these international bodies have the resources to carry out a thorough clinical evaluation of all biomarkers and the way in which national agencies would take responsibility for this is not clear.

The most appropriate infrastructure for the development of an evidence base has yet to be elucidated, but we may be able to benefit from the infrastructures developed to accelerate biomarker discovery and development discussed in the first part of the chapter. Much of the data generated to validate a candidate biomarker (*e.g.* large scale population studies) is similar to that likely required in an evidence base. Thus, once developed, communication of 'evidence base' standards to upstream initiatives may help streamline assembly of requisite information by relevant stakeholders. Since generating these data is generally a slow and expensive process, public-private partnerships between early stage researcher, industry, regulators, and clinical scientists may facilitate this process. A pathway is therefore needed to bring industry and the public sector together, to discuss these issues and to determine the roles and responsibilities of the various stakeholders: those that generate data, those that analyse data, those that rely on data for clinical or reimbursement decisions.

The importance of an evidence-based to Health Technology Assessments

With health care costs rising in OECD member and non-member countries alike, health care systems are challenged to make better decisions about the uptake and diffusion of health technologies within the constraints of fiscal policy. Many countries are using Health Technology Assessments (HTA) to help such decisions. While the process used by different countries varies (OECD, 2005) most countries try to consider the clinical utility of the test, impact on the patient, and cost (direct and indirect) of the test to determine when and how it might be incorporated into the health care system. The uptake of biomarker technologies, in particular biomarker-based tests, represents a particular challenge in this regard. Biomarker-based tests, like many other novel technologies, and especially pharmacogenetic

tests and their associated personalised therapies, are often more expensive in the short run than current treatments but may promise longer term benefits to patients and the health care system.

There is thus a pressing need to find ways to help health care systems understand and take into account the real value of novel tests. This will be especially important, and particularly difficult, for 'stand alone' diagnostic tests used for early diagnosis of disease, especially chronic disease. Chronic disease, such as diabetes, is increasing at a rapid rate in developed and developing countries alike. Diagnosed early, diabetes can be managed and many of the costs associated with cardiovascular complications, blindness, etc can be prevented. Dementia represents another challenge to health care systems serving aging populations. This disease has considerable indirect costs and socio-economic impact, and it is difficult to know how to value a test which could prolong the onset of the disease by one year, five years etc. While it is not clear how HTA will evolve to evaluate biomarker-based technologies, inclusion of an evidence base and information on clinical utility and validity should be an integral part of any HTA for biomarker-based technologies.

Several organisations have begun collecting this type of information and making it available to health care providers. In the United States, the Lewin Group Center for Comparative Effectiveness Research (CER) uses a combination of consulting, research and data assets to increase knowledge and application of the most effective clinical protocols within the health care industry. CER uses real world data to compare the effectiveness of two or more health care interventions, assess how the cost and benefits of a treatment or health care intervention compare. The National Institute of Health and Clinical Excellence (NICE) in the US performs a similar role. NICE provides guidance and sets quality standards for implementation of the best health care. Expansion of these initiatives to include novel biomarker-based tests and targeted therapies will be important to HTA and to enable clinical application of biomarker-based tests within the practice of evidence-based medicine.

Conclusions

Perhaps one of the biggest challenges to the application of biomarkers within the practice of evidence based medicine is rooted in knowledge: knowledge generation, management, sharing and use. This knowledge challenge arises from biomarkers' genomic origins and is pervasive, extending from biomarker discovery, through development to application in the clinical setting.

While the genomics revolution promises advances in personalised medicine, new genomic tools and technologies are, at the present time, generating information faster than it can be associated with biological states or converted into clinical application. Thus the first challenge is in developing the infrastructure to generate and manage this knowledge more efficiently. Fortunately all stakeholders recognise this challenge and significant investment is being made by governments and industry to support a range of collaborative mechanisms and knowledge networks to address this challenge.

As the first wave of biomarker-based tests and products find clinical application, the value of this knowledge-based infrastructure is becoming clear. At the same time, the need to improve this infrastructure to accelerate translation of molecular information to biomarker identification is also becoming evident. Ironically most of the existing networks and consortia operate in silos, operating relatively independently of other national or international initiatives. Accordingly there is the potential for redundancy or duplication of efforts, and perhaps worse, little opportunity for development of useful synergies.

Increased collaboration between consortia may, under the right conditions, further accelerate biomarker development and should be considered by relevant stakeholders. Joint priority setting, for example, could be used to reduce redundancy and ensure disease priorities are met as efficiently as possible. Similarly harmonisation of guidelines for large-scale association studies would allow for database co-development, helping increase results produced and reducing the costs of population studies. Different groups are using different processes for knowledge generation, management and sharing, however they are all founded in science and it should not be unreasonable to consider harmonising these knowledge infrastructures.

Private-public support for knowledge sharing infrastructures will continue to be important in accelerating biomarker discovery and development. Governments may be able to support and strengthen knowledge infrastructures by:

- Encouraging long-term investments in building sustainable and flexible infrastructures, especially public-private partnerships that facilitate biomarker discovery, development and validation.

- Helping to prioritise and define significant unmet scientific or health care needs in order to prioritise biomarkers research and development.

- Encouraging collaboration between networks or consortia on a national and international level.

- Promoting an open pre-competitive research environment that puts knowledge about biomarkers into the public domain.

The second major knowledge-based challenge to biomarker development and application in the clinical setting concerns the development of an evidence base by which the clinical utility and clinical validity of biomarker-based tests may be assessed. Physicians require evidence of the clinical validity and utility of biomarker-based tests in order to integrate and properly consider these options when developing treatment strategies for patients. Similarly regulators require this information to ensure the quality and efficacy of biomarker-based tests. However there are no consistent standards on the type of information required to determine the clinical utility and validity of novel biomarker-based tests.

There is a clear need for stakeholders to discuss how an evidence base may be used to provide evidence of the clinical utility and validity for novel biomarker-based tests. There is also a need to share this information with governments, payers, and primary health care providers who rely on this information to inform their decisions. Development of an evidence base raises a number of questions:

- Who is going to develop, and who will make available, the evidence base for novel molecular biomarkers' clinical evaluation to the different stakeholders, and how will this be done (*e.g.* regulatory agencies, health care payers, physicians)?

- What are industry incentives to share data and information on the clinical validity and utility of biomarker medical tests?

- How are issues regarding standardisation, integration and co-ordination between different data and study formats for different biomarker medical tests going to be resolved?

- How will the individual's information be used, stored, accessed and protected?

Stakeholders need to work together to find appropriate answers to these questions. Governments need to ensure transparency in test evaluation, establish consistency in the types of evidence required for evaluations and identify where knowledge gaps are so as to make it clear where evidence is lacking and more data are required. Some experts argue there is a role for governments in developing the infrastructures or networks that would collate, ensure comparability and access to clinical evaluations of biomarker-based medical tests. There are some existing models, notably the E-Register of Studies and the ACCE Model Process (discussed above), which may provide a model for the development of an evidence base and thus good starting point for stakeholder discussions. The OECD's Guidelines on Human Biobanks and Genetic Research Databases (OECD 2009a) aims to provide guidance for the establishment, governance, management, operation, access, use and development of human biobank and genetic research databases and may also provide a useful contribution to these discussions.

Finally, the amount of information and work required to determine clinical validity or clinical utility of biomarker-based technologies within a boarder HTA is significant and represents a challenge for many countries. While not all health care or socio-economic systems are the same, there may be some efficiencies to be gained by sharing some information between countries. This is particularly true for genetic information like an evidence base.

Chapter 3

Regulation and reimbursement of biomarkers for personalised medicine: the challenges

Regulatory and reimbursement systems have a key role to play in creating a context that encourages the adoption of biomarker-based tests in the clinical setting. However, at present, regulatory and reimbursement schemes in many countries are a significant barrier to development of personalised medicine. Existing processes were designed for drugs and simple diagnostic tests and are not well adapted to the features of novel biomarker-based tests and pharmacogenetic products at the heart of personalised medicine. Application of existing processes and structures at the present time is inefficient, variable and lacks transparency. The result is that a number of unregulated and variably regulated tests are now used in the clinical setting. Perhaps more worryingly, while the reimbursement process has often been a driver of clinical application of tests and stimulus for development of new tests, the process is now having the opposite effect. Inconsistent coverage decisions are limiting or delaying patient access to personalised medicine and hindering biomarker research and development.

This chapter addresses the challenges to the regulation and reimbursement of novel biomarker-based medical laboratory tests for personalised medicine. It presents the current situation in OECD countries and the ongoing changes to regulation and reimbursements systems. It also identifies those issues in greatest need of attention from government.

Regulatory context for novel clinical tests

Within the health care context, regulatory authorities are charged with regulating the introduction of new medicines so as to ensure their quality, safety and efficacy. The goal is to ensure that medicines and tests used within the clinical setting are effective and safe for patients. In the face of decline in the number of drugs obtaining regulatory approval and a rise in the number of adverse drug reactions (ADR) and withdrawals, regulators are generally supportive of biomarker-based tests and drugs developed with the use of biomarkers.

In the context of this generally supportive regulatory climate, it is noteworthy that there have been concerns in many jurisdictions regarding the adequacy of the oversight of clinical tests involving genome-based biomarkers. As clinical genetics moves from the realm of rare diseases to mainstream medical care, advances in testing are outpacing the establishment of regulatory frameworks that ensure their safety and effectiveness.

The need to develop an evidence base which would establish the clinical validity and utility of such tests is clear, as detailed in Chapter 2. As new 'omic' technologies emerge, reliable information that could allow regulators and health care payers to identify which tests are safe and useful will only grow in importance. At present it is difficult to identify appropriate decision-making criteria, due to the lack of data and information about new medical tests and, in many OECD countries, the lack of oversight in this domain. Indeed, it is even unclear how the necessary data and evidence may be obtained in a cost effective manner. The situation is made more complex by the fact that many genomic tests are developed as Laboratory Developed Tests (LDT) which are provided by specialised laboratories, not as kits, and are not subject to regulatory approval.

In most OECD countries market authorisation and reimbursement decisions are currently made by separate entities, though these entities often rely on similar bodies of evidence in order to inform their decisions. These decisions are generally made at the end of the development process, and rejection or refusal at such a late stage in development can have serious negative economic consequences for the developer.

There is a clear need to develop transparent and consistent policies concerning regulation and reimbursement of new molecular diagnostic tests. Further, there needs to be agreement among stakeholders on the type of data used in these decisions and the way in which this information is used to make decisions. Enhancing communication between regulatory and reimbursement agencies, and extending this communication to industry in advance of biomarker clinical test evaluation, would provide a good starting point for development of such policies.

Clarification and adaptation is needed within regulatory processes

The absence of consistent, transparent and appropriate oversight mechanisms for the clinical evaluation of novel biomarker medical tests creates an unstable business climate for manufacturers and laboratories. Investment may be deterred, as might development of innovative tests. Regulatory procedures for medical products are complex, vary by type of product (full even by type of medical test), and are not harmonised across countries. For example, in the United States, the FDA regulates both pharmaceutical products and diagnostics tests, while in Europe these two products are regulated by different agencies. Historically, neither jurisdiction has regulated the use of "home-brew" or laboratory developed tests (LDT). In 2008 it was estimated that about 1 000 biomarkers were available as diagnostic tests and these were almost universally marketed as LDTs without formal approval from regulatory agencies (Novelli, G., 2008). The safety, quality and efficacy of these tests are then left to the discretion of the developing laboratory.

Looking at the regulatory context for molecular biomarker medical tests globally, some common issues emerge across OECD countries:

- The regulatory processes and timelines for approval of diagnostic tests are not well adapted to the novel features of molecular biomarker-based tests.
- The regulatory requirements for the approval of tests need to be better defined with respect to the performance, utility and safety of these tests.
- Novel biomarker-based imaging tests will also need to be considered when adapting and clarifying any regulatory requirements for biomarker-based tests.
- Stakeholders should be consulted about which oversight mechanisms are needed and how to implement these so as not to depress innovation and the application of useful biomarkers in medical practice.
- International harmonisation is needed in order to minimise regulatory barriers and facilitate trade.

The need to adapt existing regulatory processes to novel biomarker-based tests has been recognised and Regulatory Agencies across many OECD countries are actively working with stakeholders to clarify and evolve the relevant regulatory processes and associated governance frameworks.[7]

An evolving regulatory processes

Within the OECD countries, regulatory agencies have already started to clarify and adapt their regulatory procedures for novel molecular biomarker-based tests (both standalone diagnostic tests and pharmacodiagnostic tests). The US Food and Drug Administration (FDA), has introduced a number of initiatives to accelerate the approval of diagnostics and new drugs. Among other initiatives, it launched the Critical Path Initiative (CPI) to address the steady decline in the number of new medical products being submitted for approval in the face of significant breakthroughs in genomics and biomedical science.

The Critical Path Initiative is the FDA's national strategy for transforming the way FDA-regulated products – including biomarker-based tests – are developed, evaluated, and manufactured. In 2006, the FDA issued guidance explaining the regulatory process for the joint development of both a test and a therapeutic. Since that time, the FDA has continued to engage with stakeholders to address barriers to development and application of biomarker-based tools in clinical medicine. In 2006/2007 the FDA worked with stakeholders to develop guidelines for the regulation of a specific type of LDT known as In Vitro Diagnostic Multivariate Index Assays (IVDMIAs). Revised guidelines were expected in late 2010 but they were dropped when it was decided to shift the focus to LDT more generally. The FDA has also recently initiated collaboration with the National Institutes of Health (NIH) to help focus additional funding on developing and applying the new tools, standards, and approaches needed to properly assess the safety, effectiveness, and quality of products currently in development.

In Europe, the European Medicine Agency (EMEA) is developing a new regulatory process for coupling the submission of a test and a treatment. The new procedures will be adapted to *in vivo* tests coupled with drug prescription. In June 2009 the EMA published guidelines on genomic biomarkers, detailing the context, structure and format of regulatory submissions for biomarkers. The EMA is expected to publish guidelines on the use of pharmacogenomic methods in pharmacokinetic studies in late 2010. In their 2010 draft document *The European Medicines Agency Road Map to 2015: The Agency's Contribution to Science, Medicines, Health* the EMA highlighted the need to consider the appropriateness of the current legal and regulatory framework, in particular the benefit-risk evaluation, to support advances in personalised medicine. The EMA is not, however, responsible for regulation of diagnostics and reform to regulations for clinical laboratory tests and complex biomarkers is being driven by a number of different stakeholders such as the United Kingdom's Foundation for Genomics and Population Health (PHG Foundation).

Harmonisation of regulatory procedures is also needed

Regulatory procedures for medical tests vary greatly between countries. Because of the international nature of research and commercial activities, there is a call for international collaboration to develop a coherent regulatory framework across OECD countries. The companies involved in test development typically seek global markets but regulatory procedures remain national. Across OECD countries there are common requirements to provide evidence of safety, quality and performance, but the technical requirements differ dramatically.

The call for harmonisation in regulation of medical devices has resulted in efforts by national device regulatory authorities and industry to encourage convergence in regulatory practices that ensure safety, effectiveness/performance and quality of medical devices. A number of international initiatives aimed at harmonising regulatory processes for pharmaceuticals or medical devices are leaning towards harmonising regulatory requirements for biomarker-based products (pharmaceuticals and devices). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[8] and the Global Harmonization Task Force (GHTF)[9] are two such initiatives.

ICH brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. In April 2008, the ICH launched a project called "Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions". This project aims to define the standards and formats for submitting information about genomic biomarker data to regulators. The ICH noted that "agreement on general principles for the types of data submissions required would allow consistent data packages to be produced by sponsors and facilitate data sharing by regulatory authorities. A standardised data format and content would add further to a consistent approach to biomarker qualification among the regions."

Reimbursement for biomarker-based medical tests

Despite the challenge presented by an imperfectly adapted regulatory system, it is the reimbursement system for biomarker-based tests which may represent a greater challenge to development and adoption of biomarker-based diagnostics. This may be because these tests represent such a paradigm shift to the current reimbursement system. The current reimbursement system was designed for relatively simple and inexpensive diagnostics (*e.g.* blood cholesterol) and typically provides reimbursement based on a cost recovery basis. These laboratory tests often account for less than 2% of reimbursement spending, but they influence 70% of health care decisions.

Novel molecular biomarker-based tests are more expensive to develop and perform, and are not presently well positioned for high-throughput or widespread use in the clinical setting. Moreover, unlike many existing tests which are designed for use and treatment of acute conditions, these tests are designed for use in the prevention and management of disease. Accordingly, they seek to be reimbursed on their value within the health care setting. Determining this value is the primary challenge to the existing reimbursement system.

The existing reimbursement system poses other challenges to the uptake of biomarker-base tests and the development of personalised medicine more generally. The coding system is not well suited to the complexities of these tests involving multiple tests. It does not accurately describe the novel diagnostic tests, and current practices in this regard are not clear or consistent. These process challenges are delaying the uptake of biomarker-based tests in the clinic, reducing patient access to personalised medicine, and may impede investment in the development of novel diagnostics.

The process for reimbursement of molecular biomarker medical tests is complex and varies across countries. Reimbursement decision-making often involves assessment of two factors: whether the test has proven its utility in clinics (coverage based on test clinical utility), and its value when included in the health system (payment based on cost-effectiveness). Again, a response is needed regarding the question of how to evaluate novel biomarker medical tests and how to determine their clinical utility and cost-effectiveness when applied in clinical practice.

Depending on the country, government agencies responsible for evaluating new health technologies have started performing studies on novel molecular medical tests to produce evidence on their clinical outcomes and potential economic impact (Box 6). Reliance on positive health outcomes is often a primary factor in deciding on coverage. However at present, clinical trials measuring health outcomes are rarely conducted for new molecular tests. Most pre-market notification includes data from studies that are designed to demonstrate a significant equivalence to a similar device and show equivalent performance in clinics.

Box 6. Frameworks for evidence-based reviews of new health technologies

Agency for Health care Research and Quality (AHRQ), *www.ahrq.gov/*

AHRQ is the health services research arm of the US Department of Health and Human Services (HHS), complementing the biomedical research mission of its sister agency, the National Institutes of Health. AHRQ funds research on health care quality, costs and outcomes, and on patient safety. As a part of its function, AHRQ funds evidence-based practice centres in Canada and the United States which specialise in the methods and conduct of systematic reviews.

Canadian Agency for Drugs and Technologies in Health (CADTH), *http://cadth.ca/*

The primary mission of the CADTH (formerly known as the Canadian Co-ordinating Office for Health Technology Assessment or CCOHTA) is to provide timely, relevant, rigorously derived, evidence-based information about drugs and other health technologies. It also supports the decision-making process in Canada. Federal, provincial and territorial health care decision makers rely on the CADTH to provide credible information and impartial advice. The CADTH's mandate is distinct from that of regulators, which typically focuses on determining which drugs or technologies should be used to achieve the best outcomes in terms of both patient health and effective operation of the health care system.

National Co-ordinating Centre for Health Technology Assessment (NCCHTA), *www.hta.nhsweb.nhs.uk/*

The NCCHTA is an organisation funded by the UK Department of Health to provide health technology assessment to the National Health Service (NHS). As a part of this research, the NCCHTA commissions the undertaking of broad-scale systematic reviews which cover a wide range of health care topics, including systematic review methods.

National Institute for Clinical Excellence (NICE), *www.nice.org.uk/*

NICE is part of the United Kingdom National Health Service (NHS). Its role is to provide patients, health professionals and the public with authoritative, robust and reliable guidance on current "best practice". As a part of its remit, NICE commissions technology assessments which include both systematic reviews of clinical evidence and economic evaluations of interventions, such as drugs.

Pharmaceutical Benefits Advisory Committee (PBAC),
www.health.gov.au/internet/main/publishing.nsf/Content/Pharmaceutical+Benefits+Advisory+Committe-1

PBAC is an independent statutory body (established in Australia on 12 May 1954 under Section 101 of the National Health Act 1953) with a mandate to make recommendations and provide advice about which drugs and medicinal preparations should be made available as pharmaceutical benefits. No new drug may be made available as a pharmaceutical benefit unless the committee has so recommended. In December 1993 (under Section 101A of the National Health Act), PBAC established the Economic Subcommittee. Its role is to: *i)* review and interpret economic analyses of drugs submitted to the PBAC; and *ii)* advise the PBAC on these analyses, and on technical aspects of requiring and using economic evaluations.

Coverage demands remain long and difficult to fulfil for novel molecular tests. There are no guarantees for manufacturers of the adequate reimbursement of tests, and reimbursement requests could take many years before a public (or private) reimbursement is issued. Clarity on how to proceed is needed. Communication between test manufacturers and reimbursement agencies could be enhanced to better manage expectations and develop appropriate standards. Test manufacturers should be able to easily assess the regulatory and reimbursement requirements so as to better anticipate the data they will need to provide to demonstrate the clinical utility of their product. Health care payers should provide more information regarding the information they will need about the test pre- and post-marketing. To be most effective, this information should be identified ahead of time, collected during development and used to create an evidence base (Chapter 2). It may also be possible

to develop collaborative arrangements in which insurers work with developers to gather the necessary information. Or if this is not feasible, developers could explore most market options for collection of necessary data.

This type of collaborative arrangement was left as an option for development of companion diagnostics associated with warfarin. The Centers for Medicare and Medicaid Services (CMS) in the United States announced in early May 2009 that it would not pay for genetic tests to help guide warfarin dosing for Medicare recipients, noting that the "available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries." CMS did, however, leave open an option for coverage to beneficiaries who agreed to be part of a prospective, randomised, controlled clinical study designed to show that pharmacogenomics-guided dosing strategies improve health outcomes over standard dosing methods (under its Coverage with Evidence Development programme). The new guidance document outlines circumstances under which Medicare will cover a new product while additional evidence is gathered through post-marketing studies. However lack of coverage is currently the major impediment to acceptance of genetic testing in dosing for warfarin.

Development of new models for reimbursement of biomarker-based tests

Progress is being made in understanding the problems with the current reimbursement systems and in improving the decision-making systems for the coverage of novel tests. For example, in the United States, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) recently issued a comprehensive report regarding reimbursement of genetic tests and the US Congress has considered a new Medicare payment system for laboratory diagnostic tests that would increase the transparency of its fees. The legislation would improve access to advanced diagnostic lab technologies, and thus allow physicians and patients to identify diseases earlier and target treatments more precisely while significantly reducing health care costs. By recognising the benefit that improved diagnostic tests offer patients, adequate and transparent pricing would provide greater incentives for laboratories and health care providers to adopt new innovative technologies.

A number of non-governmental organisations have also undertaken comprehensive reviews of the reimbursement system for novel diagnostics in the United States. In 2010 the Personalized Medicine Coalition (2010) produced an issues brief highlighting the weaknesses in the current system. In the same year, Health Advances (2010) performed a detailed review of the reimbursement landscape. In performing their review, they worked with a wide range of stakeholders to identify a continuum of solutions to the current challenge of reimbursement for biomarker-based tests.[10] The proposed solutions varied in impact (from low to high) and in resources and implementation timeline. This was, by design, to facilitate widespread patient access to personalised medicine. Proposed solutions included risk-sharing payment schemes, linking FDA approval to reimbursement, economic study standards and development of new biomarker specific tests codes. While these reforms were designed to address weaknesses within the United States reimbursement system they are likely more broadly applicable. Other countries seeking to improve their reimbursement system may find these reforms useful starting points.

Government initiatives are moving toward greater transparency and coherence of reimbursement processes. But work still needs to be done to increase the communication between tests manufacturers and health care insurers to better inform decisions about novel molecular biomarker-based test reimbursement.

Conclusions

Novel biomarker-based tests are proving a challenge to existing regulatory and reimbursement systems in many countries. These systems were, in many cases, developed for simple diagnostics and are not well suited to the molecular, and often complex, nature of biomarker-based tests. Governments interested in reaping the benefits of biomarker-based personalised medicine have a clear interest in working to adapt these systems. However, revision to the existing reimbursement and regulatory systems faces a number of challenges.

Existing regulatory system standards used to evaluate and verify the safety, efficacy and quality of these tests are not well suited to biomarker-based tests. While it is acknowledged that new standards will require provision of significantly more data than for simple diagnostics tests, there is as yet no consensus on what new standards should be. A lack of standards and variability in the application of

those standards is delaying uptake of biomarker-based tests in the health care setting and may also deter developers of new biomarker-based tests.

Governments need to work to establish appropriate regulatory standards which are clear and consistent and evidence-based. As other governments are working to adapt their regulatory processes there may be an opportunity to harmonise some aspects of the regulatory process. This would help enable diffusion of biomarker-based tests more broadly and may help reduce the costs to industry.

Application of biomarker-based tests in the clinical setting is further challenged by a reimbursement system which is also not well suited to complexities of molecular biomarker-based tests. These tests are not well characterised within existing systems, and there are no consistent standards for describing individuals tests or deciding reimbursement level. This lack of standards and inconsistency may also slow uptake of these tests in the clinical setting and may deter development of new tests as researchers and investors favour more certain investments of time and money.

Perhaps the biggest challenge to the reimbursement system is in determining the appropriate value of biomarker-based tests. Diagnostic tests have, historically, been reimbursed on a cost recovery basis rather than on the health care value of the test. Molecular biomarker-based tests represent a new paradigm in this regard. The tests are much more expensive to develop and perform and in many cases seek to provide a benefit (*e.g.* risk of cancer) whose value is difficult to quantify or value.

Determining the health care value of biomarker-based tests is difficult and while it may likely involve some form of Health Technology Assessment, there needs to be a discussion about what data must be collected and how this data is shared with regulatory authorities and health care providers. There needs to be a discussion on how these costs could be met and by whom, and how the process could be harmonised across jurisdictions.

Governments need to review current regulatory and reimbursement processes for biomarker-based tests and indeed many OECD countries have begun the process of doing so. Governments have acknowledged the need for increased transparency and consistency regarding the information required and how it will be used. In order to ensure that reasonable and equitable policies are developed, a broad range of stakeholders – including diagnostic test producers, health care providers and patient groups – will need to be involved in such discussions. Issues to address will include questions about what sort of evidence should be required, who will develop it, how and where it will be submitted, who will have access to the information, and how it will be analysed. The latter sort of decisional support may be the domain of health technology assessment approaches or agencies.

Chapter 4

How biomarkers and personalised medicine are challenging medical practice

Novel molecular biomarkers are poised to enable a paradigm shift in health care delivery and medical practice. The use of biomarker-based diagnostics in the clinical setting will expand the information available to physicians and primary care providers in the practice of evidence-based medicine. Disease risk and susceptibility may be identified and managed better than before, preventing or delaying the onset of symptoms which can have a negative impact on patient health and health care costs. The improved treatment strategies may be better matched to the patient, the incidence of adverse drug reactions may be reduced, and overall patient outcomes may be improved.

In order to achieve this new paradigm, some ethical, social and practical challenges must be overcome. This chapter explores these challenges in the context of health care delivery and clinical care, and identifies ways in which OECD member and non-member countries can respond to those challenges.

Molecular medical tests in clinical practice

Integration of novel biomarker-based technologies in the health care setting will be driven, to a large extent, by physicians or primary care providers; those individuals responsible for prescribing tests and treatment strategies. Physicians often have many drugs or treatment options from which to chose and no certain way to understand which ones will work best in an individual patient. Patient responses may vary and toxicity can be a significant problem. Drugs or tests are currently prescribed on the basis of familiarity, speed or costs, and what amounts to an educated and practiced process of trial and error. Most physicians would welcome the availability of additional information to include in their decision making process. Even so, there are a number of factors which may present a barrier to uptake of biomarker-based technologies in the health care setting.

One of the primary barriers concerns education regarding biomarker utility and, more generally, the associated and underlying molecular biology. Within the practice of evidence-based medicine, physicians use various parameters or clinical biomarkers to assist in diagnosing disease and identifying the best treatment strategy for each patient. The parameters are chosen based on the value of the information they provide to physicians. The incorporation of biomarker-based diagnostics in the clinical setting will thus depend on the physician's perception of the value of a biomarker to a particular patient. That is to say, it will depend on the value, or clinical utility, of the test to a physician in the practice of evidence-based medicine: *i.e.* to confirm a diagnosis or predict in advance a patient response to a certain drug or other treatment.

Determining the clinical utility of a biomarker-based test is a challenge, and one which must be overcome if biomarker-based tests are to achieve adoption in clinical practice. Chapter 2 described the need for an evidence base which can be used to show the clinical utility of individual biomarker-based tests. Dissemination of this evidence to physicians via direct access to data, publication in medical or scientific journals, conference presentations or summary publications will encourage uptake of biomarker-based tests in the clinical setting.

A physician must also have sufficient training or experience in genetics or molecular biology to be able to understand how biomarker-based tests may complement and inform his or her decision making. As of early 2011, 65 FDA approved drugs included pharmacogenomic information in their labels to guide their clinical application.[11] Companion diagnostics for these drugs, might thus be taken up over time as a matter of course. However the degree to which physicians adopt other biomarker-based tests, especially those for diagnostics purposes, will depend to a large extent on physicians' knowledge of molecular biology and genetics underlying complex diseases like diabetes, cancer and heart disease. In some cases this information may be made available by the test provider or pharmaceutical company (in the case of companion diagnostics). In other situations, training in genetics and access to information regarding the state-of-the-art of biomarker-based R&D might be needed to enable physicians to incorporate additional information when considering between multiple options in the clinical setting.

Many experts believe that a shift to personalised medicine will depend on how the evidence regarding the utility of novel biomarker-based medical tests is communicated to and within the medical community. Structures which provide physicians with access to accurate and reliable information in genetics and continuing education on biomarker evidence and utility are crucial to this shift.

Nevertheless, even tests which are well-chosen, based on a sound understanding of test options, may have limited clinical uptake if they are difficult to use in the clinical setting. Tests which are rapid, reproducible, simple to use and easy to interpret, all other things being equal, are more likely to be used than the alternatives. In particular, there is increasing demand for tests that can be performed in decentralised labs or for point-of-care diagnostics.

Routine laboratory testing may be performed in many different settings – from large reference labs that performs complex tests, to on-site hospital testing laboratories, to homes where over-the-counter tests like those that allow patients to monitor blood glucose levels may be performed. However, most molecular biomarker-based tests currently on the market (*e.g.* Trofile, Onco*type DX*) are complex tests that analyse molecular profiles of patients. These tests are typically performed in large centralised labs. These laboratories are well equipped to perform the often complex post-assay analysis and interpretation required which cannot, in many cases, feasibly be performed in the clinic. However these tests may take several weeks to generate results. In the meantime physicians must weigh the cost and benefits between waiting for the results of these tests or initiating a treatment strategy prior to receipt and review of the test results.

As testing technologies improve, decentralized lab testing and point-of-care testing (POCT) for near-patients testing is becoming a desirable practice. Diagnostic tests that have evolved to this state are well received by the medical community. For example, POTC has proven useful in treating Lower Respiratory Tract Infections (LTRI) which are predominately viral in origin but whose aetiology is difficult to distinguish without testing. Tests to determine the viral or bacterial aetiology of LRTI can take days and in the meantime antibiotics are often prescribed as a precaution.[12] The hormone prolactonin and the C-reactive protein (CRP) are biomarkers which can be used in the clinic to differentiate between bacterial and viral pneumonia within minutes. Point-of-care tests for Procalcitonin (PCT) or CRP have reduced the use of antibiotics and has no doubt contributed favourably to the treatment and recovery of individuals with bacterial pneumonia.

For diagnostics tests and companion diagnostics incorporating multiple biomarkers, however, point-of-care diagnostics may be a few years away. Development of such tests will likely involve development or convergence of other technologies in the fields of engineering, chemical and biological sensor technology, synthetic biology and nanotechnology.

Education, training and human resources

It has been anticipated that the growth in the clinical use of biomarker-based tests would create new educational and training needs. An article published in 2003 in *Trends in Pharmacological Sciences* highlighted the need for "teaching pharmacogenomics to prepare future physicians and researchers for personalised medicine". This is still a relevant topic today. The need for physicians and primary care providers to have a good understanding of molecular biology and genetics, especially as they related to complex disease is clear. For the physicians of tomorrow, a number of public-private and government initiatives are pushing for the inclusion of these topics in university programmes and many universities are responding by creating new training programmes focussing on personalised medicine or pharmacogenomics. Today, physicians can benefit from a number of platforms that provide continuing education that take into consideration the importance of new advances in biomarkers and the underlying science and technology as they relate to the practice of medicine.

For example, the National Coalition for Health Professional Education in Genetics (NCHPEG) is an 'organisation of organisations' committed to a national effort to promote health professional education and access to information about advances in human genetics. The NCHPEG is a coalition between the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute with goals including the integration of genetics content into the knowledge base of health professionals and students of the health professions, and the development of educational tools and information resources to facilitate the integration of genetics into health professional practice. The NCHPEG provides on-line resources and web-based training for health care professionals.

In a separate, university-based initiative, The University of Cincinnati Genetic Counselling Program offers an "online topics in personalised medicine" lecture series as a continuing education opportunity for genetic counsellors in the continuing formation unit. This short course is focused on personalised medicine and its different applications in health care. Indeed, there are a number of programs designed to communicate background knowledge fundamental to informing physicians on the potential for biomarker-based tests and the larger field of personalised medicine.

Just as knowledge can empower physicians and primary care providers in their decision making, dissemination of this knowledge is likely to benefit all actors in the biomarker value chain: from researchers, to regulators and project managers. These actors may be responsible for development for things such as regulations or reimbursement strategies around biomarker-based tests and a greater understanding of the science behind the technology will be of great value.

As the promise of biomarker-based personalised medicine becomes clear, some very knowledgeable stakeholders are emerging with the sole purpose of helping diffuse knowledge regarding personalised medicine. For example, the Personalised Medicine Coalition (PMC) formed in the United States in 2004 has a mission to "educate federal and state policy makers and private sector health care leaders about personalised medicine, helping them understand the science, the issues and what is needed for the positive evolution of personalised medicine". The PMC has an on-line library which regroups a large number of articles around topics linked to personalised medicine, including economics, education, regulation, technologies and others.

Fortunately, both the public and private sectors have understood the need to organise and share knowledge through courses, articles and reports. The acceptance and broader use of personalised medicine depends on this. However, there is still progress to be made in translating the knowledge of this emerging field into public acceptance and wide-spread use in clinics.

Patient knowledge and involvement

Patients stand to benefit most from diffusion of biomarker-based technologies in clinical practice. Patients are motivated by a need for the best available medicine and are generally supportive of new technologies. However, an increasingly well-informed patient population is highlighting concerns regarding a number of issues which follow from genetic testing including concerns over privacy and confidentiality. It will be important to understand and recognise these concerns and to develop effective responses to ensure that biomarker-based testing can be integrated into the health care system with appropriate respect for patients' rights.

A recent OECD report on pharmacogenetics (OECD, 2009b) highlights the need for public policy to ensure patient privacy and rights regarding genetic tests, and also to improve patient awareness regarding genetic testing. The protection of patient privacy is critical to maintaining public confidence in the collection and use of the data necessary for the practice of personalised medicine. Patients may be less willing to provide tissue or blood samples, or to disclose medical history information, if they fear that their data will be misappropriated or their privacy will be violated. Informed consent for both research and treatment is thus critical. Ensuring effective protection of sensitive information is a necessary prerequisite to the collection and sharing of the individually identifiable data underpinning personalised medicine research and practice. Conversely, if patients are reassured that their data is safe, they may be motivated to allow use of their data and clinical samples in other research projects or clinical trials.

These concerns may be addressed through legislation and other policy instruments,[13] yet others may be addressed though communication and active engagement with patients and families. The way these issues are treated will affect patient attitudes to biomarker-based tests and other new technologies.

Understanding the risks and benefits of biomarker-based technologies is especially important given the pervasiveness of the Internet. Patients today have access to a great deal of health care and drug information from diverse sources and in some instances may be better informed on a new technology or drug than a physician. Indeed, as increasingly well-informed participants in health care systems, patients are often enthusiastic advocates of new technologies and may even drive uptake of biomarker-based tests in the clinical setting. However it will be important to ensure patients have access to information which is sound and balanced.

Direct-to-consumer marketing of drugs in media, in print, electronic and audio-visual form, seems omnipresent. Not surprisingly some companies are now marketing direct-to-consumer testing (DTC) of complex biomarker-based tests. These tests promise to provide information on a range of health and lifestyle characteristics ranging from baldness and muscle performance to risk of cancer and response to caffeine. Concerns about the validity, veracity, and relevance of this information, and the use of this information by customers in decision making, have been raised,[14] underscoring the importance of educating the public on the benefits and appropriate use of biomarker-base tests in health management. The message is simple: appropriately regulated and validated biomarker-based tests may help medical practitioners make better decisions for their patients. Education of patients and the general public is needed to enable patients to become active partners with their physicians in managing their health, and participants in the development of new biomarkers and uptake of new diagnostics tests in the clinic.

There are a number of good initiatives in this regard, notably the Personalised Medicine Coalition (PMC), described above. One of the goals of the PMC is to educate the public about personalised medicine, helping them understand what is needed for the positive evolution of the practice of medicine. The PMC collaborates with member organisations and outside experts to identify, analyse and address ethical, legal and social implications of personalised medicine, and provides a forum for debating (and, where possible, reaching consensus on) public policy issues surrounding personalised medicine. In Europe, the Innovative Medicine Initiative (IMI) also aims to provide training and education programmes for patients, with priority given to understanding the benefits and risks of medicines.

Diffusing the benefits globally

The biomarker revolution is a result of research and development investment by high income countries which expect to benefit from that investment. Yet it is also recognised that the benefits of biomarkers must be extended to health care systems in developing countries. These countries may be challenged with 'old' public health issues such as infectious disease and malnutrition in addition to new public health issues like chronic disease. Uptake of biomarker technologies in developing countries faces some universal, well known barriers such as cost, as well as barriers that are unique or especially significant in the context of developing countries.

One of the major hurdles to wider application of existing biomarker-based technologies stems from the relative lack of clinical trial data in diverse populations. The majority of biomarker-based research and development[15] and numerous clinical trials, are carried out in Western countries and have historically used Caucasian populations. They take little account of how other populations' genetic backgrounds might alter patients' response to a medicine, or manifest disease susceptibility. Thus there is a risk that biomarker-based products or tests developed using genomic data from one population, could be less efficacious or have increased risk of toxicity in other populations. This barrier has been recognised and has served as the impetus of several initiatives to broader the applicability of existing biomarker- based tests.[16]

One such initiative, the Pharmacogenetic for Every Nation Initiative (PGENI) is helping countries develop the education, guidelines and infrastructure necessary to lay the groundwork for personalised medicine in a wider range of countries. In one such ambitious project, PGENI is working to screen populations in 104 countries for known biomarkers (functional polymorphisms) in genes involved in drug metabolism, transport, and target genes for the medicines on the World Health Organisation 'Essential Medicines List'. This will allow global genotype profiles to be constructed and provide a publicly available resource for polymorphism information and allele frequencies. This work will be important for enabling diffusion of biomarker-based technologies in developing countries.

Benefits of this type of work are highlighted in the case[17] of the biomarker for the NAT2 enzyme, a key enzyme in metabolic pathway of Isoniazid. Isoniazid is a medicine used to treat tuberculosis, a contagious and deadly disease infecting 2 billion people worldwide. Isoniazid is effective, cheap and is widely used around the world as a first treatment option for the disease. The drug is metabolised in the liver, however the rate at which it is metabolised varies in different populations: for example, the majority of the Egyptian population (92%) metabolise the drug slowly, while just over half of the people in Columbia (51%) metabolise it quickly. In individuals with slow metabolism, higher levels of Isoniazid remain in the body for a longer time and increase the risk of liver damage. Identification of populations, or subpopulations, likely to metabolise isoniazid slowly will allow clinicians to change follow-up care (*e.g.* monitoring schemes for liver damage) or chose alternative treatment strategies.

Development of inexpensive, simple, rapid, point-of-care tests (POCT), like Procalcitonin (PCT) and CRP, will greatly facilitate diffusion of the benefits of biomarkers globally. Numerous institutions are rising to this challenge, and are working to enable development and delivery of POC biomarker-based tests in low-income countries. In December 2010, the World Health organisation approved rapid test, fully automated NAAT (nucleic acid amplification test) for tuberculosis. The test could revolutionize TB care and control by providing an accurate diagnosis in about 100 minutes. The current tests can take up to three months to have results. Faster and earlier detection of disease will reduce the likelihood of infection and hasten patient recovery. However, as discussed above, development of often complex biomarker-based tests for point-of-care diagnostics remains a barrier to biomarker uptake and diffusion in the health care setting. Advances in this regard are likely to come from convergence of technologies and may take many years. However, once successful POCT will increase the likelihood of use of biomarker-based tests within health care systems and may revolutionise the practice of medicine around the world.

Finally, the importance of knowledge sharing to diffusion of biomarker-based tests in the clinical setting is particularly acute in developing countries. In these countries patients may have very widely varied education levels, and physicians may have similarly varied access to continuing education and other knowledge resources. Application of biomarker-based tests in the clinical setting requires sharing of this knowledge among all stakeholders. The importance of an informed partnership is especially important when using biomarker-based diagnostics to manage chronic disease before it progresses to the most costly acute or chronic stages. Incorporating information on risk factors and long-term management of risk factors requires access to knowledge and ongoing health monitoring, requiring clinical and knowledge infrastructure improvement and maintenance.

Conclusions

For biomarkers to deliver on the promise of personalised medicine, it will be important to understand the potential barriers which may inhibit the use of biomarker-based tests in the clinical setting and seek ways to address any issues. Perhaps one of the biggest challenges in this regard concerns the diffusion of knowledge of genetics and biomarkers, both to physicians or primary care providers, and to the general public.

Within the clinic, physicians decide when and how biomarker-based tests are used, and it is necessary that these individuals have the requisite knowledge and training to make informed decisions. Higher education programmes need to be adapted to include information on the role of genetics and biomarkers within the context of personalised medicine in order to facilitate uptake of biomarker-based technologies in the clinic. There has been significant progress in this regard in the last eight years and this needs to continue. Government can support these efforts through the promotion of further education and dissemination of genetics and biomarkers knowledge within the medical community.

Dissemination of knowledge regarding biomarker-based tests within the context of personalised medicine must also include patients. Patients stand to benefit most from biomarker-based technologies if they are provided with the knowledge they need to enable them to be effective partners with physicians in managing their health. Patients need to understand how biomarkers can be used to improve their health and the limits of biomarkers. This is especially important in the light of the growing trend of direct-to-consumer testing. Diffusion of knowledge on personalised medicine is being diffused over the Internet from a number of organisations, and governments may have a role to play in ensuring the validity of the information being diffused.

The use of biomarker-based tests raises several privacy concerns which will need to be addressed to maintain public support for these technologies. Government have a number of ways in which to ensure these concerns are addressed, however it will be important to be alert to the possibility that new tools may be required.

Finally, the use of biomarker-based tests in the clinical setting will be facilitated by development of quick, easy to use point of care diagnostics. Developing such diagnostics for complex molecular biomarker-based tests will be challenging, and will likely require integration of different technologies and a blend of science and engineering. Accordingly, governments may encourage development of point-of care diagnostics through policies and programmes which support technology convergence.

Chapter 5

Emerging business models for biomarker-based companies

The acceleration in biomarker discovery and development over the last decade is poised to transform the practice of medicine; providing improved diagnostics for disease and opportunities for safer, more efficacious therapeutics. The way in which biomarkers may drive the shift towards a new health care paradigm is increasingly clear, and the potential benefits of this shift to individual and collective health and wellness (detailed in Chapter 1) are undeniable. However, technological and scientific advances are out- pacing development of appropriate business models to ensure that the benefits of biomarkers are realised. This chapter provides an overview of the opportunities provided by biomarkers for the pharmaceutical and biotechnology industries and some of the current challenges to development of effective business models within these industries. The chapter also describes some considerations for the development of business models which may be used to bring biomarker technologies into the clinical setting while balancing industry's need for commercial viability.

Revisiting the blockbuster model

Since the beginning of the Human Genome Project in the 1980s, there has been speculation about how the pharmaceutical industry would use biomarkers to create products of value for patients, and in particular, the extent to which the industry would use biomarkers within the emerging field of personalised medicine. The role of biomarkers in pharmacogenetics and the way in which pharmacogenetics can benefit drug development is now clear (OECD, 2009b). Pharmaceutical companies have integrated biomarkers into most stages of their drug development process. However integration of biomarkers within the drug development pipeline and the concurrent emergence of personalised medicine is forcing a change in the industry's traditional business model.

Historically most pharmaceutical companies have relied on development of 'blockbuster' products to establish and maintain market leadership. So-called blockbuster drugs seek to address a previously unmet health need and are targeted to a broad cross section of the population. This business model encourages development of a small suite of drugs from which to generate the majority of company revenues. Under this model, companies will select for development only those medicines which appear to have huge market potential and once developed, those medicines are marketed widely. With peak annual sales in excess of USD 1 billion annually each, development of blockbuster drugs have understandably influenced a large part of the clinical focus and overall direction of corporate strategies.

An improved understanding of disease and disease processes and the subsequent stratification of disease made possible by biomarkers pose a challenge to the traditional blockbuster business model. Used to develop targeted therapies, or used to target existing therapies to subpopulations of patients, biomarkers may reduce the effective market size of a drug, wreaking havoc on the carefully constructed and optimised ratio of revenue/development cost. Increasingly, to serve the original market, two or three different drugs may be needed, potentially increasing development costs to serve the same market size and accrue the same revenue.

This challenge, however, may have arrived at the right time. Statistics detailing the rate of adverse side effects and a number of high profile market withdrawals of drugs like Vioxx illustrate the fact that one-size-fits-all blockbuster drugs do not work for a large proportion of the population. Further, while there has been some debate regarding the declining productivity of the drug development pipeline, what is less debated is the fact that the costs of drug development are rising disproportionately to the number of successful approvals (Schmid & Smith, 2005; Di Masi, *et al.* 2003, Peck, 2007). In 2009, just 26 new molecular entities (NMEs) were launched globally, a slight increase over the previous year, but little more than half the number launched in 1997.[18] New drugs represent a small (7% in 2009) and decreasing portion of sales for the industry as a whole,[2] and many companies include in their portfolio generic drugs and easily developed "me-too" compounds developed by other companies targeting the same disease and relying on a similar mechanism of action. It is increasingly clear that a new model of drug development is needed.

The increasing integration of biomarkers into many new product offerings of pharmaceutical companies suggests that there is willingness to re-evaluate the blockbuster model of drug development. Although it is currently unclear what the new model will look like, and whether all companies will adopt a similar model, the extent to which biomarkers are taken up by the industry will have a great influence on the degree to which advances in biomarker discoveries change the practice of medicine.

Challenges and opportunities for the pharmaceutical industry

There are a number of business models which might be adopted by the pharmaceutical industry and many companies are in the process of restructuring the ways in which they do business. The number of new business models is matched only by the number and variety of biomarker applications in the field of pharmacogenetics and diagnostics. The challenge in development of these models is to maintain profitability in the face of changing markets and an evolving regulatory environment. Most companies will need to adapt their existing business model to offset a reduction in revenues arising from increasingly segmented markets with some combination of faster or cheaper drug development, development of more efficacious drugs, or development of companion diagnostics.

Improving efficiencies of the drug development and delivery pipeline: new business models

Companies may seek to use pharmacogenetics to improve efficacy of existing products and processes. Pharmacogenetics may be used to understand the pharmacokinetic and pharmacodynamic differences in patient responses to a drug (OECD, 2009b). If differences in pharmacokinetics, the way a drug is metabolised by the body, are responsible for differing efficacy and side effects, it may be possible to maintain market share by simply changing the dose of the drug administered (*e.g.* as in the case of Warfarin, Chapter 1).

Other companies may use biomarkers to develop new targeted therapies, or to re-develop previously abandoned drugs. Biomarkers may be used to stratify patient populations for clinical trials to identify patients in which the drug is most likely to be safe and efficacious. For example, researchers have found that Iressa (Gefitnib) has a profound effect on a small subset of patients (10-20%) which was most probably diluted out by the lack of other patients in earlier clinical trials (Mok *et al.*, 2009; Fukuoka, 2011). Drugs developed in this way may only achieve clinical utility when used alongside companion diagnostic test to identify those individuals for whom the drug will be useful. Pharmaceutical companies may develop pharmacogenetic, or companion, tests to be marketed alongside the drug, or they may partner with a biotechnology, R&D or diagnostic laboratory to do this.

At the other end of the spectrum, a company may integrate biomarkers into pre-clinical research to identify new potential targets for drug development or to speed up the evaluation of drug candidates at an earlier stage of development. In this model, the company may do the research alone or in partnership with a biotechnology or research laboratory. Indeed, emerging models for pharmaceutical companies may span a continuum from becoming a vertically integrated 'health company' offering everything from diagnostics to targeted treatments, to simply using biomarkers to improve the drug development process.

Most of the emerging business models are predicated on the generation or acquisition of new information, technologies, intellectual property, or know-how. Access to this information and technology may be developed in-house, or acquired through mergers or through co-development with researchers, device manufacturers, diagnostics laboratories or life science companies. The way in which new information and technology is accessed and incorporated by a company will depend on the particular business strategy of the company and it will influence the company's product offerings, development costs, profits, and access to market.

The model selected will also depend on the particular areas of human health in which the company is operating or wishing to operate. For some diseases, clinically useful biomarkers may not yet have been identified, or new drug development and delivery strategies may not offer significant benefits (*i.e.* cost or efficacy) over conventional therapies. In contrast, diseases with complex aetiology, such as cancer, vascular disease, and diseases of the central nervous system, can provide significant opportunities within the pharmaceutical industry. These diseases generally arise from a number of genetic modifications in increasingly well understood disease pathways and there is a need for rapid and accurate diagnosis to establish appropriate treatment plans.

New drug development models are expected to be predominantly market-led, but they may also be influenced by policy and indeed there may be a need for policy intervention in some instances. The need for a clear, viable, commercialisation pathway may deter some companies from development of drugs with small markets that may not be seen as economically viable targets. Similarly, rare diseases constituting small markets may not be viewed as attractive to the pharmaceutical industry regardless of the health care benefit. It may be necessary in these cases to introduce measures that draw on experience from orphan drug legislation to attract investment in, and development of, medicines for these diseases. Measures such as tax incentives for clinical trials, market exclusivity or extended IP protection may be useful in these cases.

Building a new diagnostics industry

Beyond the advances biomarkers are bringing to the pharmaceutical industry, biomarkers seem poised to spawn a new diagnostics industry, or perhaps, revitalise an existing industry. New molecular diagnostics provide an opportunity for early detection of disease allowing earlier intervention, therapeutic or otherwise, potentially improving patient care and reducing overall health care costs. Used as a tool to inform therapeutic treatment, pharmacogenetic companion tests can improve apparent drug efficacy and reduce the likelihood of adverse drug reactions or toxicity, and their associated costs.

Despite the clear potential for diagnostics to improve the way disease is diagnosed and managed, the manner in which biomarker-based tests, in particular complex molecular tests, will figure within the business models of diagnostic companies is not clear. Presently, most complex biomarker-based tests on the market (*e.g.* Oncotype DX, Genomic Health, and Trofile, Monogram Bioscience), are offered by new biotechnology-diagnostic companies, and in many cases represent their sole or primary molecular test product. Single biomarkers, in contrast, like that for the Her2 biomarker associated with breast cancer, have been developed into a number of molecular and non-molecular diagnostic offerings by a number of companies. For instance Dako, a global diagnostic company providing cancer diagnostics and Monogrom Bioscience offer assays for over expression of Her2 to guide treatment with Herceptin.

Existing diagnostic companies, especially those offering simple non-molecular testing may attempt to incorporate previously developed biomarkers into existing platforms. These tests may be relatively inexpensive and will be aimed at a well growing and relatively established health care market segment of companion diagnostics. Established biotechnology companies on the other hand may seek to develop increasingly complex tests attempting to provide a more comprehensive and information rich diagnostics, or to provide genetic or pharmacogenetic services to other companies. The products and services of these companies might target pharmaceutical companies (in the case of pharmacogenetic services and possible companion diagnostics) or health care providers (in the case of stand-alone diagnostics for disease).

The incorporation of single biomarkers into simple molecular or non-molecular tests might be a natural extension of the business models of existing diagnostic companies. These companies have an established market and the use of existing technology platforms might enable provision of low-cost tests. This is especially the case for companies with access to validated biomarkers. However it is not at all clear how complex biomarker-based tests would be integrated into these companies or emerging diagnostic companies. These tests are typically expensive to develop and, with a few exceptions, are not guaranteed to generate equal returns in a market geared to high-volume, low-value tests.

In order for molecular biomarker-based diagnostics to provide benefit to the health care industry there is a clear need for identification and development of new business models. The global biomarker market for companion diagnostics and use of biomarkers in pharmacogenetics activities (see Table 1) reached USD 5.6 billion in 2007 and is forecast to grow. The market for standalone diagnostics based on novel molecular biomarkers is not well developed. However if the growth in companion based diagnostics is viewed as indicative of a general trend towards acceptance of the utility and value of new molecular biomarker-based technologies in the health care system, the market may yet develop, offering economic incentive for the development of business models for biomarker-based diagnostics.

Table 1. Revenue forecast for global biomarker markets by segment, 2005-2012

Market segments	2005	2006	2007	2012	CAGR (%) 2007-12
Clinical trials	0.4	0.5	0.6	1.8	**23.5**
Clinical practice (MDx)	1.7	1.9	2.3	5.2	**17.5**
Total	**4.2**	**4.8**	**5.6**	**12.8**	**18**

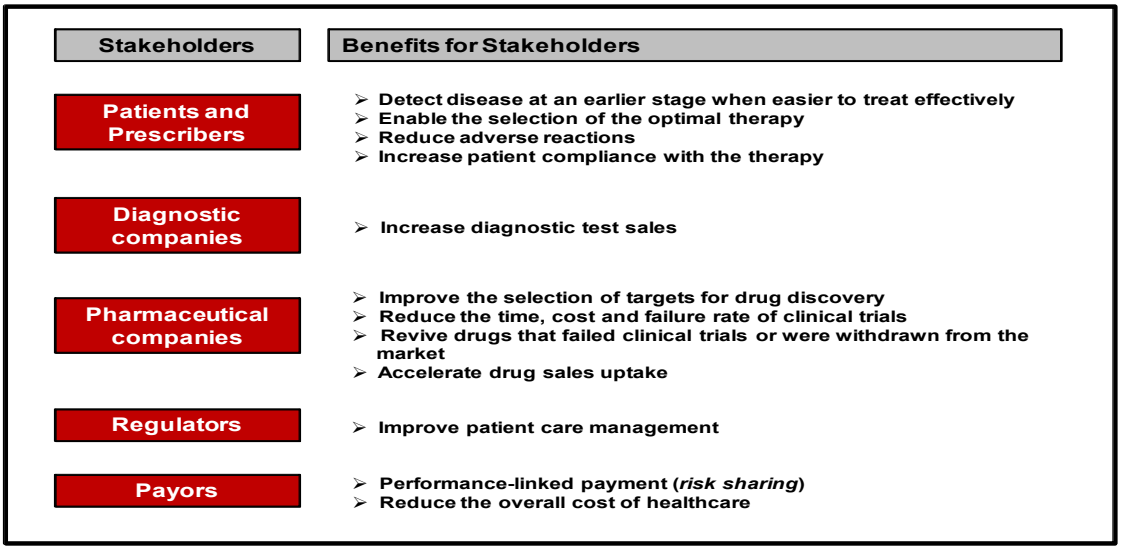
Source: Discussion paper, OECD Workshop on "Policy Issues for the Development and Use of Biomarkers in Health" 2008.

Challenges and opportunities in the diagnostics industry

Development of business models for an emerging diagnostic industry will involve challenges and considerations quite different from those of the pharmaceutical industry. While the pharmaceutical industry considers new models to adapt to changes in existing markets and better understanding of disease and disease processes, the diagnostic industry must develop business models to meet smaller or relatively underdeveloped markets. This is especially true for complex biomarker-based tests involving many biomarkers. The lack of a well established business models for these tests, and apparent 'undervaluation' of diagnostics within the health care system, especially compared to the much larger pharmaceutical industry, represent significant challenges to many within the diagnostics industry. This is of course above and beyond challenges to development of biomarker-based diagnostics discussed in previous chapters. Addressing these challenges can be time-consuming and costly.

The diagnostics industry will need to adopt business models which will allow them to attain commercial viability while working with stakeholders (see Figure 2) to demonstrate the benefits, and value of new medical tests and to create a market which considers diagnostics on a health care value rather than a cost basis. This will continue to be important as more complex diagnostics tests are developed and as the resulting diagnostics tests become more costly to develop and validate.

Figure 2. Overview of molecular diagnostic test benefits for each stakeholder



Source: Discussion paper, OECD Workshop on "Policy Issues for the Development and Use of Biomarkers in health" 2008.

Current diagnostic reimbursement levels and economic models do not allow most diagnostic companies to finance the demonstration of clinical utility on their own. Diagnostic companies involved in biomarker discovery or development are thus often challenged to find collaborative business models in order to bring their products to the market.

Emerging business models for comparison diagnostics

For the development of companion diagnostics, pharmaceutical companies are often partners of choice. Pharmaceutical companies have a growing interest in the development of companion diagnostics and may be willing partners in their development. This partnership may confer a number of benefits to the diagnostic company. For instance, linkage of a specific companion test and drug may facilitate regulatory approval and uptake in the clinical setting. Diagnostic companies may also benefit from established commercialisation pathways and processes which enhance the overall value of the pharmacogenetic test. However, collaboration with a pharmaceutical company may create additional risks for the diagnostic company: interest alignment, time-to-market alignment and dependence on successful drug development.

Some biotechnology companies have found success in developing and marketing complex biotechnology tests themselves and now operate across the biomarker discovery-development-commercialisation spectrum. Increasingly well established, these companies may collaborate with pharmaceutical companies, other diagnostic companies or research companies to develop companion diagnostics. The challenge to diagnostic companies is to negotiate deals in which they leverage their intellectual property and investment to capture a significant share of the value created.

Emerging business models for stand-alone diagnostic tests

Diagnostics tests developed for diagnosis and disease management, rather than to guide drug delivery are generally complex tests that analyse multiple biomarkers to produce information-rich diagnostics results. These tests can provide important information on disease risk factors and disease susceptibility allowing for early intervention and management. Controlling and managing a disease prior to progression to the acute or chronic phases can have a positive impact on patient outcomes and on the indirect and direct costs associated with disease progression. However as they are not linked to a specific drug, these kinds of tests are often developed without the support of a pharmaceutical company and are usually marketed to clinical or health care providers directly. This business model thus relies on marketing a superior multi-parametric predictive value to clinicians or health care providers and requires a high price to enable self-financing of the clinical utility phase. Indeed the market for this type of test is not well established—and there are few examples of companies succeeding in this space.

Some companies have begun marketing complex biomarker-based diagnostic tests directly to consumers. The advertising of health-related products, drugs and tests (*e.g.* pregnancy tests) in mainstream media, directly to consumers is a well established multibillion dollar a year industry. However despite efforts to market direct-to-consumer (DTC) biomarker-based genetic tests by several companies over the last decade, a viable business model is yet to emerge.

Some DTC tests for biomarker panels which have been actively marketed have been criticised by federal agencies and consumer groups alike for reasons from inaccurate advertising, providing incomplete or inaccurate information, failing to accurately convey risk information, to absence of necessary scientific support. The genetic testing industry as a whole has also been criticised more generally for lack of regulation. In addition there are privacy concerns related to the use of genetic information gathered from customers. Nevertheless companies such as Navigenetics and 23andMe continue to market DTC genetic testing. The long term viability of this business model will depend in part on how these companies respond to this criticism.

Vertical integration: a factor in development of business models for diagnostic companies

As the market for molecular biomarker-based diagnostic tests grows, three main business models based on integration strategy are emerging. The first business model is the case of a diagnostic company that only does research. The company Genizon Biosciences is a good example of this type of company. Genizon Biosciences identifies new therapeutic targets and potentially interesting biomarkers for its clients, the pharmaceutical companies, or other diagnostic companies marketing directly to clinical or health care providers. It receives fees for its research and can expect to get royalties of up to 2-3% on marketed products.

The second business model goes a step further requiring a combination of proprietary technology and demonstration of clinical and economic benefits. Successful companies will focus on tests that address an underlying biology or disease state, and have access to high-throughput techniques and bioinformatics technologies to identify valuable biomarkers. Diagnocure is an example of this model where the technology is licensed. It carries out the proof-of-concept work and develops the prototype; final development and commercialisation are completed by another company with more resources and a robust, proven technology platform.

The third business model is that of a vertically integrated standalone company. Genomic Health and Myriad Genetics are examples of this business model as they are each able to manage all the steps from research to test commercialisation as well as have their own sales forces.

As public health expenditures reach all-time peaks around the world, some components of personalised medicine such as predictive biomarkers may be perceived as unnecessary costs when compared to therapeutics. Further, since novel biomarker-based diagnostics are, to most investors, lower value than novel therapeutics, diagnostic companies may have more difficulties raising private funds (*e.g.* venture capital) to prove clinical utility, thereby impeding their path to clinical adoption. Small and medium-sized enterprises and start-up companies involved in biomarker discovery may find it especially difficult to develop biomarker products and to reach markets with these products.

Ultimately, the success of the different business models will depend on expansion of the market for diagnostic tests to include high-value, multi-parameter biomarker-based diagnostics. The development of this market will require re-evaluation of diagnostic tests in the health care context, a task which will involve many stakeholders and will likely involve some form of Health Technology Assessment or health economic assessment. There is a role for governments in the co-ordination of such assessments. In addition, as for the pharmaceutical industry, there may be some contexts in which public policy intervention may be warranted to improve the development and commercialisation of biomarkers so crucial to the delivery of personalised medicine for all sorts of diseases and conditions.

As biomarker discovery and development outpaces clinical adoption, some novel biomarkers with proven clinical validity and clear clinical value may still not be made available to patients. This situation may arise often and may warrant public policy involvement to support development of such biomarkers, when no alternative self-evident business model exists.

Conclusions

Diffusion of the benefits of biomarker-based technologies and products within the health care system will depend in large part on development and adoption of new business models by pharmaceutical and diagnostic companies. Development of new business models for pharmaceutical and diagnostic companies alike will be disruptive. The extent to which new models emerge, and the type of business models which emerge, will depend on the way in which various companies view the opportunities presented by biomarkers.

Pharmaceutical companies, established diagnostic companies, and emerging biomarker-based companies have different incentives to develop and adopt new business models and will likely approach the opportunity differently. Still there may be some applications for which no industry perceives sufficient opportunity or incentive to develop viable business models for some biomarker-based products. In these cases government support may be required to ensure the benefits of biomarkers are realised within the health care system.

Biomarker-based opportunities for improved drug development will likely be seen as attractive by pharmaceutical companies seeking to reduce reliance on a blockbuster model of drug development and will provide an incentive to adoption of new business models. Opportunities related to development of companion diagnostics are expected to provide further incentive to develop new business models. These new business models may involve new collaborations with research laboratories, diagnostic companies or other technology-based companies.

The diagnostic industry will face different challenges in identifying appropriate business models to drive development and delivery of biomarker-based products within the health care setting. While the growing field of companion diagnostics provides some incentive for the industry, many new companies will be unable to fund the unavoidable clinical utility milestone themselves, and may seek partnership with existing pharmaceutical or diagnostic companies. Each of the different partnering options has distinct business model implications, and value preservation will remain a challenge for each partner.

Outside the field of companion diagnostics however, diagnostic companies may perceive little incentive to develop diagnostic tools for early detection and prevention of disease. Diagnostic companies may be financially challenged to prove the clinical utility of their product. Or they may not perceive sufficient market value for reasons of size of reimbursement level. Indeed, proving the value of biomarker-based diagnostic tests to actors in the health care system remains a challenge for diagnostic companies. Governments seeking to benefit from improved diagnosis enabling early

intervention and disease management need to find a way to evaluate the value of novel biomarker-based tests to the health care context. As discussed in Chapters 2 and 3, this may well involve development of some form of health technology assessment and participation of many stakeholders.

As biomarker discovery clearly outpaces clinical adoption it will be important to find new business models which can bring the technology to market. This will likely involve rupture and rethinking of existing models and creation of new models. Development of new business models may be aided by a transparent and consistent regulatory and reimbursement system appropriate for biomarker-based technologies. It will also require expansion of the existing market for diagnostic tests—this may be achieved in part by promoting the potential value of these tests to patients and the health care system more generally. In some instances, the market may not provide significant incentives for companies to develop biomarker-based products and services. In these cases, public policy intervention may be warranted to ensure the promise of biomarker-based personalised medicine are realised.

Conclusion

Arising from a decade of genomics research and development, novel molecular biomarkers are poised to drive a shift in the practice of evidence-based medicine. These biomarkers are enabling a better understanding of disease and disease processes at the molecular level and are the foundation on which personalised medicine is being built. Translation of new molecular knowledge into biomarkers for disease is allowing proactive identification of disease, development of new drugs and the targeting of treatments so that individual patient treatment is safer and more efficacious than before. This new trend in medicine has already provided significant proof of its efficiency and promises to improve health outcomes and reduce socio-economic impact of diseases. For governments in OECD and non-OECD countries alike that are challenged with balancing steadily rising health care costs, and maintaining the wellness of its growing and aging populations, the promise of biomarkers cannot be realised soon enough.

To deliver on the promises of biomarker-based tests and products, there are still a number of barriers which need to be addressed. Some of these could directly benefit from an adaptation of health and innovation policies, others are linked to market evolution and industry adaptation. This chapter provides an overview of some of the ways policy makers can facilitate the translation of biomarker opportunities to applications in the clinical setting.

Supporting large-scale networks and infrastructures for biomarker discovery and development

The translation of molecular information into a biomarker for a particular disease state can be an expensive and time-consuming process. It typically involves large scale association studies in which candidate biomarkers are studied in populations with a particular phenotype (*e.g.* disease state) in order to confirm a specific biomarker-disease association. These studies involve collection and analysis of large amounts of patient data and are typically beyond the resources of any one stakeholder. The need to develop infrastructure to generate, manage and share this information has been identified, and a number of initiatives, especially public-private partnerships, have arisen to encourage or facilitate biomarker discovery and development.

These knowledge sharing infrastructures are crucial to biomarker discovery and development and continued support for such initiatives is needed. At the same time, there is an opportunity to improve these infrastructures and indeed, to accelerate biomarker development. Greater communication and interaction between knowledge sharing infrastructures will minimise redundancy and duplication and may increase efficiencies. At the international level increased collaboration may provide access to other populations in which biomarkers can be validated, enabling diffusion of biomarker-based tests to developing countries. Finally, harmonisation of standards for data generation and knowledge management will enable sharing of knowledge and co-development of necessary databases. It may also reduce the downstream costs associated with providing evidence of the clinical validity of biomarker-base tests. Governments may thus enable development of biomarkers by supporting and strengthening infrastructures for knowledge sharing, and encouraging harmonisation and collaboration between initiatives both nationally and internationally.

Co-ordinating creation of an evidence base

Application of biomarker-based tests in the health care setting will require prior demonstration of the analytical and clinical validity, and clinical utility of new biomarker-based tests. This information is vital to regulators seeking to determine the quality, safety and efficacy of the test; physicians choosing to use a test; agencies determining appropriate reimbursement levels; and industry and academic researchers wishing to ensure their innovations are developed efficiently and used effectively. There is a clear need to develop standards and a structure for an evidence base by which the clinical validity and utility of biomarker-based tests can be demonstrated.

Creation of an evidence base is a complex undertaking, requiring collection and analysis of a range of biological, molecular and patient data, from, and by, different stakeholders. Development and use of an evidence base also raises a number of ethical, legal and social implications which will need to be addressed. It is clear that co-ordination of numerous stakeholders will be required to develop a structure and associated standards for these evidence bases. Several model structures and processes have been developed which may be used as a starting point for this work. Nevertheless, governments will need to co-ordinate the identification of any knowledge gaps to make it clear where evidence is lacking and what additional data are required.

There are a number of additional challenges associated with the construction and management of an evidence base for biomarkers, including: determining the scope of the evidence base (*i.e.,* national *versus* international); its funding; its format and structure; the participants and the responsibilities for setting up and maintaining an evidence base; and the oversight and quality control of the evidence base. It will be critical to bring these elements together in a rationalised and harmonised way and governments may have a role to play in co-ordinating this process.

Adapting regulatory and reimbursement policies

If the benefits of biomarker-based diagnostic tests are to be realised, regulatory and reimbursement processes must be adapted to the specificities of novel biomarker-based clinical tests. The current regulatory process and reimbursement procedures were developed for simple diagnostic tests or drugs, and are not well optimised for the characteristics of molecular biomarker-based tests. This is slowing uptake of these technologies in the clinical context and worse, is discouraging investment in development of new biomarker-based tests. The development of regulatory processes for biomarker-based diagnostic tests which are evidence-based and transparent may help remove this barrier. Development of such regulations will require *i)* clarification of which regulatory procedures will best help to oversee the development, performance, safety and utility of new tests; *ii)* clarification about what new oversight frameworks should be developed and implemented (without blocking innovation and slowing down the translation of useful biomarkers into medical practice); and *iii)* international harmonisation so as to minimise regulatory barriers and facilitate trade.

To provide predictability for the reimbursement of diagnostic tests and to stimulate the development of biomarker-based tests with clear clinical utility, reimbursement should also be evidence-based and transparent, and should reflect the value of the test to the health care system. Determining the health care value of biomarker-based tests is difficult, and should involve some form of health economic analysis or Health Technology Assessment. It will be important to identify the sort of evidence necessary for such analyses and a means to share this information. Much of this information (*e.g.* cost savings, infrastructure costs) may be country, or jurisdiction, specific. However information of a molecular nature, like data from disease association studies or genotyping data used to show clinical validity or utility, might usefully be shared amongst countries. Sharing of data across borders may reduce the costs of generating or collecting such data but will require co-development of appropriate standards for data collection and sharing.

In both reimbursement and regulation systems, there is already much discussion about what sorts of adaptations are necessary for biomarker-based tests. Better communication between test manufacturers (and the pharmaceutical industry in the case of companion diagnostics), regulatory agencies and health care payers, upstream to the demand for approval or reimbursement will be key to better anticipate needs and problems, inform procedures and knowledge about how to adapt policies in the future.

Communication and sharing of knowledge

Within the clinical setting, diffusion of biomarker-based tests is driven by the physician or primary care provider. These front line practitioners seek to provide the best possible care for patients based on the best available evidence. Physicians are more likely to use biomarker-based testing if they know the value of the test to the patient and value of the test in guiding their treatment decisions. Accordingly, physicians with a good understanding of genetics and biomarker technologies are more likely, all things being equal, to incorporate these tests into their practice of evidence based medicine.

Networks and other mechanisms that communicate knowledge about biomarkers, advances in biomarker research, or evidence of the clinical utility of biomarker-based tests should, thus, be supported and strengthened. A number of initiatives now exist to educate current and future medical practitioners. These programmes are also expanding to include regulators, and other health care professionals to help inform their decision-making regarding biomarker-based technologies. Dissemination of information on biomarkers to patients is equally important and government should work with stakeholders to develop appropriate communication strategies.

Patients see personalised medicine and novel molecular tests as a normal evolution of medicine and realise the potential benefits that it could bring to the management of their health. Communication of information on biomarker-based tests to patients provides an important opportunity to inform patients of medical advances and to engage them as active partners with physicians in managing their

health. However an increasingly well-informed patient population is highlighting concerns regarding patient privacy and confidentiality of data. There is a need to ensure these concerns are addressed in order to maintain patients' confidence and acceptance of these tests in the clinical setting. There are a number of policy instruments available to governments which may guide development of appropriate measures to address these concerns.

Supporting technology convergence

Novel biomarker-based diagnostics are more likely to be integrated and broadly diffused in the clinical setting if they are inexpensive, simple to use, and provide information which can be used immediately to guide diagnosis or treatment. Use of near-patient, or point-of-care tests will allow for faster diagnosis and treatment, and may also be safer for the patient, reducing the likelihood of sample mix-up in an off-site laboratory. They may also further reduce health care costs by reducing the need for a follow on visit.

Development of such diagnostics, especially for complex biomarker-based tests, will require advances in new detection and amplification technologies involving nanotechnology, engineering and biochemistry to enable rapid, accurate and sensitive diagnostics. Development and application of such convergent technologies should be encouraged and supported through development of novel infrastructures or collaborative mechanisms which allow sharing of ideas and creation of synergies across these different fields.

Development of new business models

As the promise of biomarkers evolves into clinical application, the market for drugs and diagnostic is changing. The pharmaceutical and diagnostic industries are accordingly seeking new viable business models to adapt to evolving market opportunities. Within the pharmaceutical industry, biomarkers provide opportunity for companies to improve their drug development process and to improve the safety and efficacy of drugs. Opportunities for companion diagnostics exist for both pharmaceutical and diagnostic companies. However, opportunities or incentives for development of stand-alone diagnostics may be difficult to see and may pose a challenge to uptake of biomarker-based products with clinical validity and clear clinical utility. At present, while some biomarker-based tests have reached market, a clear business model by which biomarker-based tests can be efficiently brought to the market has not yet emerged.

Development and application of biomarker-based technologies in the clinical setting will depend on the development of viable business models by industry. These new models will be driven in large part by the way in which the pharmaceutical and diagnostic industries perceive the market opportunities and other associated incentives. Government has a role to play in monitoring progress of the associated industries to ensure there is sufficient incentive to drive development of new business models. Even so, there may be some instances in which market conditions may not be conducive to development of some biomarker-based tests of products. These situations may warrant policy interventions to enable the development of biomarkers with a clear clinical value and proven clinical validity in the health care setting.

Notes

1. *www.oecd.org/document/13/0,3343,en_21571361_44315115_46092237_1_1_1_1,00.html* (accessed 30 November 2010) Issues for Discussion, OECD Health Ministerial meeting, 7-8 October 2010.
2. Pharmacogenetics deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a medicinal product's efficacy or toxicity. Pharmacogenomics is the broader application of genomic technologies
3. Omics is a general term for a broad discipline of science and engineering for analysing the interactions of biological information objects in various 'omes'. These include genome, proteome, metabolome, expressome and interactome. The main focus is on: *i)* mapping information objects such as genes, proteins, and ligands; *ii)* finding interaction relationships among the objects; *iii)* engineering the networks and objects to understand and manipulate the regulatory mechanisms; and *iv*) integrating various omes and omics subfields (from *www.omics.org*).
4. IVDMIA combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (*e.g.* a "classification", "score", "index", etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.
5. *www.oecd.org/document/13/0,3343,en_21571361_44315115_46092237_1_1_1_1,00.html* (accessed 30 November 2010) Issues for Discussion, OECD Health Ministerial meeting, 7-8 October 2010.
6. The OECD has done some recent work in this area—the following publication provides some further reading in this regard: OECD (2011) Collaborative Mechanisms for Intellectual Property Management in the Life Science, OECD, Paris, France.
7. The challenge of governance of health innovation was the focus on the OECD workshop "Better Health through Bio-medicine: Innovative Governance" held in Berlin in 2010. *www.oecd.org/document/29/0,3746,en_2649_34537_45825245_1_1_1_1,00.html*
8. See *www.ich.org/.*
9. See *www.ghtf.org/.*
10. The reimbursement Landscape for Novel Diagnostics (2010) Health Advances *www.bio.org/healthcare/personalized/Health_Advances&BIO_Novel_Diagnostics_Reimburs_20110103.pdf*
11. *www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm* (accessed January 2011)
12. See: Diagnostic Technology: Point –of-care test (POCT) for C-reactive protein (CRP) Horizon Scan Report 0017 (28 July 2011) and references within: *http://madox.org/horizon-scanning-reports/20110017/point-of-care-test-poct-for-c-reactive-protein-crp* (accessed September 2011)
13. Instruments address elements of such issues namely: Guidelines for Quality Assurance in Molecular Genetic Testing (2007); OECD Best Practice Guidelines on Biological Resource Centres (2007); and OECD Guidelines on Human Biobanks and Genetic Research Databases (2009a)
14. Direct-to-consumer Genetic Testing: Report on the Secretary's Advisory Committee on Genetics health and Society (April 2010) http*://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_DTC_report_2010.pdf*
15. The sequencing of the human genome and the International HapMap effort first focussed on Caucasian populations.
16. For example, the Mexican Genome Diversity Project, a flagship project of the INMEGE, Mexico's National Institute of Genomic Medicine, set out to develop a genetic map of the mestizo population in Mexico to help extend applicability of biomarker-based tests in the Mexican population.

17 *http://pgeni.unc.edu/site/index.php/case-studies.html* (accessed January 2011)

18 www.*reuters.com/article/2010/06/27/us-pharmaceuticals-rd-idUSTRE65Q3IM20100627* (accessed September 2011)

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