Australian Centre for Health Research

Improving the Quality Use of Medicines in Australia

Realising the Potential of Pharmacogenomics

October 2008

Acknowledgements

This report was completed by Deloitte Economics in collaboration with Dr Stan Goldstein of SRGB Solutions and Mr Malcolm Crompton of Integrated Information Solutions.

The project team would like to thank the following stakeholders for their time and input into the project:

Ms Diana Macdonell	Department of Health and Ageing, Pharmaceuticals Benefits Branch
Dr John Primrose	Department of Health and Ageing, Pharmaceuticals Benefits Branch
Ms Elisabeth Haslett	Department of Health and Ageing, Medical Benefits Branch
Dr David Barton	Department of Health and Ageing, Medical Benefits Branch
Mr Paul Fennessy	Department of Human Services, Victoria
Ms Jenny Everist	Department of Human Services, Victoria
Mr Ashley Fletcher	Department of Human Services, Victoria
Ms Amanda Capels	Department of Innovation, Industry and Regional Development
Dr Annette Gross	GlaxoSmithKline
Dr Stephen Blamey	Medical Services Advisory Committee
Dr Lloyd Sansom	Pharmaceutical Benefits Advisory Committee
Dr David Bowtell	Peter MacCallum Institute
Dr George Koumantakis	Roche Diagnostics
Dr Simon Mallel	Royal Perth Hospital
Dr Winston Liauw	St George Hospital
Dr Ajeet Singh	Royal Australian College of General Practitioners
Ms Shelley Tang	Therapeutic Goods Administration
Ms Robin Wood	Therapeutic Goods Administration
Dr Andrew Somogyi	University of Adelaide
Dr Evan Begg	University of Otago
Dr Michael Murray	University of Sydney
Dr Ric Day	University of NSW

Contents

Statement of Responsibility **8**

Acronyms **9**

Glossary **10**

Executive Summary **12**

1 Pharmaceuticals in Australia **28**

1.1 Pharmaceuticals in Australian healthcare 28

1.2 Optimising expenditure on pharmaceuticals in Australia 30

1.3 Current barriers to the quality use of medicines 33

1.4 Economic costs of sub-optimal use of medicines 36

2 Pharmacogenomics: using diagnostics for safer, more effective care **37**

2.1 What is Pharmacogenomics? 37

2.2 Emerging pharmacogenomics technologies 38

2.3 The translation of pharmacogenomics into clinical practice 41

2.4 Regulation and reimbursement of pharmacogenomics 42

2.5 Technological change and the future of pharmacogenomics 46

3 The health and economic impacts of pharmacogenomics **49**

3.1 Benefits of pharmacogenomics technologies for patients and governments 49

3.2 Improving care for patients with colorectal cancer 50

3.3 Improving outcomes for patients on anti-coagulants 52

3.4 Improving care for patients with inflammatory bowel disease 54
3.5 Improving outcomes for patients with HIV 55
3.6 Improving care for patients with depression 57
3.7 Improving care for patients with breast cancer 58
3.8 Improving health outcomes for patients on statins 60
3.9 Exploring the full economic impact 61

4 Barriers to pharmacogenomics uptake 66
4.1 Regulatory challenges 66
4.2 Reimbursement challenges 70
4.3 Barriers to research translation 71
4.4 Privacy, legal and ethical issues 72
4.5 ICT infrastructure 80

5 Implementing pharmacogenomics in Australia: a roadmap for Australian governments 81
5.1 Creating a framework for pharmacogenomics uptake in Australia: overview of recommendations 81
5.2 Recommendation 1: Enhance horizon scanning and reporting requirements 83
5.3 Recommendation 2: Expand the responsibilities of the National Medicines Policy Executive to include pharmacogenomics recommendations 83
5.4 Recommendation 3: Create a pharmacogenomics advisory body 84
5.5 Recommendation 4: Reform reimbursement for pharmacogenomics tests 86
5.6 Recommendation 5: Develop pharmacogenomics clinical guidelines 86
5.7 Recommendation 6: Develop ICT decision support tools and privacy standards 87
5.8 Recommendation 7: Invest in education and training for healthcare providers and the public 87

Appendix A **88**
References 88

Statement of Responsibility

This Scoping Study was prepared for the Australian Centre for Health Research solely for the purpose of analysing the potential health and economic impacts of pharmacogenomics and identifying a roadmap for implementation as set out in our engagement letter dated 7 August 2008.

In preparing this Report we have relied on the accuracy and completeness of the information provided to us by the ACHR and from publicly available sources. We have not audited or otherwise verified the accuracy or completeness of the information. We have not contemplated the requirements or circumstances of any one other than the ACHR.

The information contained in this Report is general in nature and is not intended to be applied to anyone's particular circumstances. This Report may not be sufficient or appropriate for your purposes. It may not address or reflect matters in which you may be interested or which may be material to you.

Events may have occurred since we prepared this Report which may impact on it and its conclusions.

No one else, apart from ACHR, is entitled to rely on this Report for any purpose. We do not accept or assume any responsibility to any one other than AHRC in respect of our work or this Report.

Deloitte is a member of Deloitte Touche Tohmatsu (a Swiss Verein). As a Swiss Verein (association), neither Deloitte Touche Tohmatsu nor any of its member firms has any liability for each other's acts or omissions. Each of the member firms is a separate and independent legal entity operating under the names 'Deloitte,' 'Deloitte & Touche,' 'Deloitte Touche Tohmatsu,' or other related names. Services are provided by the member firms or their subsidiaries and affiliates and not by the Deloitte Touche Tohmatsu Verein.

Acronyms

ADR	Adverse Drug Response
AHMAC	Australian Health Ministers' Advisory Council
CISH	Chromogenic In Situ Hybridization
CTEPC	Clinical, Technical and Ethical Principal Committee
CYP450	Cytochrome P450
DNA	Deoxyribonucleic Acid
DoHA	Department of Health and Ageing
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FISH	Fluorescent In Situ Hybridization
HealthPACT	Health Policy Advisory Committee on Technology
IHC	Immunohistochemistry
MBS	Medical Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NRTI	Nucleoside Reverse-Transcriptase Inhibitor
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase Chain Reaction
PGx	Pharmacogenomics
SNPs	Single Nucleotide Polymorphism
SSRI	Selective Serotonin Reuptake Inhibitor
TGA	Therapeutic Goods Administration
TPMT	Thiopurine methyltransferase
VKORC1	Vitamin K Epoxide Reductase Enzyme

Glossary

Allele	One of two or more alternative forms of a gene that arise by mutation. An example is the gene for blossom color in many species of flower — a single gene controls the color of the petals, but there may be several different versions (or alleles) of the gene. One version might result in red petals, while another might result in white petals. The resulting color of an individual flower (the phenotype) will depend on which two alleles it possesses for the gene and how the two interact.
CYP2D6	The CYP2D6 is the source of the sparteine/debrisoquine oxidation polymorphism. Seven to ten per cent of Caucasian populations are 'poor metabolisers'. The frequency of poor metabolisers in Asian ethnicities is only about two to three per cent. CYP2D6 has approximately 80 known variants, mainly in the form of single nucleotide polymorphisms in the gene. CYP2D6 oxidises approximately 60 drugs including all of the tricyclic antidepressants, some antipsychotics, selective serotonin reuptake inhibitors, antiarrhythmics, beta-adrenoceptor blockers and opiates.
Cytochrome P450 (CYP450)	Most drugs are lipophilic chemical compounds that are mainly eliminated by oxidation, catalyzed by the cytochrome P450 (CYP450) enzyme system in the liver. The human CYP450 family of genes consists of 57 CYP450 genes and 33 pseudogenes organized in 18 families and 42 subfamilies. CYP450 play a key role in the metabolism of more than half of all drugs and also represent the most important way for detoxification of many drugs.
Genome	A genome is all of the genetic information or hereditary material in an organism. The genomes of individuals within a species are more similar to each other than they are to the genomes of individuals of other species.
Genotype	A genotype is the genetic constitution of an individual organism. This is the 'internally coded, inheritable information' carried by all living organisms. Genotypes are the stored information that is used as a 'blueprint' or set of instructions for building and maintaining a living creature. These instructions are found within almost all cells, they are written in a coded language (the genetic code), they are copied at the time of cell division or reproduction and are passed from one generation to the next ('inheritable'). Genotypes control everything from the formation of proteins, to the regulation of metabolism and synthesis.
Metabolite	A substance formed in or necessary for metabolism.
Pharmacodynamics	Pharmacodynamics is the study of what a drug does to the body (e.g., by mimicking or inhibiting normal biological or physiological reactions by a reaction that depresses activity,

	stimulates activity, destroys cells or replaces a substance).
Pharmacogenetics	Pharmacogenetics is the science about how heritability affects the response to drugs.
Pharmacogenomics	Pharmacogenomics is the science of how the systematic identification of all the human genes, their products, inter-individual variation, intra-individual variation in expression and function over time may be used both to predict the right pharmaceutical treatment in individual patients and to design new drugs.
Pharmacokinetics	Pharmacokinetics is the study of what the body does to a drug (e.g., through absorption, distribution, metabolism, and excretion).
Phenotype	This is the 'outward, physical manifestation' of the organism, or the expressed characteristics of a gene. These are the physical parts, the sum of the atoms, molecules, macromolecules, cells, structures, metabolism, energy utilisation, tissues, organs, reflexes and behaviors — anything that is part of the observable structure, function or behavior of a living organism.
SNPs	The 'letters' of DNA are molecules called nucleotides: adenine, cytosine, guanine, and thymine (A,C,G,T) strung together in long chains called sequences. The occasional single-letter differences that distinguish DNA among people are called single-nucleotide polymorphisms (SNPs).

Executive Summary

Pharmaceuticals are an integral component of a high quality healthcare system in Australia. Advances in pharmaceutical technologies have contributed to substantial improvements in Australians' quality of life and life expectancy. New medicines have contributed to a significant increase in cancer survival rates, a reduction in deaths from cardiovascular disease and the effective eradication of many infectious diseases that were once the primary burden of disease for Australians. Improvements in the health and welfare of patients have supported increased labour force participation and productivity, which in turn have generated major returns to communities in the form of economic growth. Moreover, treatment of disease with pharmaceuticals has been highly cost-effective; research has shown that for every US$1 increase in spending on medicines there has been a US$3.65 saving in hospital care expenditure. This has facilitated the efficient allocation of scarce public funds, which has, and continues to contribute to the strong economic growth and prosperity of Australian communities.

As a consequence of the potential for significant improvements in patients' quality of life and their relative cost-effectiveness as a therapy, the use of pharmaceuticals in Australia has been increasing rapidly, with pharmaceuticals accounting for an increasing proportion of total health expenditure. Pharmaceuticals currently account for more than 13 per cent of total healthcare expenditure ($11.5 billion) and are projected to grow significantly over the coming decades. Pharmaceutical expenditure accounts for 0.7 per cent of GDP today and is projected to grow to 2.5 per cent of GDP by 2046-47 by the 2007 Intergenerational Report.

Current model of pharmaceutical care: one size fits all

In spite of the significant improvements in health and wellness that have been realised through the use of medicines, many patients today are prescribed pharmaceuticals that are either not effective or have bad side effects.

The current model for drug development is, and has been, a 'one size fits all' model for pharmaceutical therapy. In the current 'blockbuster' model of drug development and pharmaceutical care, drugs are developed for large patient groups displaying a particular physical characteristics or 'phenotypes', such as high blood pressure. Doctors prescribe patients medicines from broad therapeutic groups that have been shown to treat patients displaying that characteristic. Patients experience varying levels of efficacy or side effects depending on the particular medicine (molecule) selected by the doctor. It is not possible to know how particular patients within the population will respond to different molecules; if one does not work, the doctor will try a different molecule. On average, patients in the phenotype population realise 'similar' health outcomes, such as a reduction in their blood pressure.

Prescribing practices today are therefore premised on the idea that the medication will provide 'similar' health outcomes 'on average' for all patients displaying that characteristic. There are significant differences, however, in how patients with a common condition respond to some medicines. Most are likely to respond as expected. But some may display side effects, which can be severe and result in hospital admission, while others may not respond to the treatment at all.

To date there has been no simple way or technology available to determine whether people will respond well, poorly, or not at all to a medication. As a result, doctors must use 'trial and error', empirical methods to find the drug that works best for the patient. Often, a patient must return to their doctor over and over again until the doctor can find a drug that is right for them. Patients often discontinue therapy as a result of side effects or frustration. The technological inability to identify which patients will respond to which medicines significantly limits the optimal use of pharmaceuticals, which is manifest in:

- adverse drug responses;
- poor response or no response to drugs among some patients;
- poor patient compliance; and
- poor access for some individuals if pharmaceuticals fail cost-effectiveness assessments based on 'population' analyses.

These symptoms of sub-optimal use of pharmaceuticals cost Australians billions of dollars in unnecessary spending across a variety of care settings and poor health outcomes.

- Wasting expenditure on drugs that are not appropriate for a patient diverts scarce resources away from other, better uses, and depresses economic growth; potentially half of all medicines are estimated not to be effective for patients.
- Adverse drug responses have been implicated in between two to four per cent of all adverse events, with the average cost of adverse drug events has been estimated to be approximately $14,027 per event.
- Poor patient response, compliance or access to life-saving drugs can reduce patients' quality of life and increase their use of other healthcare resources, resulting in lower workforce participation and productivity than would otherwise have been the case and higher costs of care to the community.

Improving the quality use of medicines: pharmacogenomics

While there are a number of reasons for sub-optimal pharmaceutical use in Australia, recent research has shown that more often than not poor drug response is due to the presence of particular genetic characteristics or 'biomarkers' that affect how an individual responds to a medicine. Some people may have biomarkers that prevent their body from metabolising a drug, which raises the risk of poisoning the patient and adverse events, while others may have biomarkers that mean they will process the drug too quickly, such that it will not have any benefit for the patient.

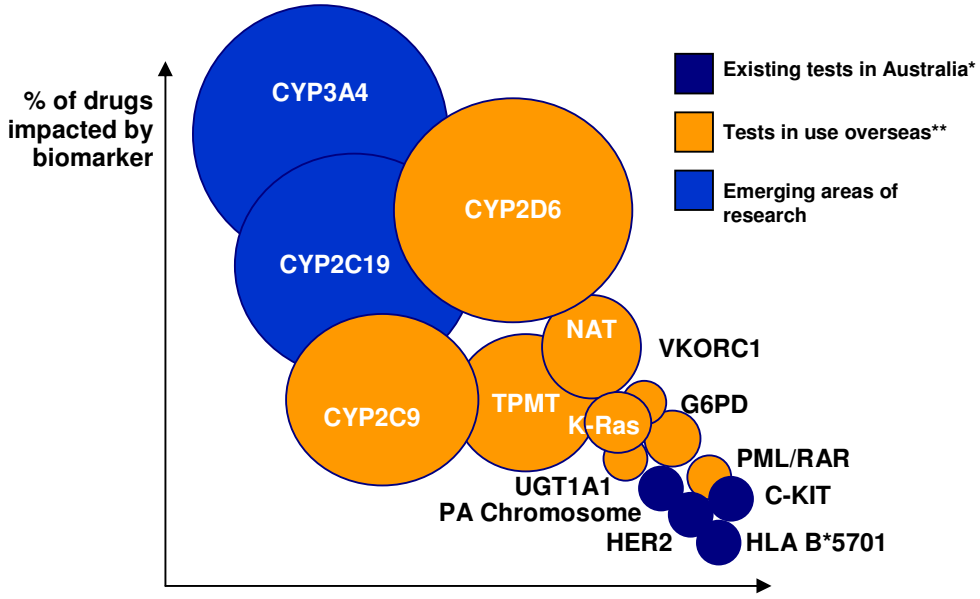
Pharmacogenomics (PGx) is a medical science arising from the convergence of advances in pharmacology, genetics and, more recently, human genomics. PGx enables doctors to examine the presence of individual biomarkers that will dictate drug response and to know *before prescribing a medicine* whether the patient will have a good response to a drug, a poor response to a drug, or no response at all. With PGx, doctors can test for biomarkers *first* and prescribe the safest, most effective medicines available the first time.

While PGx technologies are only just beginning to reach clinical settings, there have been a few notable successes. Foremost among these has been the use of PGx to target the prescribing of trasutuzmab (Herceptin®). Other examples include other anti-cancer drugs gefitinib (Iressa®) and imatinib (Gleevec®), as well as testing to improve the prescribing of HIV therapy abacavir (Ziagen®).

Beyond these major examples, the translation of PGx into clinical practice is only beginning to emerge. There is currently a race to catalogue as many biomarkers as possible, both overseas and in Australia. Australian researchers, for example, were critical in establishing the validity of biomarkers for HIV therapies and a number of Australia's major research institutes are focused on PGx research, particularly in oncology. In total worldwide spending on new PGx technologies is projected to be more than $3.7 billion in 2009, having increased at an average annual growth rate in R&D expenditure of 24.5 per cent since 2003.

Research in PGx is currently focused to a large extent on drug metabolising enzymes, and in particular, the CYP450 gene family. The reasons for this are several. CYP450 biomarkers are highly polymorphic or variable, and therefore drug response varies significantly between patients. Second, most drugs are metabolised by these enzymes; approximately 25 per cent of all prescription drugs are metabolised by either CYP2D6 or CYP2C19, while 55 per cent are metabolised by CYP3A4. While research on CYP450 biomarkers represents a significant opportunity to improve the quality use of medicines, research is also being progressed for a wide range of other biomarkers as well (Figure ES.1).

Figure ES.1: PGx biomarkers – areas of research and existing tests



** This refers to tests that are available on the MBS or conditions of PBS listing. There may be some inconsistent use of other tests.*

*** This shows current recommendations by the FDA for PGx testing*

The successful translation of PGx research into the clinical setting will catalyse a step change in the way that medicine is practiced in Australia and overseas. Currently only a handful of tests are recommended or required in Australia compared to what is recommended and in use in other major markets (Figure ES.1). In the United States, for example, the Food and Drug Administration (FDA) has implemented a number of initiatives aimed at reviewing the PGx evidence base in order to make recommendations for clinical practice where valid biomarkers have been identified. Examples of valid PGx biomarkers that are recommended by the US FDA but either not used, or inconsistently used, in

Australia, include testing for biomarkers to prescribe anti-cancer drugs (TMPT and CYP2D6) and warfarin (CYP2C9 and VKORC1).

The corollary of this analysis is that the number of tests likely to enter the Australian market and clinical settings will accelerate over the next five to ten years, from only a few today to potentially hundreds in ten years' time. The range of tests recommended by the US FDA, which represents the most proactive effort globally to identify and harness PGx technology, represents only the start of a major shift in technology and medical practice. Within a decade PGx will likely be a common medical practice.

Potential benefits of pharmacogenomics

While the realisation of PGx remains a long term goal, and the clinical utility of PGx biomarkers continues to be established, it is clear the potential health and economic benefits for the system of PGx are significant.

The most important aspect of PGx is the potential to improve patient safety and the quality of care. PGx technologies can be used to reduce the incidence of adverse drug events, improve the effectiveness of pharmaceuticals by getting the right dose the first time and increase patient compliance by reducing patient anxiety and side effects associated with therapy.

Improving patient safety and quality, however, will also yield significant economic benefits for Australian communities. New research has shown that testing can improve health and economic outcomes for patients across a range of diseases, including patients with:

- *Colorectal cancer* — Colorectal cancer, also called bowel cancer, is the third most common form of cancer in Australia and the second leading cause of cancer related death in Australia. Pharmaceutical therapies have been shown to be important adjuvant therapies for patients undergoing chemotherapy. However, recent research shows that between 35 to 45 per cent of patients will not respond to one of the leading therapies, cetuximab, which provides comparable survival rates to alternative therapies but has reduced risks of severe side effects. Testing to improve patient outcomes would reduce unnecessary expenditure on cetuximab for patients that will not respond, with net savings of between $4.5 million and $6.5 million possible each year in drug costs alone. More importantly, patients that will not respond to cetuximab can begin treatment with alternative therapies (such as bevacizumab) that will be effective in combating the cancer for them, thus improving patients' survival rates.
- *Inflammatory bowel disease* — Inflammatory bowel disease (IBD) comprises ulcerative colitis, Crohn's disease and indeterminate colitis. Azathiopurine is the first line therapy used for the treatment of IBD and is more effective in generating remission than alternative therapies. However, for some patients azathiopurine is also associated with considerable side effects, including myleosuppression, pancreatitis, gastrointestinal upset, hepatotoxicity and hypersensitivity reactions. More than 25 per cent of patients prescribed azathiopurine discontinue treatment due to adverse side effects. PGx testing for a TMPT biomarker can identify which patients will experience severe side effects and facilitate treatment with alternative medicines. The net savings of TMPT testing would be expected to be $2.1 million each year.
- *Risks of thromboemolism and stroke* — Warfarin, an anti-coagulant prescribed to patients at risk of stroke, is one of the most commonly prescribed prescriptions in Australia. It is the most frequent cause of adverse medical events due to its narrow

therapeutic window and highly variable dose-response relationship. More accurate warfarin dosing through the use of PGx has been shown to be expected to reduce the incidence of serious bleeding and stroke in the community. The benefits from avoided bleeding and stroke among true positive and negative patients would be expected to be between $219 million and $680 million, compared to costs of approximately $41 million to test all patients, and potential adverse outcomes due to test inaccuracy of approximately $27 million. In total, the *net savings* to Australia could be between $151 million and $612 million each year through the avoidance of bleeding and stroke in the community, depending on the incidence of poor metaboliser risk.

- *HIV* — HIV and AIDS is perhaps one of the greatest challenges to face modern medicine. In Australia, 998 people are diagnosed with HIV infection each year. Abacavir is an effective first line pharmaceutical treatment for HIV, which works by slowing the spread of HIV infection in the body. In white populations, between five per cent and eight per cent of patients receiving abacavir will have a serious hypersensitivity reaction characterized by fever, rash, and symptoms in the gastrointestinal tract, other organ systems, or both. PGx testing is regularly undertaken in Australia, with an MBS Item Number available to clinicians. The reduction in adverse events was estimated to save Australia on net $415,000 per annum, expected to improve patient outcomes and compliance with abacavir. Patients that are able to continue with abacavir are less likely to seek care from emergency physicians or specialists.
- *Depression* — In Australia, one in five people will be diagnosed with depression in their lifetime. Treatment for depression is expensive and protracted, and if inadequately treated, depression can result in suicide, a common cause of death. Serotonin Selective Reuptake Inhibitors (SSRIs) are the first line of pharmaceutical therapy for patients. While there is substantial evidence of a positive effect of SSRIs for patients with depression, the response rate for these drugs, however, is only 60 per cent to 70 per cent. Similarly the response rate for another class of antidepressants, tricyclic antidepressants, is only 50 to 80 per cent. This defines a large group of patients with 'difficult-to-treat' depression. There are a wide range of biomarkers being examined to better target pharmacotherapy for depression, including a number of CYP450 enzymes (CYP2D6 and CYP2C19), and other biomarkers, such as 5-HTT. With current spending on antidepressants of approximately $458 million each year, and depression significantly affecting Australians' health, wellbeing and ability to participate in the community, improving the efficacy and efficiency of this spending holds the potential to significantly improve the quality and safety of care as well as economic outcomes.
- *Cardiovascular disease* — Statins are the highest value and largest volume items on the PBS and used to treat hypercholesterolemia. Research has shown that their efficacy across a large population could be enhanced by evaluating inter-individual differences; it has been estimated that between ten and 60 per cent of patients do not respond to statins. Other cardiovascular drugs include ACE-inhibitors and beta-blockers, which are estimated to be ineffective in between ten to 30 per cent, and 15 to 35 per cent of all patients, respectively. Current expenditure on lipid lowering and beta-blocking agents is more than $1.2 billion each year. Better targeting the use of these medicines therefore represents a substantial opportunity for cost savings to the community.
- *Breast cancer* — Breast cancer was the most common newly diagnosed cancer among females in 2001 (11,791 new cases diagnosed). Treatment of breast cancer

varies by patient and the progression of the cancer, and can include surgery to remove the cancer, mastectomy, and chemotherapy. Approximately a quarter of all women diagnosed with breast cancer are prescribed tamoxifen. Tamoxifen is only effective, however, if the body can properly metabolise it. Recent research on tamoxifen has shown that up to seven to ten per cent of Caucasian women with breast cancer may not receive the full medical benefit from taking tamoxifen, because they are poor metabolisers of CYP2D6. These women have been found to be twice as likely to see their breast cancer return. If improved prescribing could improve women's survival rates so that women without CYP2D6 were expected to survive on average as frequently as women that were normal metabolisers of CYP2D6, the potential benefits of avoided relapse could range from $543,000 to $776,000 each year depending on the rate of poor metabolisers in the female population, the potential improvement in health outcomes through alternative therapies, and the costs of treatment for relapsed patients.

These are only a few case studies of the potential benefits that would be expected from PGx. These case studies show that PGx will likely touch almost every disease currently affecting Australians (for which pharmaceuticals are prescribed as therapy). They also show the safety and economic benefits of these technologies will be significant.

The case studies, however, consider the benefits on a disease-by-disease basis, which potentially understates the benefits of some tests that will deliver, through better prescribing for a wide range of pharmaceuticals (e.g., where a test identifies a biomarker that is important for multiple medicines). More than half of all medicines are metabolised by a handful of biomarkers. Proving up the evidence base for these biomarkers in particular will unlock significant benefits for the community through avoided adverse events, more effective care, reduced waste and improved patient compliance:

- *The potential macro benefits of reduced adverse events* — Adverse drug events currently account for between two to four per cent of all adverse events. Three quarters of these are considered preventable, while the other quarter is not considered preventable based on current medical practice. In 2003-04, adverse events were estimated to cost $14,027 on average per hospital admission. If in ten years time these adverse events currently 'non-preventable' ADRs could be avoided using PGx, the potential net benefits from avoided ADRs would be between $1 billion and $1.6 billion each year (one per cent of total spending). In reality it is likely that not all currently unpreventable ADRs would be avoided with PGx and that some currently preventable ADRs may be more effectively controlled with PGx. Over a five year horizon, net benefits of between $2.1 billion and $5.5 billion would be expected if all of the ADRs not due to medical error could be avoided through PGx technologies. In addition, over this five year horizon 63 per cent of Australians would have had their PGx profile defined, which will guide prescribing for the rest of their lives.
- *The potential macro benefits of avoided wastage* — Related to the improvement in the quality of care, doctors will be able to avoid current 'trial and error' methods of prescribing. Currently more than half of all medicines require the presence of particular biomarkers that between five and ten per cent of the population lack. Over a five year period, this could add a further $360 million to $720 million in additional benefits.
- *The potential macro benefits of improved quality of care and patient compliance* — In addition, PGx would enhance the effectiveness of prescribing and the quality of care, by enabling doctors to target the right dose for a patient. On top of cost savings from avoided adverse events and wasted drug expenditure, Australian quality of life

would improve, leading to lower utilisation of healthcare resources and higher labour force participation. It is difficult to credibly quantify the potential benefits from improved quality of life that would be derived from PGx in aggregate. Nevertheless the case studies provide examples of how improved quality of life translates into lower healthcare utilisation and labour force participation.

- For example, in the case of warfarin, more effective prescribing would reduce utilisation of the healthcare system by reducing the incidence of stroke, saving the community between $219 million to $680 million each year. In ten years time, this could add a further $5.7 billion in savings on top of avoided ADRs and wasted expenditure.
- In the case of tamoxifen, more effective prescribing would reduce recurrence of breast cancer, avoiding expenditure of between $543,000 to $776,000 each year through lower rates of recurrence. Indexing this to 2018, this could provide an additional $6.5 million in reduced healthcare costs over a five year horizon.

The net economic benefits from avoided ADRs and unnecessary pharmaceutical spending are estimated to be approximately $2.5 billion to $6.2 billion over five years time once fully implemented, which would represent an approximate one per cent reduction of total health care expenditure.

On top of this, the burden of many diseases would likely be reduced through more effective care, which would lead to significant improvements in patients' quality of life and leading to further reductions in healthcare resources over time. Considering only the savings from safer and more effective care with warfarin and tamoxifen would add more than $6 billion to the total potential savings expected over the same time period, bringing the total benefits to more than $12 billion (two per cent of total healthcare spending). This is a conservative estimate of the potential benefit, as it ignores potential improvements in the effectiveness of care for other major categories of PBS spending, including cardiovascular medicines and antidepressants.

With government spending on health care projected to grow from nine per cent today to an estimated 16 to 20 per cent of GDP by 2045, and with Australia facing a growing crisis in the shortage of skilled medical professionals, any ability to constrain growing health care costs will directly support the future sustainability of the Australian health care system.

Pharmacogenomics barriers and challenges

PGx technologies will bring new opportunities for improved patient care but also challenges for regulatory and reimbursement systems that have been developed on the basis of the 'one size fits all' model of drug development. Government will need to also invest in the systems and resources to ensure it is able optimise the uptake of cost effective technologies to drive quality use of medicines.

Regulatory challenges

Regulatory silos

PGx represents the convergence of previously separate technology platforms: pharmaceuticals and diagnostics. This is a growing feature of modern healthcare and technology, and creates challenges for regulatory bodies that were set up on the basis of a particular technology or service focus, such as the Pharmaceutical Benefits Advisory Committee and the Medical Services Advisory Committee. To date, there have been only a handful of PGx technologies requiring review. These have been evaluated on an

'exceptional' basis, and there have been no examples of co-listings of pharmaceuticals and PGx tests, even with several in use in Australia. Thus although there has been some collaboration between the pharmaceutical and medical services divisions and bodies of government on these issues, their comparative siloed nature and the expected increase in the number of technologies that are likely to enter the Australian market and clinical practice over the next five to ten years create risks for poor patient access to cost-effective technologies, significant delays in technology listings, and poor process consistency, predictability, and transparency.

In the US, the FDA has responded to this challenge by creating the Office of Combination Products. In Europe, the EMEA has been scoping options for improvements to its regulatory structure through the Pharmacogenetics Working Party.

Australia has not implemented any reforms to provide for the convergence of pharmaceuticals and other technologies. While PGx diagnostics should be listed on the MBS, and therefore come under the purview of MSAC, most technologies have been introduced through PBAC to secure approval for the listing of new high cost drugs, with Herceptin testing being the most well known example.

As a result of the fragmented system, no systematic reviews of evidence are being undertaken, as is currently conducted in the US. No guidelines for clinical practice have been developed and significant inconsistencies exist in clinical settings, which create concerns for patient equity. No body has a role to recommend revised labelling requirements for existing medicines to the TGA.

There is also an emerging risk of inequity in the community with patients having to fund tests that have been established as valid biomarkers in other markets but are not available on the MBS in Australia. Already a number of tests are recommended in the US that are not provided on the MBS and performed inconsistently in practice.

Under the current regulatory framework these inconsistencies and disparities between world's best practice and Australian clinical practice are likely to increase.

Long MSAC evaluation timelines

In addition, the current time to list a service on the MBS is between two and three years, with recent examples of a four year wait for a recent PGx application. The long evaluation times are due to MSAC's current requirements to undertake its own reviews of evidence, as opposed to reviewing dossiers submitted by companies (as is done for PBAC), as well as a lack of expertise and resources to evaluate PGx technologies in a more timely manner. These timelines are only likely to lengthen as more and more PGx technologies enter the Australian market. Extending the National Medicines Policy to PGx, this creates risks for timely access to technologies required to provide high quality use of medicines.

Moreover, any potential benefits of improvements to streamline the TGA and PBAC evaluation and listing processes will be eliminated if parallel processes and timetables can not be developed for MSAC as well.

Poor regulation of quality

The advent of PGx will have the effect of shifting the burden of quality and safety from the clinic to the lab. Currently accreditation of laboratory facilities through National Association of Testing Authorities (NATA) is only required if MBS funding is sought. If PGx tests are not funded by the government, under current legislation no accreditation required. This could result in poor quality testing, with patients making potentially major healthcare decisions based on inaccurate results.

Reimbursement challenges

The current requirement for offsets to list on the MBS, combined with the long listing times for MSAC, creates a disincentive for companies to list on the MBS, which creates concerns for patient access and equity.

Pricing PGx diagnostics will likely require a new approach to what has been the historic pricing model for diagnostic tests in Australia. There is likely to be significant variability in the price of different tests depending on the equipment and skilled staff requirements. Some tests may require specialised, high cost equipment or personnel while others may be based on high throughput (and lower cost) technologies. Prices on the private market currently range from $50 per test to several thousand dollars per test. In addition, different tests will provide very different health and economic benefits to Australia. A test for a CYP450 biomarker or biomarkers could improve health outcomes for a range of therapies, potentially saving Australia millions of dollars and generating significant QALY benefits each year. Other tests will be more focused and produce benefits for smaller patient groups. If these benefits are inadequately valued, there will be a disincentive for the test to be listed on the MBS.

Barriers to research translation

For PGx to significantly enhance the quality use of medicines the evidence base around the clinical utility of biomarkers needs to be improved. There is a need to validate biomarker tests and to support the uptake of these tests, but also to ensure that medical practice does not 'get ahead' of the science.

Poor clinical uptake of valid PGx tests in Australia is due in the main to poor clinician understanding of PGx and its potential to improve patient outcomes, as well as a lack of decision support tools to interpret PGx test results. In the US, the FDA updates quarterly a list of valid PGx tests, which provides advice for clinicians on whether the test is 'mandatory' or 'recommended' (and for what populations) and links to medical literature. It also requires updates to medicine labels to ensure consistency of advice to clinicians. No advisory body has taken up this role in Australia. There are currently no algorithms available to guide clinical practice, or labelling to indicate when PGx testing should be undertaken. Australia needs general guidelines to improve clinical practice as well as drug specific guidelines to ensure appropriate interpretation and revisions of therapy.

Ethical, legal and social challenges

There are potentially a wide range of privacy, ethical and legal issues for Australia in the implementation of PGx. In many ways PGx is only a specific case of a broad class of health information, all of which is considered sensitive information in Australia under the Privacy Act. Thus the treatment of health information is being considered as part of a broader reform context, with PGx included in this.

The largest areas of focus specific to PGx for Australia lie in the ethical and legal issues associated with PGx implementation. In the absence of guidance for clinicians regarding which patients should be tested, when they should be tested and how they should be counselled regarding that information, there are currently risks patients receive inconsistent advice or care, leading to substandard health outcomes or poor quality of care. Without adequate counselling support, some patients may develop 'stigma' issues over PGx data that are not warranted. Currently there is no training or guidelines provided to help clinicians counsel patients on these issues. Moreover, while current rules for limitation and consent of medical information would be expected to apply to PGx, there are potentially unforeseen outcomes that patients will also need to be advised to consider. For example, what may not

appear to be sensitive information today may be perceived to be sensitive in the future as research continues. From a legal perspective, issues may also emerge with respect to the potential for legal action where a test produces a false positive or a false negative and the patient has an adverse event.

Australia needs a plan for how information is shared and stored, and critically needs to deliver training to clinicians and further develop guidelines to help clinicians provide best practice care to their patients.

ICT infrastructure

The individual healthcare consumer has potentially the greatest stake in maximising the efficacy of treatment and avoiding adverse outcomes. Readily accessible patient information will encourage informed decision making and will encourage consumers to raise the prospective use of testing to improve outcomes with their treating health professionals.

In addition, to minimise the risk of unnecessary duplication, there needs to be the infrastructure to ensure that PGx data can be stored and shared in a way that is easy for both the patient and their carers. Because of the large volume of data (potentially a whole genome scan), the development of an E-Health record will facilitate the sharing of patient data effectively across providers. The development of electronic decision support tools will also help clinicians implement PGx.

Australia currently lacks the ICT infrastructure to optimally share PGx information and provide for best practice in the clinic, and this represents a major barrier to optimising the uptake of PGx in Australia.

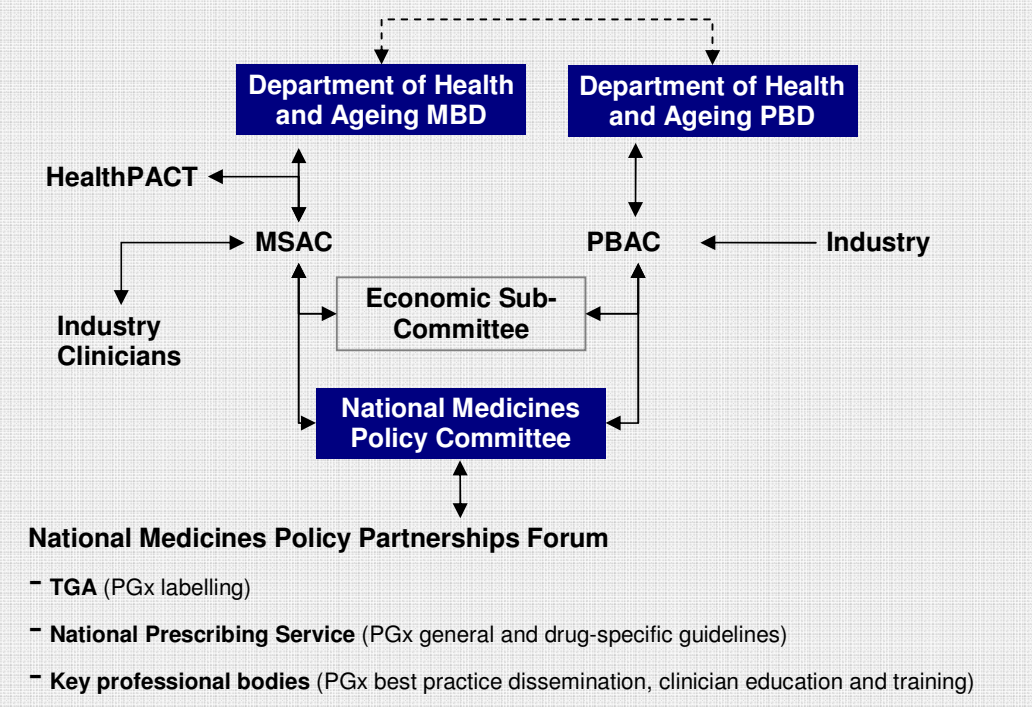
A national framework

The Australian Government has committed itself to the quality use of medicines and timely access to those medicines through the National Medicines Policy.

While the National Medicines Policy is a sound foundation for optimising the uptake of PGx in Australia, PGx does not sit neatly within this policy framework, nor within the broader regulatory structures. To date PGx recommendations have been made on an exceptional or ‘case by case’ basis by a range of bodies. This approach has been broadly acceptable to date; however, with the expected increase in the number of PGx technologies and their potential clinical application this approach is unsustainable and ineffective, creating growing risks for system inconsistencies, patient inequity and wasted expenditure.

It is proposed that the government establish a national framework for PGx. This would involve establishing new responsibilities for PGx among current stakeholders and the creation of a health technology assessment (HTA) body that would have sole authority to provide all advisory opinions on the therapeutic value and the cost-effectiveness of PGx.

Figure ES.2: A National Framework for Pharmacogenomics



The implementation of a national PGx policy would involve:

- recognition that PGx is an *emerging, core pillar of the National Medicines Policy* and an essential tool for the rational, quality use of medicines;
- the clear enunciation that the *National Medicines Policy Executive should oversee policy development related to all technologies, including PGx*, that will improve the quality use of medicines in Australia;
- *enhanced horizon scanning* by HealthPACT to ensure that new PGx technologies are identified, particularly for drugs that are already listed on the PBS;
- *reviews of PGx evidence* to be commissioned by the National Medicines Policy Executive and Committee;
- *applications to be brought by the Government* (via MSAC) where there is no private incentive to list a test on the MBS;
- *the creation of a new HTA advisory body* that will have sole authority to evaluate the cost effectiveness of PGx technologies with responsibilities to make recommendations to both MSAC and PBAC;
- *reimbursement for PGx testing to be provided on the basis of cost effectiveness analysis*, outside current price volume caps for diagnostic tests, to provide incentives for innovation and to encourage the listing of items on the MBS;
- *the development of general and drug specific guidelines* by the National Prescribing Service to ensure standardised, equitable PGx practice;
- *the development of decision support tools* to help clinicians implement best practice in pharmaceutical therapy on the basis of PGx testing; and

- *the roll out of education and training programs*, with priority given to clinicians in fields where tests are mandatory or recommended.

In total seven key recommendations are made to provide a framework for PGx in Australia.

Recommendation 1: Enhance horizon scanning and reporting requirements

HealthPACT currently undertakes horizon scanning on behalf of MSAC and AHMAC's Clinical, Technical and Ethical Principal Committee (CTEPC) for a range of technologies, including diagnostic technologies. HealthPACT has a number of Sub-Committees with particular areas of focus, such as highly specialised surgeries.

Given the rapid developments in PGx technologies expected to occur over the next five to ten years, a further committee should be created under HealthPACT focused on PGx to identify new technologies that could improve the rational use of medicines. In particular, the committee should focus on the emergence of new technologies that might improve the quality use of medicines that are already listed on the PBS, where there may not be a private sector incentive to apply for a PGx test listing on the MBS.

Reporting should be provided not only to MSAC and AHMAC but also the newly formed National Medicines Policy Executive and Committee (via MSAC), which has terms of reference to commission research that would improve the functioning of the National Medicines Policy. This will strengthen the role of the National Medicines Policy Executive as the key body to drive the quality use of medicines in Australia.

Recommendation 2: Expand the responsibilities of the National Medicines Policy Executive to include pharmacogenomics recommendations

The newly created National Medicines Policy Committee is required to:

- provide advice on medicines policy related issues to the National Medicines Policy Executive, the Government and other bodies as requested;
- consult with the National Medicines Policy Executive to determine work plan and priorities;
- conduct, oversee or consider medicine policy related projects and/or research identified by the National Medicines Policy Executive; and
- refer to the National Medicines Policy Executive, where appropriate, specific medicines policy issues that could be considered for research/project funding.

The National Medicines Policy Executive and Committee should receive quarterly reports from HealthPACT and have a responsibility to commission reviews (on authority of the National Medicines Policy Executive) of the evidence.

The National Medicines Policy Executive should also:

- commission the development of education and training programs for medical professionals as appropriate to ensure equal access to therapies;
- liaise with key professional bodies through the National Medicines Policy Partnerships Forum to promote best practice in PGx therapy; and

- as a long term objective, provide recommendations to the Therapeutic Goods Administration (TGA) to update labelling requirements for pharmaceuticals as the evidence base evolves.

Recommendation 3: Create a pharmacogenomics advisory body

The National Medicines Policy requires not simply access to new medicines, but *timely access* to new medicines, facilitated by *streamlined* regulatory processes.

The current time required to achieve MBS listing takes an average of two to three years, and there are recent examples of MSAC assessments for a PGx test taking more than four years. This is due in part to the requirement for MSAC to evaluate the evidence as well as limited expertise available to MSAC to undertake the assessment. Currently, MSAC reviews approximately 19 submissions each year, compared to PBAC's review of more than 100 dossiers annually.

As PGx technologies emerge, MSAC's case load will begin to look more like that of the PBAC and less like the historical MSAC submission profile. The current time to listing raises significant concerns for patient access, and to some extent may encourage item creep or the non-listing of PGx technologies on the MBS. The increase in the number of potential evaluations required will only exacerbate the current delays in the system. The delays to MBS listing may create inequalities for some patients or frustrate the National Medicines Policy quality use of medicines objective where conditions of PBS listing have been applied. Moreover, the potential benefits of reforms to streamline the current TGA and PBAC listing processes (recommended in the recent Productivity Commission *Annual Review of Regulatory Burdens on Business*) would be reduced, as diagnostic testing becomes more widespread.

The current regulatory structure is inadequately resourced and lacks the skills to evaluate PGx technologies on a timely basis. Mechanisms need to be created to:

- increase clarity and consistency of PGx evaluation processes across PBAC and MSAC; and
- reduce the time required to evaluate PGx technologies.

There are a number of models that could formally improve collaboration between MSAC and PBAC, which would also be expected to reduce the time to listing for PGx technologies:

- Option 1 — Require the Economic Sub-Committee to serve both PBAC and MSAC with respect to PGx;
- Option 2 — Create a new PGx Sub-Committee in MSAC; or
- Option 3 — Increase resourcing to MSAC to fund an approved panel of PGx experts that serve both MSAC and PBAC.

Option 1 would formally link the activities of PBAC and MSAC by creating a single economics advisory body for linked pharmaceuticals and PGx technologies. Such an approach could be extended over time so that a single body would perform HTA for all medical technologies as occurs in other markets, such as Canada (CADTH), the United Kingdom (NICE) and the US (FDA Office of Combination Products). The clear advantages of the pharmaceuticals and PGx HTA body are that:

- PGx would be clearly recognised as a tool to improve the quality use of medicines in Australia;
- the body would harness synergies with the pharmaceuticals evaluation committee which will be essential for evaluating the costs and benefits of a PGx test;

- the body would be able to take a comprehensive view of both the costs and benefits to the community of the pharmaceutical and companion PGx test, and provide appropriate recommendations to inform the reimbursement of each; and
- this would provide a platform for the potential further reform to HTA in Australia.

This option represents the most significant break from the status quo and would not be without its hurdles. PBAC is a statutory advisory body and MSAC is a Ministerial Advisory Committee, which creates administrative barriers to its implementation in the short run. The current PBAC Economic Sub-Committee is also already short of the required resources to review new applications for PBAC listing; there is a concern in government that expanding the requirements for this Committee would compromise its ability to meet its obligations for timely reviews of applications. Clearly, however, if such an approach were considered, *there would need to be a complete review of the resourcing of the body* to ensure it had adequate skills and funding to undertake timely reviews of technologies. This would require a several year commitment to evaluate the resourcing strategy for the body in order to identify more effective and sustainable operating protocols and more funding to attract, develop and retain the appropriate skills within the organisation. However, given the potential benefits to the community through safer care and rational use of medicines, this would appear to be a prudent investment by the community.

While the creation of a single HTA authority for PGx and pharmaceutical medical technologies would provide a natural, long run solution, a move to rationalise the number of HTA bodies in Australia may be seen as more effectively considered as part of a larger government strategy to respond to the broader trend of medical technology convergence. It is also likely that the number of PGx applications is going to be uneven over the next five years (though likely increasing thereafter), which would indicate that a less formal arrangement could be developed in the short run to ensure the efficient review of PGx technologies while minimising the reform burden to existing agencies. Options 2 and 3 would not place additional demand on the PBAC system, although each would require additional resourcing and funding than is currently provided to MSAC to attract, develop and retain the appropriate skills to provide a national HTA services for PGx. Option 2 provides for a formal Sub-Committee to be created in MSAC to evaluate and fast track PGx technology listings. Option 3 represents an 'enhanced status quo option, and provides effectively the same outcome as Option 2 but through a less formal panel arrangement, which is how MSAC currently undertakes reviews: through the commissioning of consultant medical professionals.

The advantages of Options 2 and 3 are that they offer the possibility of a phased approach, and would enable action to be taken on PGx without a major revision to the HTA system in Australia. Clarifying the roles and responsibilities and processes for PGx assessment will reduce risks arising from the current system for PGx review, and provide a mechanism for harmonising listings on the PBS and MBS. Given the current trends towards medical technology convergence, however, these approaches represent only half-measures towards a long run solution and would likely be rationalised under a broader reform agenda.

Overall it is recommended that Option 1 is pursued as this would provide for the greatest collaboration between MSAC and PBAC, and would more clearly cement PGx as a major tool for improved quality use of medicines. The HTA authority would be able to establish conditions for the fast tracking of evaluations through the development of levels of review required depending on a risk-impact assessment. It should also commit to fast tracking MBS listing reviews where companies provide PGx data as part of its PBAC submission.

Recommendation 4: Reform reimbursement for pharmacogenomics tests

PGx technologies are not the same as other diagnostic tests; there is likely to be significant differences between:

- the costs of tests (depending on technologies/personnel involved, and the size of potential patient populations); and
- the potential benefits provided to the community in terms of improvements in the quality of life and avoidance of wasted expenditure on the PBS.

PGx technologies will provide significant savings to the PBS, similar to the introduction of new PBS items that deliver health outcomes more cost effectively. Where some tests are able to provide significant value in terms of controlling spending across a wide range of pharmaceuticals, there should be incentives for the technology to be listed so that spending on the PBS can be controlled. The current MBS offsets approach to diagnostics does not allow government access to these more sophisticated pricing tools and as a result, items may not be MBS listed. To the extent that technologies are not listed on the MBS that improve patient safety and the cost-effectiveness of care, patient access will be compromised and allocative inefficiencies would be expected to arise.

It is proposed that reimbursement for PGx be provided outside current price-volume arrangements and based on a cost-effectiveness (cost per QALY) basis, similar to the evaluation of PBS technologies, with the principles of cost effectiveness applied with equal rigor to PGx technologies.

Recommendation 5: Develop pharmacogenomics clinical guidelines

The National Prescribing Service should be required to develop general and disease specific guidelines to support ethical use and equitable access to PGx in collaboration with appropriate clinical groups. Specialised clinical bodies should be involved in the development of drug-specific guidelines, which the National Prescribing Service would disseminate while the National Prescribing Service would develop the general guidelines for PGx to support clinician uptake. Guidelines should provide for standardised use of PGx, interpretation of results and therapy algorithms. Where biomarkers have been shown to be valid, testing should be indicated as mandatory.

As a long run objective, the National Prescribing Service Guidelines should be harmonised with TGA labels.

Recommendation 6: Develop ICT decision support tools and privacy standards

ICT infrastructure and solutions will be an important enabler of better healthcare over the next decade, including PGx solutions. The need to invest in better ICT is not driven by PGx; nevertheless, to ensure the benefits of PGx and E-Health investments can be maximised, it is important that considerations are made for imminent technological change in medicines.

In particular, the development of decision support tools will enable clinicians to implement best practice prescribing, which increasingly will involve PGx. Decision support tools will help guide better dosing of patients, reducing wastage and side effects while also improving compliance.

Patients will increasingly have significant volumes of personal data that will need to be kept private. Critically, some patient data that may not appear to be sensitive today may become sensitive information in the future as technology improves. To reduce duplication of testing

and improve health outcomes, solutions (such as an IEHR) should be developed to facilitate the appropriate sharing of patient PGx data across providers.

Recommendation 7: Invest in education and training for healthcare providers and the public

Stakeholder consultations and literature reviews have shown there are very significant differences in education levels among clinicians, with current PGx technologies being provided *ad hoc* and inconsistently to patients.

The National Medicines Policy Executive and Committee should work with the National Medicines Policy Partnership Form to ensure that where tests are required, education and training for medical professionals (specialists and GPs) is developed and provided. The Executive should also, through the National Medicines Policy Partnership Forum, engage with professional colleges, journals and other therapeutic guideline groups to disseminate best practice guidelines among professional communities. Professional colleges should also engage with undergraduate medical schools to ensure teaching integrated into curricula.

Patients also need to be educated about PGx technologies and the ethical, legal and social issues that may be associated with PGx. Patients need to be informed about NATA accreditation, so that they can be confident of the quality and accuracy of the test, and their options. In the development of education and training for professionals, materials should also be developed and distributed to patients.

1 Pharmaceuticals in Australia

This chapter outlines the impact of pharmaceuticals in health outcomes, total spending on medicines in Australia, the policy framework governing the sector and key areas where Australia can improve the quality use of medicines.

1.1 Pharmaceuticals in Australian healthcare

The health and wellness of Australian communities determines the quality of life that its members enjoy, and in turn, their ability to be productive participants in their communities and the labour force. A high quality healthcare system is therefore a cornerstone of Australians' social and economic prosperity, and maintaining equal access to safe and effective healthcare is a chief goal of Australian governments.

1.1.1 Delivering cost-effective health outcomes

Pharmaceuticals are an integral component of a high quality healthcare system in Australia. Advances in pharmaceutical technologies have contributed to substantial improvements in patients' quality of life, as well as significant extensions in life expectancy. New medicines have contributed to an increase in cancer survival rates, a reduction in deaths from cardiovascular disease and the effective eradication of many infectious diseases that were once the primary burden of disease for Australians. Improvements in the health and welfare of patients has supported increased labour force participation and productivity, which in turn has provided major returns to communities in the form of economic growth.[1]

Moreover, treatment of disease with pharmaceutical technology is highly cost-effective. Pharmaceuticals often eliminate the need for other, more expensive interventions. Illnesses that once required hospitalisation, nursing homes or surgery can now be treated more cost-effectively with medicines; for example:

- statins are used to reduce the risk and frequency of heart attacks and strokes in the community, which would otherwise be treated through expensive hospital care;
- omeprazole assists in the healing of stomach ulcers, reducing the need for surgery; and
- salmeterol/fluticasone helps manage asthma which also reduces hospital costs.[2]

Research published in the *American Economic Review* found that for every US$1 increase in spending on medicines there was a US$3.65 saving in hospital care expenditure.[3] Other

---

1 Gross, P., 2003, *The economic value of innovation: measuring the linkages of pharmaceutical research, use of innovative drugs and productivity gains*, Health Economics Monograph No. 80, Health Group Strategies, March; Burton, W., Morrison, A., and Wertheimer, A., 2003, 'Pharmaceuticals and workers productivity loss: A critical review of the literature', *Journal of Occupational and Environmental Medicine*, 45(6), June; Lichtenberg, F., 2002, *The Effect of Changes in Drug Utilization on Labor Supply and Per Capita Output*, Working Paper No. w9139, National Bureau of Economic Research, September: Cambridge, Mass.; MEDTAP International, 2004, *The Value of Investment in Health Care*, Seattle; Bloom, D.; Canning, D., and Jamison, D., 2004, 'Health, Wealth and Welfare', *Finance and Development*, 41(1):10-15; Bloom, D., and Canning, D., 2000, 'The Health and Wealth of Nations', *Science*, 287, 18 February; quoted in Medicines Australia, 2005, *Medicines Australia Submission to the Productivity Commission Inquiry Impact of Advances in Medical Technology on Healthcare Expenditure in Australia*, Canberra, pp 80-88.

2 *Ibid.*

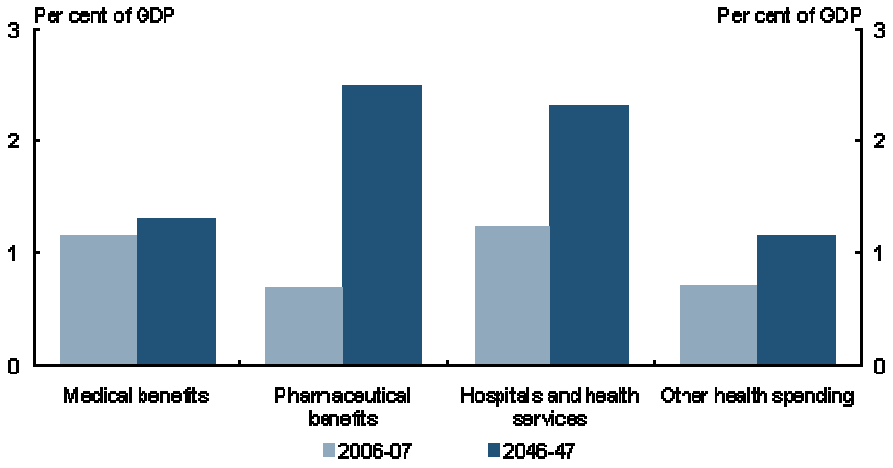
studies have similarly reported a net saving through the use of pharmaceuticals compared to the counterfactual where no pharmaceuticals were available.[4]

1.1.2 Rapid and growing expansion of pharmaceuticals projected

As a consequence of the potential for significant improvements in patients' quality of life and their relative cost-effectiveness as a therapy, the use of pharmaceuticals in Australia has been increasing rapidly, with pharmaceuticals accounting for an increasing proportion of total health expenditure. In 2005-06, the Australian Institute for Health and Welfare (AIHW) reported that pharmaceuticals accounted for $11.5 billion or approximately 13 per cent of direct health expenditure.[5] Government expenditure on the Pharmaceuticals Benefits Scheme (PBS) was reported to have grown by 4.9 per cent in 2006-07 and the PBS is forecast to grow by 9.3 per cent in 2007-08.

Pharmaceuticals are expected to remain the fastest growing component of healthcare spending in Australia over the next 40 years. According to 2007 Intergenerational Report projections,[6] pharmaceutical expenditure is projected to grow from 0.7 per cent of GDP in 2006-07 to 2.5 per cent of GDP in 2046-47. By contrast, medical benefits expenditure is expected to grow only marginally as a proportion of GDP (Figure 1.1).

Figure 1.1: Expenditure by healthcare portfolio



Source: Australian Treasury, 2007, *op. cit.*

---

3 Lichtenberg, F., 1996, 'Do (More and Better) Drugs Keep People Out of Hospitals?,' *American Economic Review* 86, May, 1996, 384-388.

4 Kleinke, J. 2001 'The Price of Progress: Prescription Drugs in the Health Care Market', *Health Affairs*, 20(5), Sept-Oct; Cowper, P.A., 2004, 'Economic Effects of Beta-Blocker Therapy in Patients with Heart Failure,' *The American Journal of Medicine*, 116: 2, 104-111; Greenberg, P.E., 2003, 'The Economic Burden of Depression in the United States: How Did It Change Between 1990 and 2000?', Journal *of Clinical Psychiatry*, 64: 1465-1475; Wagner, E.H., 2001, 'Effect of Improved Glycemic Control on Health Care Costs and Utilization,' *Journal of the American Medical Association*, 285: 2, 182-189; Berger, J., 2001, 'Economic Impact of a Diabetes Disease Management Program in a Self-Insured Health Plan: Early Results,' *Disease Management*, 4: 2, 65-73; Hill, J.W., 2002, 'The Effect of Donepezil Therapy on Health Costs in a Managed Care Plan,' *Managed Care Interface*: 63-70; Cady, R.C., 1998, 'Sumatriptan Injection Reduces Productivity Loss During a Migraine Attack: Results of a Double-Blind, Placebo-Controlled Trial,' *Archives of Internal Medicine*,158; Cockburn, I.M., 1999, 'Loss of Work Productivity Due to Illness and Medical Treatment,' *Journal of Occupational and Environmental Medicine*, 41: 11, 948-953; National Committee for Quality Assurance, 2003, *State of Health Care Quality: 2002*, quoted in Medicines Australia, 2005, Medicines Australia, 2005, *Submission to the Productivity Commission Inquiry: Impact of Advances in Medical Technology on Healthcare Expenditure in Australia*, Medicines Australia, Canberra.

5 Australian Institute for Health and Welfare, 2006, *Health Expenditure Australia 2005-06*, Australian Government, Canberra.

6 Australian Treasury, 2007, *Intergenerational Report 2007*, Part 3: Long Term Fiscal Projections, http://www.treasury.gov.au/documents/1239/HTML/docshell.asp?URL=04_Part_3.htm [August 2008]

Within the PBS, government expenditure on new, highly specialised drugs is likely to outpace total PBS expenditure. In the past ten years these drugs have consistently grown faster than the PBS on average; in 2006-07, the cost of highly specialised drugs increased by 13.7 per cent[7] on the previous year, compared to 4.9 per cent for the whole PBS. The growth in the number of high cost pharmaceuticals is expected to drive a significant proportion of the growth in the PBS to 2046-47.

1.2 Optimising expenditure on pharmaceuticals in Australia

With such a significant and growing proportion of healthcare spending being allocated to pharmaceutical therapies, and with community health and wellness contributing so substantially to Australia's future prosperity, it is essential that the use of pharmaceuticals in the community is optimised to ensure Australians are maximising the benefits from new medicines while also minimising their costs to the community.

The Australian Government has introduced a number of policies aimed at maximising the use of pharmaceuticals in the Australian healthcare system. Chief among these are the National Medicines Policy and the Pharmaceutical Benefits Advisory Committee (PBAC).

1.2.1 The National Medicines Policy

First developed in 1999, the National Medicines Policy[8] governs the use of pharmaceuticals in Australia and is comprised of four key objectives:

- ensure timely access to the medicines that Australians need, at a cost individuals and the community can afford;
- medicines meeting appropriate standards of quality, safety and efficacy;
- quality use of medicines; and
- maintaining a responsible and viable medicines industry.

Timely access to affordable medicines

The first objective outlines three key aims — access, timeliness and affordability; critically, the realisation of each sub-objective depends on the realisation of the other two.

The primary focus of the first objective is to ensure Australia optimises *access* to medicines for all Australians; specifically, that 'cost should not constitute a substantial barrier to people's access to medicines they need'. However, the access principle does not ignore cost altogether, and highlights that optimal access is contingent on controlling the use and prices of medicines:

> *Access to medicines should support the rational use of those medicines. Users should be encouraged to understand the costs, benefits and risks of medicines, and wherever possible the public benefit of provision of medicines should be achieved through the regulated marketplace in which medicines are placed.*[9]

---

7 Pharmaceuticals Benefits Advisory Authority, 2007, *Annual Report*, Australian Government, Canberra.

8 Department of Health and Ageing, 2000, *National Medicines Policy*, Australian Government, http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-objectives-policy.htm/$FILE/nmp2000.pdf [September 2008], Canberra.

9 *Ibid.*

Thus the first objective establishes that all medicines need to be shown to be *cost effective* to ensure the community can afford public subsidy of as many medicines as possible on the PBS. The corollary is that funding arrangements should be developed that both optimise health outcomes and represent value for money for the community.

The third essential element to realising the first National Medicines Policy objective is *timeliness*. The National Medicines Policy clearly states that evaluation processes should also be made 'as simple and streamlined as possible, so that subsidisation of medicines is timely, mechanisms are understood, and unnecessary administrative barriers and expenses are avoided'. In other words, it is not 'enough' to have access: Australians need access to safe and high quality care as these medicines become available, and this creates a responsibility for the government to *streamline* the uptake of new technologies where they are shown to be cost effective.

Safety and Effectiveness

The second objective establishes the goal that the quality, safety and efficacy of medicines available in Australia should be equal to that of comparable countries. This requires the government to maximise public safety through the development of transparent, national regulations and post-market surveillance that is appropriate to the benefits and risks of individual technologies, while also ensuring that the compliance burden does not become so great or so out of step with international regulatory requirements that it limits access to new medicines. The Therapeutic Goods Administration (TGA) is the body with the primary focus on ensuring medicines are safe and effective for Australians to use.

Quality Use of Medicines

The third objective for the use of pharmaceuticals in Australia turns on the quality use of medicines. This principle establishes that all medicines should be used:[10]

- *Judiciously* — medicines, whether prescribed, recommended, and/or self-selected should be used only when appropriate, with non-medicinal alternatives considered as needed;
- *Appropriately* — choosing the most appropriate medicine, taking into account factors such as the clinical condition being treated, the potential risks and benefits of treatment, dosage, length of treatment, and cost;
- *Safely* — misuse, including overuse and underuse, should be minimised; and
- *Efficaciously* — the medicines must achieve the goals of therapy by delivering beneficial changes in actual health outcomes.

Maintaining a responsible and viable medicines industry

The final objective articulates the nexus between health policy and industry policy. That is, the realisation of the first three objectives is contingent on 'the continued existence of a responsible and viable medicines industry in Australia'. This principle explicitly states that Australia should provide appropriate returns for the research and development, manufacture, and supply of medicines.

Implementing the National Medicines Body: governance framework

Taken together, the four pillars of the National Medicines Policy have provided a clear and transparent foundation for the development of further policies in the pharmaceuticals sector as new technologies have emerged.

---

[10] Department of Health and Ageing, 2000, *op. cit.*

The National Medicines Policy was recently reviewed and its governance framework revised to support the future implementation of the National Medicines Policy in light of changes to the use of pharmaceuticals in healthcare over the past decade, and emerging technology trends. The National Medicines Policy is now governed by:

- a National Medicines Policy Executive;
- a National Medicines Policy Committee; and
- an annual National Medicines Policy Partnerships Forum.

The Terms of Reference for each of these groups is shown in Box 1.1.

Box 1.1: National Medicines Policy governance framework – Terms of Reference

National Medicines Policy Executive

- Providing timely and responsive advice on National Medicines Policy issues within the Health portfolio (and cross portfolio medicines issues where appropriate) to Government and other bodies as necessary.
- Identifying required action on issues of importance in relation to the National Medicines Policy.
- Determining the medicines policy priorities to be undertaken by the National Medicines Policy Committee in line with associated stakeholder consultations and consistent with Government priorities.
- Identifying appropriate medicines policy issues to be referred to the National Medicines Policy Partnerships Forum.
- Monitoring outcomes/achievements resulting from the activities of the National Medicines Policy Committee.

National Medicines Policy Committee

- Providing advice on medicines policy related issues to the NMP Executive, the Government and other bodies as requested;
- Consulting with the NMP Executive to determine work plan and priorities;
- Conducting, overseeing or considering medicine policy related projects and/or research identified by the NMP Executive; and
- Referring to the NMP Executive, where appropriate, specific medicines policy issues that could be considered for research/project funding.

Source: Department of Health and Ageing, 2000, *National Medicines Policy*, Australian Government, http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-objectives-policy.htm/$FILE/nmp2000.pdf [September 2008], Canberra.

1.2.2 The Pharmaceutical Benefits Advisory Committee

The PBAC is an independent statutory body under charged under Section 101 of the *National Health Act* (1953) to make recommendations and give advice to the Minister for Health about pharmaceuticals that should be listed and subsidised on the PBS. It is the main lever by which Australia controls expenditure on medicines to ensure maximum access by the community to new drugs. Since its inception in 1954, the PBAC's monopsony power has enabled the cost-effective purchasing of pharmaceuticals on behalf of the Australian community. More recently, in 1993, the PBAC was also one of the first regulatory authorities to introduce cost effectiveness requirements to gain listing on the PBS. The Economics Sub-Committee of PBAC evaluates the effectiveness and cost of a proposed

benefit compared to alternative therapies, which form the basis for listing and price recommendations. PBAC is also supported by the Drug Utilisation Sub-Committee, which advises on medicines use and financial forecasts for major medicine submissions.

1.3 Current barriers to the quality use of medicines

In spite of the solid policy foundations for pharmaceutical purchasing and use in Australia, there remains significant scope for improving the use of pharmaceuticals. Part of the scope for improvement turns on reducing medical errors; the remainder depends on technological change.

1.3.1 Medical errors

Medication is implicated more than any other factor in the high rate of adverse events in healthcare. Adverse drug events (ADEs) are a significant cause of morbidity and mortality, and generate very significant costs to the community. Many of these are avoidable: patients are given medications to which they are known to be allergic, or for which there are recognised potentials for drug-drug interactions. Errors can be organized into administrative errors, ordering/prescribing errors, dispensing errors and/or errors in recording allergy histories.

For example, the 1995 Quality in Australian Healthcare Study[11] showed that as many as ten per cent of hospitalisations in Australia were associated with significant adverse events and approximately 50 per cent of these were ADEs. The Quality in Australian Healthcare Study estimated that 50 per cent of the adverse events were considered avoidable; that is, based on current technologies it would be possible for the event to have been avoided. The Study estimated the cost of these preventable ADEs to be more than $1.1 billion, or around 2.5% of total healthcare costs in 1992. In addition, the Study calculated that if costs arising from legal expenses and compensation for medical errors were also considered the cost would increase by $400 million per year.

Similarly, a more recent 2003 review[12] of reporting of ADEs and medication errors in Australia found that based on a review of medical records between two to four per cent of all hospital admissions, including up to 30 per cent for patients more than 75 years of age, were medication-related and that most were due to medical error (75 per cent were estimated to be preventable).[13] While the study did not estimate the costs of these medical errors, they represent a significant waste of public funding that might have gone to other, better uses and have significant implications for patient's quality of life. The Study found that the most common drugs implicated in ADEs were anti-coagulants.

1.3.2 Technological barriers

The current model for drug development is and has been a 'one drug for one phenotype' model, or a 'one size fits all' model for pharmaceutical therapy. Doctors prescribe drugs on the basis of observed physical characteristics or 'phenotypes', such as high cholesterol levels, and prescribe medicines from broad therapeutic groups to treat patients displaying

---

[11] Wilson, R., Runciman, W.B., Gibberd R.W., *et al*., 1995, 'The Quality in Australian Health Care Study', *Medical Journal of Australia,* **163**(458-471).

[12] Runciman, W.B., Roughead, E.E., Semple, S.J., and Adams, R.J., 2003, 'Adverse Events and Medication Errors in Australia', *International Journal for Quality in Health Care*, 15:i49-i59.

[13] Australia is not alone in this trend in hospital admissions. A 1998 study of hospitalized patients published in the Journal of the American Medical Association reported that in 1994, adverse drug reactions accounted for more than 2.2 million serious cases and over 100,000 deaths, making adverse drug reactions (ADRs) one of the leading causes of hospitalization and death in the United States.

that characteristic. Medicines within the therapeutic group vary in their chemical structure, and therefore produce different levels of side effects or efficacy between patients, but on average improve health outcomes for the patient populations (such as by lowering cholesterol levels, for example). Prescribing practices are premised on the basis that the medication will provide 'similar' health outcomes 'on average' for patients displaying that characteristic.

There are significant differences, however, in how patients with a common phenotype respond to a medicine. Most are likely to respond as expected. But some may display side effects, which can be severe and result in hospital admission, while others may not respond to the treatment at all.

To date there has been no simple way to determine whether people will respond well, poorly, or not at all to a medication. Doctors must use 'trial and error' empirical methods to find the drug that works best for the patient.

Technological limitations therefore limit the optimal use of pharmaceuticals. The current inability to determine how individual patients will respond to a drug is manifest in:

- adverse drug responses (ADRs);
- poor or no response to drugs among some patients;
- poor patient compliance due to adverse drug responses or non-response; and
- poor access for some individuals if pharmaceuticals fail cost-effectiveness assessments based on 'population' analyses.

Adverse drug responses

While medical error is a significant factor in the rate of ADEs observed within the community, some may be due to unpreventable patient response due to genetic variation or other environmental factors. ADRs are a subset of ADEs and defined as an 'unintended event due to the use of a medication that could have harmed or did harm the patient'. 'Harm' includes physical, psychological or emotional suffering.[14] While studies have found that between 50 and 75 per cent of ADEs are medication-related and potentially preventable, the remainder are due to historically unpredictable patient reactions, with genetics likely to play a significant role, among other environmental factors.

Drugs that don't work: non-response

In today's model for drug development and prescribing, in which physical manifestations of disease are described in a standardised way that indicates a particular drug should be taken by a large group of patients with the same condition, produces drugs that are generally effective for only 60 to 70 per cent of the population.[15] Key examples include:

- *Antidepressants* — Worldwide over 45 million people are either depressed or schizophrenic, with more than 400,000 new cases of depression estimated to be diagnosed each year. Approximately 15 million are on medication, with the first line of treatment being Selective Serotonin Reuptake Inhibitors (SSRIs). Approximately 20 to 25 per cent of patients have been estimated not to not respond to SSRI therapies.[16] Similarly, it is estimated that between 20 and 50 per cent of patients do not respond to tricyclic antidepressants.

[14] Runciman, W.B., Roughead, E.E., Semple, S.J., and Adams, R.J., 2003,
[15] Deloitte, 2007, Targeted Therapies: Navigating the Business Challenges of Personalised Medicine, Deloitte Centre for Health Solutions, p 6.
[16] Kirchheiner, et. al, ACTA Psychiatry, Scandanavia, 2001, 104:173-192.

- *Cardiovascular drugs* — Statins are the highest value and largest volume items on the PBS and used to treat the common phenotype hypercholesterolemia. Research has shown that their efficacy across a large population could be enhanced by evaluating inter-individual differences; it has been estimated that between ten and 60 per cent of patients do not respond to statins.

  Other cardiovascular drugs include ACE-inhibitors and beta-blockers, which are estimated to be ineffective in between ten to 30 per cent, and 15 to 35 per cent of all patients, respectively.

Moreover, new drugs often offer the potential to achieve significant improvements in health outcomes, but many of these will come at a significant cost. To the extent that drugs are inappropriately prescribed to persons, this will represent an increasing burden on the healthcare system. Improving the quality use of medicines and the affordability of the PBS going forward will hinge on reducing prescribing of ineffective drugs to the wrong patients.

Poor medication compliance

Compliance to medications is one of the most challenging and complex behaviours shown by patients. The international literature suggests that approximately 50 per cent of patients with chronic diseases do not take their medications in full therapeutic doses as intended by the prescriber. For example, about half of patients starting long term statin treatment have discontinued their treatment within six months. Adherence in clinical trials is generally very high, due to the extra attention patients receive; however, even in clinical trials patients average between 43 per cent and 78 per cent per cent compliance for chronic conditions.[17]

Non-compliance may result in a poorly managed medical condition, which may in turn affect a patient's quality of life. Importantly, non-compliance can be costly from an economic point of view. A poorly controlled disease may require additional therapy or hospitalisation due to non-compliance. Non-compliance to medications has been linked to increased utilisation of healthcare resources, including emergency department and hospital admissions, general practice visits and nursing home admissions,[18] and is the primary reason for sub-optimal disease state management.[19] Several studies in the United States have estimated the costs of non-compliance to be around US$100 billion annually.[20]

1.3.3 Poor access by some cohorts

With the growth in the availability of high cost drugs, particularly in the areas of oncology, immunology and even chronic disease such as arthritis, cost-effectiveness assessments based on large groups of patients with a common phenotype often fail cost-effectiveness hurdles to gain listing on the PBS. This can result in sub-optimal access to medicines as some patients may be denied access to drugs that might have significant therapeutic potential for them. Poor access to new drugs may influence patient morbidity and mortality, and have flow on impacts for the economy due to lower labour force participation and productivity, as well as raise concerns for equity of access among Australians for pharmaceutical therapies.

---

17 Osterberg, L., Blaschke, T., 2005, 'Adhereence to medication', New England Journal of Medicines, vol. 353, 487-497.

18 World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva; 2003.

19 Ibid.

20 Hughes, C.M., 2004, 'Medication non-adherence in the elderly: how big is the problem?', *Drugs and Aging*, 21(12):793-811; and Forum on Patient Compliance 2002 (Center for Business Intelligence).

1.4 Economic costs of sub-optimal use of medicines

These barriers to the optimal use of pharmaceuticals have real economic outcomes for the community.

- The average cost of adverse events has been estimated to be approximately $14,027 per event.[21]
- Poor patient response, compliance or access to life-saving drugs can reduce patients' quality of life and increase their use of other healthcare resources, resulting in lower workforce participation and productivity than would otherwise have been the case and higher costs of care to the community.
- Wasting expenditure on drugs that are not appropriate for a patient diverts scarce resources away from other, better uses and depresses economic growth.

Thus, notwithstanding the immense good arising from improvements in the treatment of disease through pharmacotherapy, there is significant scope for improvement in the wellbeing and quality of life of individuals and their carers through more effective and efficient pharmacotherapy. This would be expected to greatly improve the performance of the healthcare system and national economy.

[21] Jonathon P Ehsani, Terri Jackson and Stephen J Duckett, 2006, The incidence and cost of adverse events in Victorian hospitals 2003, *MJA* 2006; 184 (11): 551-555.

2 Pharmacogenomics: using diagnostics for safer, more effective care

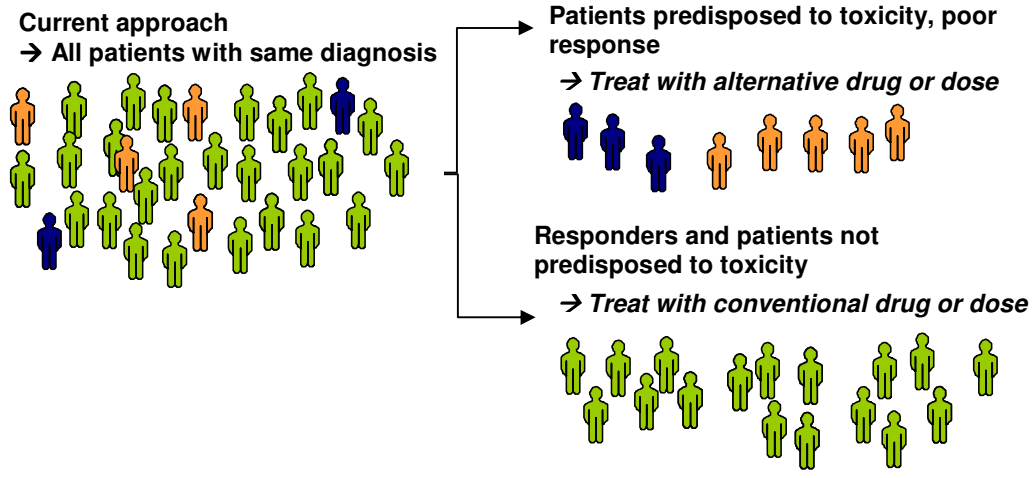
This chapter defines pharmacogenomics, identifies the opportunities for improvements in patient care expected as a result of pharmacogenomics, and current translation of research into clinical practice.

2.1 What is Pharmacogenomics?

In Australia today patients are given medications that cause some patients side effects or are not effective. Poor drug response is often due to the presence or absence of particular genetic characteristics or 'biomarkers' that affect how an individual responds to a medicine. Doctors must use simple 'trial and error' empirical methods to try to find an effective medicine if the first attempt is ineffective or unsafe. Often, a patient must return to their doctor over and over again until the doctor can find a drug that is right for them. Many patients do not comply with their therapies, even though it is not safe for them to do so.

Pharmacogenomics (PGx) is a medical science that examines the presence of individual biomarkers that dictate drug response and enables the doctor to know *before prescribing a medicine* whether the patient is likely to have a good response to a drug, a bad response to a drug, or no response at all. With PGx, doctors will be able to test for biomarkers and prescribe the safest, most effective medicines available.

Figure 2.1: The Pharmacogenomics Potential: Improving the Safety and Quality Use of Medicines



Source: Modified from Mallel, S., 2008, *Clinical Applications of Pharmacogenetics in HIV*, Symposium: Clinical Applications of Pharmacogenetics in HIV, Ritz Carlton Hotel, Isla Verde, Puerto Rico, 7 September.

Specifically, PGx technologies identify differences in the function of drug transporters, drug metabolising enzymes and drug targets between people. It can be viewed as a subset of a wider analysis of biomarkers and their use in genetic research, clinical practice and public health.[22] Importantly, however, PGx is specifically focused on *improving the use of pharmaceuticals* within the community to improve patient outcomes and is not used to predict any other aspects of a patients' health.

2.1.1 Pharmacogenomics or pharmacogenetics?

PGx arises from the convergence of advances in pharmacology, genetics and, more recently, human genomics.[23]

Among many clinicians, distinctions are drawn between pharmacogenomics and pharmacogenetics. To these scientists, 'pharmacogenomics' refers to the general study of *all* of the many different genes that determine drug behaviour, whereas 'pharmacogenetics' technically refers to the study of inherited differences in drug metabolism and response. That is, these scientists would use the term 'pharmacogenetics' to depict the study of *single genes* and their effects on inter-individual differences in drug metabolising enzymes, and the term 'pharmacogenomics' to depict the study of not just single genes but *the functions and interactions of all genes in the genome* in the overall variability of drug response, whether this is caused by pharmacokinetics, pharmacodynamics or both.

The distinction between the two terms, while important from a research perspective, is general considered arbitrary outside scientific communities and now the two terms are used interchangeably both in Australia and internationally.[24] The term 'Targeted Therapies' is also sometimes applied to canvass both terms, including the Commonwealth Department of Health and Ageing.

This report uses 'pharmacogenomics' or 'PGx' to broadly describe any research that provides information about drug response based on the presence or absence of biomarkers in a patient, and therefore should be interpreted to encompass both pharmacogenomics and pharmacogenetics technologies.

2.2 Emerging pharmacogenomics technologies

The study of pharmaceuticals and inter-individual differences due to the presence or absence of particular genetic characteristics is at least 40 years old. Research into the area was initially fuelled by observations of adverse drug reactions in a single subject or just a few patients, which generated speculation that pharmaceuticals may act differently in the body depending on the presence, absence or variation of particular biomarkers.

More recently, the focus on PGx and the potential to improve the use of pharmaceuticals has accelerated and expanded, following a number of advances in gene mapping technologies, which culminated with the completion of the first human genome sequence in 2003. Since this time R&D spending has being strongly focused on developing drugs using technologies based on genomic technologies or drug targets.

PGx is still an emerging field. The level of predictive value of PGx testing varies depending on the particular biomarker in question, and the proportion of patient variation determined by that biomarker. Thus some biomarkers are well established, 'valid' predictors of drug response while others provide biological clues but currently have limited clinical value (and

---

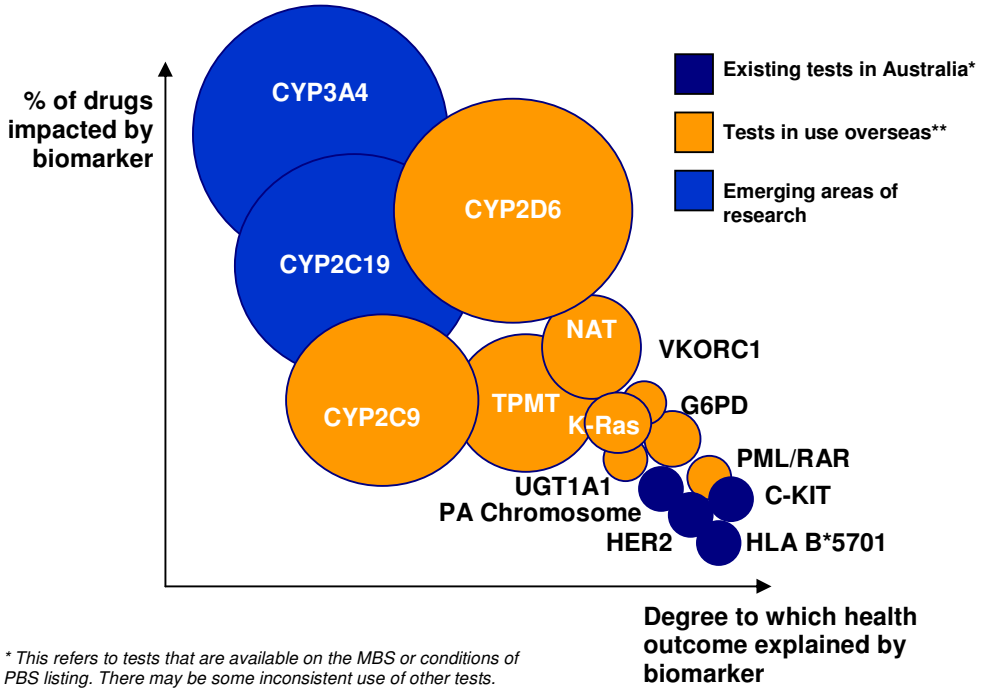
[22] Department of Health and Human Services, 2008, Realising the Potential of Pharmacogenomics: Opportunities and Challenges, Report of the Secretary's Advisory Committee on Genetics, Health and Society, Washington DC, May.

[23] *Ibid.*

[24] See for example the US National Centre for Biotechnology Information, 2008, *One Size Does Not Fit All: the Promised of Pharmacogenomics*, http://www.ncbi.nlm.nih.gov/About/primer/pharm.html [September 2008]

should be viewed as emerging areas of research). Some of the major areas of research and the potential impact on drug prescribing is shown in Figure 2.2.

Figure 2.2: Pharmacogenomics biomarkers – areas of research and existing tests



** This refers to tests that are available on the MBS or conditions of PBS listing. There may be some inconsistent use of other tests.*

*** This shows current recommendations by the FDA for PGx testing*

As shown in Figure 2.2, there are a handful of PGx tests in use today in Australia and overseas. These tests tend to be focused on biomarkers that affect patient outcomes for particular drugs. Increasingly, the validity of PGx testing for biomarkers that affect a large number of drugs is being shown and implemented in clinical practice overseas. Major examples of valid biomarkers include tests for the CYP450 family of genes, the TMPT gene, the HER2 biomarker and the Human Leukocyte Antigen (HLA) set of biomarkers.

2.2.1 The CYP450 family of genes

Research in PGx has focused to a large extent on drug metabolising enzymes,[25] and in particular, the CYP450 gene family. The reasons for this are several. First, these genes are highly 'polymorphic' or variable, and therefore drug response varies significantly between patients. Second, most drugs that are available to patients today are metabolised by these

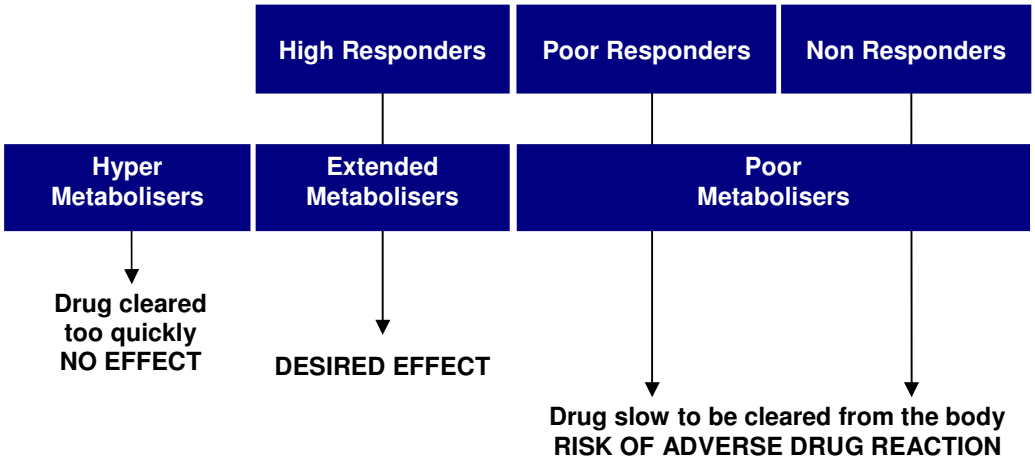
[25] Genes that are currently known to be associated with adverse drug reactions or non-response can generally be classified three main categories: drug-metabolizing enzymes; drug transporters; and HLAs. Genes in the first two categories influence the pharmacokinetics and pharmacodynamics of drugs; therapies that are affected by the presence or absence of these genes are known as 'dose dependent' drugs (Type A). Poor clearance of these drugs from the body as a result of polymorphisms in these genes can increase the concentration of the drug to a toxic level and result in adverse drug reactions. Or, the body can clear the drug too quickly and it has no effect. Genes in the latter category can result in severe dermatological reactions. Therapies that depend on a patient's HLA status are known as 'idiosyncratic' or 'dose-independent' (Type B) therapies.

enzymes. Approximately 25 per cent of all prescription drugs are metabolised by either CYP2D6 or CYP2C19,[26] while 55 per cent are metabolised by CYP3A4:

- CYP2D6, a gene in the CYP450 gene family, is involved in the metabolism of beta-blockers, antidepressants, anti-psychotics, neuroleptics, anti-arrhythmics, and a number of other major drugs, including codeine and tamoxifen. Approximately six to ten per cent of Caucasian and two per cent of Asian populations are 'poor metabolisers' with no CYP2D6 function.
- CYP2C9 is involved in the metabolic clearance of warfarin, one of the most commonly prescribed drugs in hospitals in Australia, and the most frequent causes for adverse drug events.[27] Overall, CYP2C9 variants are predicted to account for five per cent to 22 per cent of the observed variability in individual warfarin dose requirements (about 10 per cent in Caucasians).[28]
- CYP2C19, another gene in the CYP450 family, is involved in the metabolism of proton pump inhibitors, antidepressants and anti-epileptics. Approximately three to five per cent of Caucasian and 15 to 20 per cent of Asian populations are 'poor metabolisers' with no CYP2C19 function.
- CYP34A is the mechanism by which statins are metabolised. Approximately 58 per cent of African populations and nine per cent of Caucasians do not respond to statins.

Depending the presence or absence of CYP450 genes, a patient will metabolise drugs in varied ways. While patients are in reality distributed across a continuum, they are generally classified into one of four types: a 'hypermetaboliser', an 'extended metaboliser', a 'poor metaboliser' or a 'non-responder' (Figure 2.3).

Figure 2.3: Factors determining an individual's drug reaction



Source: PricewaterhouseCoopers, 2005, *Personalised Medicine: the Emerging Pharmacogenomics Revolution*, http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf [September 2008].

[26] Ingelman-Sundberg, M., and Rodriguez-Antona, C., 2005, Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy, *Philos Trans R Soc Lond B Biol Sci*., 360(1460): 1563–1570.

[27] Runciman, W.B., Roughead, E.E., Semple, S.J., and Adams, R.J., 2003, *op. cit.*

[28] Warfarin dosing is also affected by another biomarker, VKORC1 (Vitamin K Epoxide Redcutase Enzyme).

2.2.2 The TMPT biomarker

The TPMT (thiopurine S-methyltransferase) gene is another important drug metabolising enzyme important in the metabolism of thiopurine drugs, which are used to treat rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and Crohn's disease, bullous pemphigoid (a dermatological condition) and acute lymphoblastic leukaemia.

Identification of the TPMT genotype can be used to predict differences in the activity of the TPMT enzyme, also differentiating between extended and poor metabolisers.

For patients that are poor metabolisers, thiopurine drugs can accumulate in the body, which can possibly lead to life-threatening side effects, including leucopoenia. These patients should therefore receive a lower dosage of the thiopurine drug. Current treatment strategies involve frequent monitoring by means of a white blood cell count. With PGx, screening of the TPMT gene can be used to determine the optimal dosage beforehand.

The prevalence of patients with decreased TPMT activity caused by gene polymorphisms has been estimate at approximately 11 per cent. About five per cent of all thiopurine therapies have been reported to fail due to toxicity.

2.2.3 HER2 tests

Testing for the Her-2/neu (HER2) biomarker is used in the context of PGx to predict the effectiveness of trasutuzmab (Herceptin®), a therapy designed to treat women with breast cancer. Trasutuzmab will not be effective in women that are negative for the HER2 biomarker, and therefore should not be prescribed the pharmaceutical.

2.2.4 Human Leukocyte Antigen (HLA) biomarkers

HLA biomarkers are another major area of PGx research. Whereas genetic factors are understood to explain varying levels of inter-individual difference in the case of drug metabolising enzymes, and clinicians seek to modify the dose of the drug based on PGx technologies, HLA biomarkers enable dose-independent decisions to be taken. That is, should the clinician prescribe or not. For example, patients with the HLA B*5701 biomarker have an increased risk of developing hypersensitivity reactions to particular drugs (abacavir), which can lead to life-threatening hypotension. Current research shows that approximately eight per cent of all Caucasian patients have the HLA B*5701 polymorphism.[29] These patients should be provided alternative treatments.

2.3 The translation of pharmacogenomics into clinical practice

The translation of genetic information from research into clinical practice has been inconsistent in Australia and overseas. Some tests have shifted rapidly from research to clinical practice, while for others it has taken time for the clinical utility of PGx testing to be fully appreciated. Knowledge about the contribution of genomics to disease and its influence in drug prescribing also varies widely among healthcare professionals. There are significant skills gaps to assist in the interpretation of PGx tests where they are used.

Thus to date there are only a few PGx tests in use in clinical practice. Most of the testing to improve the use of pharmaceuticals has been focused on the interactions between single biomarkers with a particular drug. Testing to target the use of trasutuzmab (Herceptin®) is the most prominent example of a linked test and drug for treating breast cancer, and the test

[29] Mallel, S., 2008, *op. cit.*

is required by the Australian government to gain access to the publicly subsidised therapy. Consultations with clinicians also indicated that in Australia PGx testing was also sometimes used:

- to improve the prescribing of abacavir (Ziagen®) for patients with HIV;
- to improve the prescribing of rituximab (Rituxan®) for patients with non-Hodgkin's lymphoma, B-cell leukaemias, and some autoimmune disorders; and
- to improve the use of anti-cancer drugs, such as gefitinib (Iressa®), imatinib (Gleevec®) and tamoxifen (Valodex®).

However, overall clinicians indicated that the use of PGx in clinical practice is inconsistent. This was supported by the literature as well. Research undertaken by the University of Otago to determine the frequency of PGx diagnostics in Australia and New Zealand found that testing was frequently undertaken for a small number of biomarkers,[30] generally at the cost of the patient, but otherwise there was very poor take up by clinical communities. Genotyping and phenotyping tests for other biomarkers, including CYP450 enzymes,[31] were reported to effectively never undertaken for clinical purposes. The authors concluded that tests for drug metabolising enzymes are rarely performed in clinical practice, despite repeated claims that they may benefit patient care, and that the cause for the low clinical utilization was due to a poor evidence base, unestablished clinical relevance and, in the few cases with the strongest rationale, a slow translation to the clinical setting.[32]

2.4 Regulation and reimbursement of pharmacogenomics

Valid genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety.

The FDA has taken an active role in identifying and promoting 'valid' PGx tests, where a 'valid' biomarker is described as a 'biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.' The FDA has classified genomic biomarker tests on the basis of their specific use, including clinical response and differentiation; risk identification; dose selection guidance; susceptibility, resistance and differential disease diagnosis; and polymorphic drug targets. Its recommendations are updated on a quarterly basis.

PGx information is now contained in about ten per cent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade and several labels now either recommend or require genetic testing for PGx biomarkers to reach a therapeutic decision. For example, the commonly used drug warfarin, used to prevent blood clotting and strokes, now includes on its label a FDA suggestion that physicians be aware that genetic testing can help choose the proper maintenance dose of a drug that has a very narrow therapeutic window. Examples of other drugs whose labels have changed due to FDA regulation are:

---

30 Testing was reported to be frequently undertaken by some clinics for thiopurine methyltransferase (TPMT); pseudocholinesterase; and CYP2D6 phenotyping for perhexiline (by one active clinic only).

31 Other tests identified as not frequently undertaken include N-acetyltransferase-2 and dihydropyrimidine dehydrogenase

32 Begg, et al. [#add citation]

- irinotecan (Camptosar®), used to treat colorectal cancer;
- mercaptopurine (Purinethol®), used to treat inflammatory bowel disease and childhood leukaemia; and
- tamoxifen, used to treat breast cancer.

Reference is made to the requirement of testing for the biomarker, where:

- 1 = test required;
- 2 = test recommended;
- 2* = test for at risk populations; and
- 3 = information only.

Table 2.1 shows current FDA requirements, recommendations and evidence summaries for PGx technologies.

Table 2.1: FDA Label Recommendations and Requirements for pharmacogenomics testing

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	Aus testing req'd or funded?
	Representative Label	Test Rcmd or Rqmt	Drug		
C-KIT expression	Gastrointestinal stromal tumor c-Kit expression	3	Imatinib		✓
CCR5 - Chemokine C-C motif receptor	CCR5 is a receptor site on the human T-cell that HIV uses to bind to the cell allowing it to enter and begin replication.	1	Maraviroc		✗
CYP2C19 Variants	CYP2C19 Variants (Poor Metabolisers-PM and Extensive Metabolisers-EM) with genetic defect leads to change in drug exposure.	3	Voriconazole	Omeprazole Pantoprazole Esomeprazole diazepam Nelfinavir Rabeprazole	✗
CYP2C9 Variants	CYP2C9 Variants PM and EM genotypes and drug exposure	3	Celecoxib		✗
CYP2C9 Variants with Alternate Context	CYP2C9 Variant genotypes and drug dose	2	Warfarin		✗
CYP2D6 Variants	CYP2D6 Variants	3	Atomoxetine	Venlafaxine; Risperidone; Tiotropium bromide inhalation; Tamoxifen; Timolol Maleate;	✗
CYP2D6 with alternate Context	CYP2D6 PM and EM Variants and drug exposure and risk- 'population,	3	Fluoxetine HCL	Fluoxetine HCL and Olanzapine; Cevimeline hydrochloride	✗

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	Aus testing req'd or funded?
	Representative Label	**Test Rcmd or Rqmt**	**Drug**		
	who are known to have a genetic defect leading to reduced levels of activity of P450 2D6.			Tolterodine; Terbinafine; Tramadol + Acetamophen Clozapine Aripiprazole; Metoprolol; Propranolol; Carvedilol Propafenone Thioridazine; Protriptyline HCl;	
Deletion of Chromosome 5q(del(5q))	Cytogenetic abnormality in management of Low- or Intermediate-1 risk myelodysplastic syndromes	3	Lenalidomide	*Deletion of Chromosome 5q(del(5q))*	✗
DPD Deficiency	Deficiency of Dihydropyrimidine Dehydrogenase	3	Capecitabine	Fluorouracil Cream Fluorouracil Topical Solution & Cream	✗
EGFR expression	Epidermal Growth Factor Receptor presence or absence	3	Erlotinib	*EGFR expression*	✗
EGFR expression with alternate Context	Epidermal Growth Factor Receptor presence or absence	1	Cetuximab	Panitumab Gefitinib	✓ Gefitinib only
Familial Hypercholestremia	Dosage adjustment for Homozygous and heterozygous Familial Hypercholestremia	2	Atorvastatin		✗
G6PD Deficiency	G6PD deficiency and risk	2	Rasburicase	Dapsone	✗
G6PD Deficiency with alternate Context	G6PD deficiency and tolerance	3	Primaquine	Chloroquine	✗
Her2/neu Over-expression	Over-expression of Her2/neu necessary for selection of patients appropriate for drug therapy	1	Trastuzumab	Lapatinib	✓
HLA-B*1502 allele presence	'SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE.'	2*	Carbamazepine		✓
HLA-B*5701 allele presence	HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY	2	Abacavir		✓

Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	Aus testing req'd or funded?
	Representative Label	**Test Rcmd or Rqmt**	**Drug**		
NAT Variants	N-acetyltransferase slow and fast acetylators and toxicity	3	Rifampin, isoniazid, and pyrazinamide	Isosorbide dinitrate and Hydralazine hydrochloride	✖
Philadelphia Chromosome-positive responders	Philadelphia (Ph1) chromosome presence (effective)	3	Busulfan		✓
Philadelphia Chromosome-positive responders with alternate context	Philadelphia (Ph1) chromosome presence (effective)	1	Dasatinib		✓
PML/RAR alpha gene expression (Retinoic acid receptor responder and non-responders)	PML/ RAR (alpha) fusion gene presence	3	Tretinoin	Arsenic Oxide	✖
Protein C deficiencies (hereditary or acquired)	Hereditary or acquired deficiencies of protein C or its cofactor, protein S	2	Warfarin		✖
TPMT Variants	Thiopurine methyltransferase deficiency or lower activity due to mutation at increased risk of myelotoxicity.	2	Azathiopurine	Thioguanine Mercaptopurine	✖
UGT1A1 Variants	UGT1A1 mutation in patients, exposure to drug and hence their susceptibility to toxicity.	2	Irinotecan		✖
UGT1A1 variants with alternate context	Pharmacogenomics (safety)	3	Nilotinib		✖
Urea Cycle Disorder (UCD) Deficiency	Urea cycle disorders	2	Valproic acid	Sodium Phenylacetate and Sodium Benzoate; sodium phenyl butyrate	✖
Vitamin K epoxide reductase (VKORC1) Variants	Vitamin K epoxide reductase (VKOR) Variant	2	Warfarin		✖

Source: US Food and Drug Administration, 2008, *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels*, Department of Health and Human Services, http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm [September 2008].

In Australia, progress has been more limited, although the importance of PGx as a tool to improve the quality use of medicines has been recognised by the Department of Health, PBAC and MSAC. To date here has been no systematic identification of valid biomarker tests, and no recommendations for when these tests should be undertaken, for what populations except for a small number of conditions placed on the listings of ultra high cost drugs, including trasutuzmab, imatinib, and gefitinib[33], and a handful of HLA and chromosome tests funded on the MBS (Table 2.2). In three cases of PBS conditional listings, the PBAC has restricted the subsidy of a pharmaceutical to patients that have undertaken a test and shown they will respond to the medicine and/or not suffer a severe adverse event. Critically, however, the cost of the tests has been either funded by the pharmaceutical company, on condition of listing, or by the patient.

Table 2.2: MBS item numbers for pharmacogenomics

Item No	Biomarker	Description	Fee
73220, 73321, 73323,	HLA-B27, HLA-B5701	Detection of HLA-B27 by nucleic acid amplification includes a service described in 71147 unless the service in item 73320 is rendered as a pathologist determinable service.	$41.25
71203		Determination of HLAB5701 status by molecular techniques or cytotoxity assay prior to the initiation of Abacavir therapy including item 71203 if performed.	
73314	HLA	Characterisation of gene rearrangement by nucleic acid amplification in the diagnosis and monitoring of patients with laboratory evidence of: (a) acute myeloid leukaemia; or (b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia; each test to a maximum of 4 tests in a 12 month period	$235
71139, 71141, 71143, 71145	HLAs	Characterisation of 3 or more leukocyte surface antigens by immunofluorescence or immunoenzyme techniques to assess lymphoid or myeloid cell populations, including a total lymphocyte count or total leukocyte count by any method, on 1 or more specimens of blood, CSF or serous fluid.	$105.85-$431.95
73287, 73289	Philadelphia chromosome	Chromosome studies, including preparation, count, karyotyping and identification by banding techniques of 1 or more of any tissue or fluid except blood - 1 or more tests.	$401.45

Source: Department of Health and Ageing, 2008, *Medical Benefits Schedule*.

Other PGx testing, such as to improve prescribing for other oncology drugs or other PGx therapies identified by the FDA (Table 2.1), is at the discretion of the clinician and generally funded by the patient in the hospital setting.

2.5 Technological change and the future of pharmacogenomics

Realising the benefits of PGx on a large scale remains a long term goal; however, there is broad industry consensus that PGx will be firmly entrenched in mainstream medical practice within ten years:

[33] Hall, W., Ward, R., Liauw, W.S., Brien, J. E., and Lu, C. Y., 2005, 'Tailoring access to high cost, genetically targeted drugs', *Medical Journal of Australia*, 182(12):607-608.

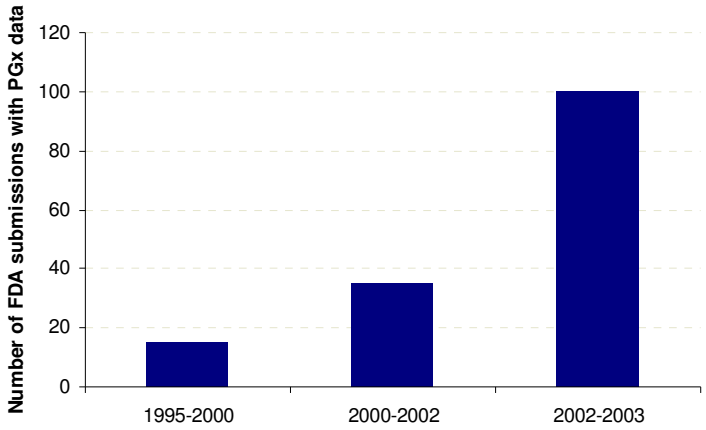
> DNA sequencing will be a routine part of the workup for patients, at the very least to identify a patient's sensitivity to drugs that are likely to produce adverse effects.[34]

Greater understanding of the role of certain drug-metabolising enzymes has the potential to improve the health of large patient populations and subgroups. Although there are currently limited applications today, there is currently a race to catalogue as many of the genetic variations found within the human genome as possible and the number of new technologies that are expected to enter the market over the next five to ten years is likely to increase exponentially. Worldwide spending on new PGx technologies[35] is projected to rise at an average annual growth rate of 24.5 per cent to reach $3.7 billion by 2009.[36] The significant investment in new PGx diagnostics development is expected to significantly reduce the costs of these technologies and increase their availability and use over the next five to ten years. For example, in May 2007 the cost of genome sequencing was approximately $1 million. Since then, the cost of genotyping has fallen below $350,000 (Knome). Another company (23andMe) offers biomarker mapping (555,000 SNPs) for $399.[37]

Similarly, DNA microarrays (or DNA chips) are an evolving technology that should make it possible for doctors to examine their patients for the presence of specific biomarkers quickly and affordably. A single microarray can now be used to screen 100,000 biomarkers (SNPs) found in a patient's genome in a matter of hours. As DNA microarray technology is developed further, biomarker screening in the doctor's office to determine a patient's response to a drug, prior to drug prescription, will be commonplace. These microarray technologies will provide data for better prescribing for multiple therapies.

As such, the number of PGx products entering the market over the next five to ten years will climb significantly above today's levels and applications. This trend is reflected in the exponential growth in FDA submissions with PGx data in the ten years to 2003 (Figure 2.4).

Figure 2.4: Increase in the number of FDA submissions with pharmacogenomics data



It is expected that a consequence of this technology change that over time, drug development and prescribing therapies will evolve from the 'one size fits all' model that is used today to increasingly personalised medicines (Figure 2.5).

---

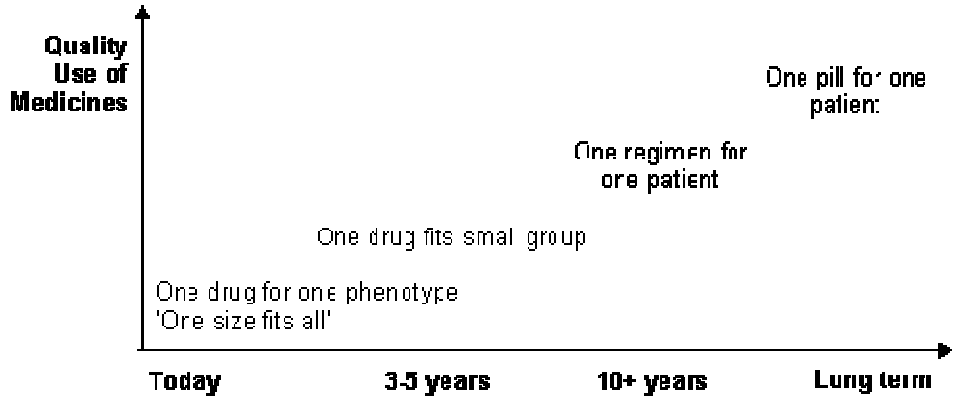
[34] Shurin, S.B., and Nabel, E.G., 2008, 'Pharmacogenomics — Ready for Prime Time?', *NEJM*, 358:10, March 6.

[35] Including SNP identification technologies, genotyping technologies and other diagnostics.

[36] Business Communications Company, June 2005, quoted in Deloitte, 2007, Targeted Therapies: Navigating the Business Challenges of Personalised Medicine, Deloitte Centre for Health Solutions.

[37] Kennedy, M., 2008, Pharmacogenomics in an Era of Personal Genomes, Carney Centre for Pharmacogenomics, Christchurch School of Medicine and Health Sciences, University of Otago.

Figure 2.5: The evolution of pharmaceutical and pharmacogenomics therapies



These technologies will bring new opportunities but also challenges for regulatory and reimbursement systems that have been developed on the basis of the 'one size fits all' model of drug development. Government will need to also invest in the systems and resources to ensure it is able optimise the uptake of cost effective technologies to drive quality use of medicines.

3 The health and economic impacts of pharmacogenomics

This chapter explores the economic rationale for PGx testing from a community perspective, identifying both the direct benefits of the technology, as well as identifying the potential costs of not adopting the technology (ADRs, sub-optimal clinical outcomes, and poor patient compliance).

3.1 Benefits of pharmacogenomics technologies for patients and governments

The use of pharmaceuticals has expanded rapidly over the past half century due to their strong contribution towards higher quality of life and longer life expectancy, as well as their cost effectiveness compared to other acute therapies.

Nevertheless, it is clear that the quality use of pharmaceuticals could be improved. High rates of ADRs, poor patient response to medicines, poor compliance by patients and poor access by some patients indicate that the large and growing expenditure on pharmaceuticals could be better targeted. PGx offers the potential to radically improve the use of pharmaceuticals through:

- avoiding ADRs;
- improving medicine efficacy and the quality of care;
- avoiding wasted expenditure on ineffective drugs; and
- improving compliance through fewer side-effects and greater risk-benefit balance.

This chapter presents a series of case studies where evidence has shown the potential for improving patient outcomes and delivering economic savings to the community through the use of PGx technologies. Improvements in health outcomes and potential economic benefits are considered for treating patients with:

- colorectal cancer;
- inflammatory bowel disease;
- risks of thromboemolism and stroke;
- HIV;
- depression;
- cardiovascular disease; and
- breast cancer.

These case studies show that over time PGx research is likely to touch almost every disease currently treated by pharmaceuticals and that the benefits to patients of improved quality and

safety in care will be significant. The chapter concludes with some exploratory analysis of the potential reductions in total healthcare expenditure as PGx advances will make it possible to improve pharmaceutical therapies for a wide range of disease rapidly and inexpensively.

3.2 Improving care for patients with colorectal cancer

Colorectal cancer, also called bowel cancer, includes cancerous growths in the colon, rectum and appendix. It is the third most common form of cancer, causing 655,000 deaths worldwide each year, and is the second leading cause of cancer-related death in the Western world. Patients experience changes in bowel movements, weight loss, anaemia and fatigue. In Australia about 12,500 new cases are diagnosed each year, and around 4,400 people die annually, making it the second most common site (after lung) to cause cancer death in Australia. The risk of being diagnosed by age 85 is 1 in ten for men and 1 in 15 for women.[38]

Once diagnosed (by colonoscopy), patients are classified into one of four stages depending on how far the cancer has penetrated through the bowel wall. Stage I is superficial, stage II is deeper and stage III is when the cancer has gone through the thickness of the wall or out into the tissues or lymph nodes beside the bowel. Stage 4 means the cancer has spread to other organs, commonly the liver.[39] With stage I colorectal cancer 90 per cent of patients will still be alive at five years. This falls to 87 per cent with stage II, 57 per cent with stage III and ten per cent for widespread disease.

Stage I and II of the disease can be treated with surgery alone to remove the bowel and surrounding lymph nodes. Stage III disease requires surgery and additional chemotherapy to try to prevent recurrence. Widespread disease is treated with chemotherapy.

More recently, pharmaceutical therapies have been trialled in addition to chemotherapy. Approximately 70 to 75 per cent of all colorectal cancers are due to the over-expression of epidermal growth factor receptors (EGFR). Pharmaceutical therapies prescribed to patients are known as EGFR inhibitors. EGFR inhibitors bind to the extracellular domain of EGFR on the tumour cell and inhibit the action of receptor-associated tyrosine kinase. This inhibition blocks the intracellular pathways associated with tumour cell proliferation, preventing tumour growth and dissemination as well as inducing cell death (apoptosis).[40] Examples of well known, widely used EGFR inhibitors include bevacizumab (Avastin®) and cetuximab (Erbitux®).

EGFR inhibitors are high cost drugs that have been shown to be effective in the improvement of cancer patient survival rates when combined with chemotherapy. Both bevacizumab and cetuximab have been shown to produce roughly comparable improvements in cancer survival rates. Median overall survival was 11.3 months in patients receiving cetuximab compared with 10.1 months in those receiving chemotherapy alone (p=0.044). Median survival was 12.3 months in the bevacizumab treatment arm, compared with 10.3 months in the control group that received chemotherapy alone. However, bevacizumab has been reported to associated with higher levels of toxicity. Bevacizumab has been shown to have higher risks bleeding and haemoptysis, as well as thromboses, proteinuria, hypertension, would healing delay, and rare serious events such as bowel perforation or posterior leukoencephalopathy syndrome which are not experienced by patients treated with

[38] Cancer Council, 2007, Colorectal Cancer, http://www.cancer.org.au/Healthprofessionals/cancertypes/colorectalcancer.htm
[39] Ibid
[40] Drug Development-Technology, 2008, Erbitux (Cetuximab) - Biological Cancer Therapy

cetuximab.[41] Side effects of cetuximab include uncommon infusion reactions, rash, and diarrhoea.

Due to genetic variations, however, these drugs are not effective in all people. Research released in 2008 has shown that patients with colorectal cancer that have a mutated K-Ras biomarker do not benefit from cetuximab. It is estimated that 35 to 45 per cent of all patients have the mutated K-Ras and therefore will not respond to cetuximab.

The use of cetuximab in patients that have the mutated K-Ras biomarker has potentially serious health consequences for patients. Patients are delayed, potentially by months, from receiving effective treatment, which can have very serious impacts on their survival rates. A patient taking cetuximab with the K-Ras biomarker could otherwise be on bevacizumab, which could potentially provide them with therapeutic benefit.[42] At the same time, the patient is at risk of experiencing side effects from cetuximab (without receiving any benefit in terms of cancer therapy), with four per cent of patients experiencing uncommon infusion reactions compared to less than one per cent in a non-cetuximab control group; ten per cent of patients experiencing rash compared to less than one per cent in a non-cetuximab control group; and five per cent of patients experiencing diarrhoea compared to approximately two per cent in a non-cetuximab control group.

From an economic perspective, expenditure is also wasted by providing patients with ineffective therapies. In 2007-08, 385 scripts for cetuximab were provided, at a cost of more than $17 million to the government. If between 35 and 45 per cent of patients were non-responsive to the therapy, then expenditure of between $6.1 million and $7.8 million could have been wasted. By contrast the PGx diagnostic to test for mutated K-Ras is offered in the United States at US$450 and US$500 per test. Assuming a cost of A$500 per test, the total cost to test between 2,500 and 3,750 patients (assuming between 20 and 30 per cent of all identified patients require chemotherapy)[43] would be between $1.3 million to $1.9 million, such that savings of up between $4.2 million and $6.5 million each year could be possible each year in drug costs alone. Patients that have access to the test and are shown to be non-responsive may also begin treatment with alternative therapies.

More importantly, patient health outcomes will be improved. For patients that would be expected to respond to cetuximab, clinicians are able to prescribe a drug that has equivalent improvements in health outcomes but lower levels of toxicity.

Cetuximab has been approved by the FDA for use in patients with EGFR-expressing metastatic colorectal cancer. The FDA has also provided labelling indicating that PGx testing for the K-Ras biomarker is mandatory before prescribing the drug. Testing is not currently required or practiced in Australia. In addition, the National Comprehensive Cancer Network in the United States has updated its colorectal cancer guidelines and now recommends that a determination of the KRAS gene status of either the primary tumour or a site of metastasis should be part of the pre-treatment work-up for all patients diagnosed with metastatic colorectal cancer. These modifications are based on results of a number of recent studies demonstrating that the tumour KRAS gene status is highly predictive of outcome with anti-EGFR therapies.[44]

---

41 Centre for Oncology Research and Treatment, 2008, http://cancernews.wordpress.com/2008/06/06/metastatic-lung-cancer-survival-improved-by-the-addition-of-cetuximab-to-chemotherapy-flex-study/

42 Note that while these drugs are both EGRF inhibitors, they involve different mechanisms of action. Cetuximab is affected by the mutated K-Ras biomarker, whereas bevacizumab is not.

43 Morris, M., Iacopetta, B., and Platell, C., 2007, 'Comparing survival outcomes for patients with colorectal cancer treated in public and private hospitals', *MJA*, 186 (6): 296-300.

44 National Comprehensive Cancer Network, 2008, 'NCCN Updates Guidelines for Colorectal Cancer', National Comprehensive Cancer Network, http://www.nccn.org/about/news/newsinfo.asp?NewsID=194 [3 November 2008].

3.3 Improving outcomes for patients on anti-coagulants

Warfarin is an anticoagulant commonly used to prevent and control blood clots. It is prescribed for patients with a history of atrial fibrillation, recurrent stroke, deep vein thrombosis, or pulmonary embolism, as well as for patients who have had heart valve replacements.[45]

However, warfarin has significant limitations due to its narrow therapeutic window and highly variable dose-response relationship. If the warfarin dose is too strong, the risk of serious bleeding increases; if the dose is too weak, the risk of stroke increases.

Two biomarkers are understood to effect the metabolism of warfarin: CYP2C9 and VKORC1. If a patient is a poor metaboliser of CYP2C9 and VKORC1, the probability of clearing the drug is greatly reduced, and the risk of an adverse event significantly increased. These people need a lower dose of warfarin.[46] Other non-genetic factors, such as age, body surface area, hypertension, heart disease, other prescription drugs renal status, bleeding history and certain foods can also interfere with warfarin absorption or anticoagulation response.[47] Nevertheless, VKORC1 variants are reported to be responsible for about 30 per cent of the variation in the final warfarin dose, and CYP2C9 responsible for about ten per cent.[48]

Testing has the potential to reduce the health care costs associated with serious bleeding among people with variant CYP2C9 and VKORC1 biomarkers. The most common serious bleeding associated with warfarin use is gastrointestinal bleeding, followed by intracranial bleeding.[49] In the US, the average direct medical cost of gastrointestinal haemorrhage was estimated to be $13,500 in 2006.[50] In Australia, the average cost of an adverse event in was estimated to be $14,027 in 2003-04.

In addition, correctly identifying patient risk for bleeding could also improve the effectiveness of care for patients who are not at risk of bleeding. Currently doctors, wary of bleeding risk, may under-dose or under-prescribe warfarin therapy. Increasing the dosage would reduce the risk of preventable stroke for patients that can tolerate higher doses.[51] According to the Australian Stroke Foundation, approximately 88,000 Australians have strokes each year,[52] with lifetime costs of stroke estimated to be $44,428 in 2003-04.[53] More effective warfarin dosing would prevent some of these strokes from occurring.

In 2007, approximately 473,000 patients were prescribed warfarin in Australia, with approximately 21 per cent of all patients being 'new patients' (approximately 99,000 new patients). Approximately 28 per cent of poor metabolisers have been shown to have serious or life-threatening bleeding events after initiation of warfarin therapy, as opposed to

---

45 McWilliam, A., Lutter, R., and Nardinelli, C., 2006, *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin*, AEI-Brookings Joint Centre for Regulatory Studies, Working Paper 06-23.

46 *Ibid.*

47 Department of Health and Human Services, 2008, op. cit., p 15.

48 Warfarin action is also affected by the VKORC1 gene. The optimal maintenance doses of warfarin can vary depending on whether an individual has two copies of the low-dose VKORC1 variant or two copies of the high dose variant. See Rieder, M.J., Reinder, A.P., et al,, 2005, 'Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose', *New England Journal of Medicine*, 352(22):2285-93.

49 Jack Ansell et al., 'Managing Oral Anticoagulant Therapy,' Chest 2001; 119:22S-38S.

50 Joyce H .S. You et al., 'The Potential Clinical and Economic Outcomes of Pharmacogenetics-Oriented Management of Warfarin Therapy – A Decision Analysis.' Thromb Haemost. 2004; 92:590-597.

51 *Ibid.*

52 Stroke Foudnation, 2008, Facts, figures and stats, http://www.strokefoundation.com.au/facts-figures-and-stats

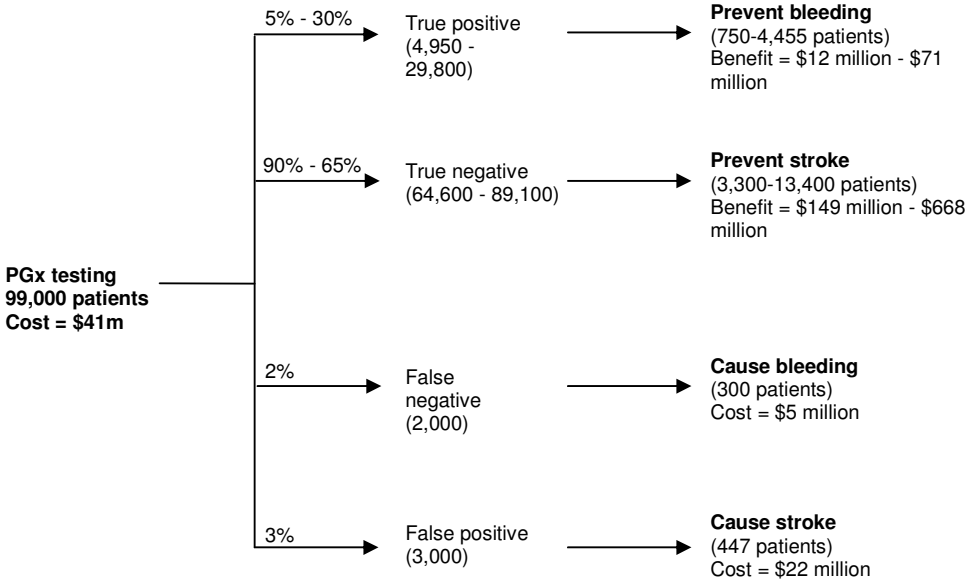
53 Helen M. Dewey, Amanda G. Thrift, Cathy Mihalopoulos, Robert Carter, Richard A.L. Macdonell, John J. McNeil and Geoffrey A. Donnan, 2003, 'Lifetime Cost of Stroke Subtypes in Australia: Findings From the North East Melbourne Stroke Incidence Study (NEMESIS)', *Stroke*, 34: 2502-2507.

approximately 13 per cent in the non-variant population.[54] Assuming that between five and 30 per cent of the population (approximately 4,950 to 29,800 patients) are at risk of being poor metabolisers of warfarin,[55] and that more accurate warfarin dosing would reduce the incidence of serious bleeding by approximately 15 per cent,[56] it was expected that between 750 and 4,470 bleeding events could be avoided each year, at a cost of approximately $15,800 per adverse event.[57]

Moreover, the more accurate dosing was also expected to reduce the risk of stroke. The number of strokes prevented depended on the incidence of the biomarker for poor warfarin metabolism in the community: if only five per cent of the population had biomarkers for poor metabolism, then dosing could be increased for the other 90 per cent of the population, reducing the risk of stroke; if 30 per cent were poor metabolisers, then dosing was assumed to be able to be increased for 65 per cent of the population.

The risk of false positives and false negatives was also considered. Two per cent of tests were assumed to yield a false positive, which would cause the dose to be reduced for these patients thereby increasing the risk of stroke. Three per cent was assumed to yield a false negative, which would cause the dose to be increased, and in turn, increase the risk of stroke for those patients.

Figure 3.1: Health outcomes under warfarin testing



The cost to test for warfarin variants was approximately US$350 and was assumed to be 95 per cent positive (i.e. five per cent of tests will yield false positives or false negatives).[58] We have assumed the cost in Australia would be approximately $410 per test and that where false negatives or positives occurred, the dosing would be modified such that these patients were at greater risk of bleeding or stroke.

54 McWilliam, A., Lutter, R., and Nardinelli, C., 2006, *op. cit.*

55 Approximately 88 per cent of the population is Caucasian, with 5 per cent being poor metabolisers, and

56 *Ibid.*

57 This is the 2003-04 cost indexed to $2008 dollars at a rate of three per cent per year.

58 US Food and Drug Administration, 2008, *Critical Path Initiative Warfarin Dosing*, Department of Health and Human Services, Washington DC, http://www.fda.gov/oc/initiatives/criticalpath/warfarin.html [September 2008].

The benefits from avoided bleeding and stroke among true positive and negative patients would be expected to be between $219 million and $680 million each year, compared to costs of approximately $41 million to test all patients, and potential adverse outcomes due to test inaccuracy of approximately $27 million. In total, the *net savings* to Australia could be between $151 million and $612 million each year through the avoidance of bleeding and stroke in the community, depending on the incidence of poor metaboliser risk.

3.4 Improving care for patients with inflammatory bowel disease

Inflammatory bowel disease (IBD) comprises ulcerative colitis, Crohn's disease and indeterminate colitis. Onset is typically in young adulthood, and the disease usually follows a chronic relapsing-remitting course. Symptoms include rectal bleeding and mucous discharge, diarrhoea, urgency and abdominal pain. Problems may extend beyond the gastrointestinal tract and may affect organs such as the liver and skin. Patients with IBD experience a high level of morbidity and make substantial use of health services.[59]

IBD is generally treated with thiopurine drugs such as azathiopurine, mercaptopurine (azathiopurine's metabolite) and methotrexate.

- Azathiopurine is the first line therapy used for the treatment of IBD; however, it is also associated with considerable toxicity for some patients, including myleosuppression, pancreatitis, gastrointestinal upset, hepatotoxicity and hypersensitivity reactions.[60] A recent study indicated that more than 25 per cent of patients prescribed azathiopurine discontinued treatment due to adverse side effects.[61]
- Methotrexate is reserved for patients that do not tolerate azathiopurine. Methotrexate has a 66 per cent probability of achieving remission in patients compared to a 90 per cent probability of achieving remission for azathiopurine.[62]

These therapies are both highly cost effective compared with health outcomes that would be expected if no immunosuppressant therapy were used.[63] A New Zealand study found that net cost savings of approximately $2.1 million and $830,000 annually, would be realised for azathiopurine and methotrexate, respectively, compared to no immunosuppressant treatments.[64] Azathiopurine is more effective, generating 877 QALYs compared to methotrexate, which would be expected to produce 633 QALYs.[65]

Azathiopurine, however, is metabolised by an enzyme known as TPMT (thiopurine methyltransferase or thiopurine S-methyltransferase). The activity of TMPT varies significantly between patients, and some patients have a higher risk of side effects because they do not metabolise the drug adequately, which causes an accumulation of the unmetabolised drug in the body. The costs to treat these side effects are significant (Table 3.1).

---

59 Priest, V.L., Begg, E. J., Gardiner, S.J., Frampton, C. M.A., Gearry, R. B., Barclay, M. L., Clark, D.W.J., and Hansen, P., 2006, 'Pharmacoeconomic Analyses of Azathiopurine, Methotrexate and Prospective Testing for the Management of Inflammatory Bowel Disease', *Pharmacoeconomics*, 24(8): 767-781.

60 *Ibid.*

61 *Ibid.*; Pearson, D.C., May, G.R., Fick, G., et al, 2004, Azathiopurine for maintenance of remission in Crohn's disease, Cochrane Library; Bouhnik, Y., Lemann, M., Mary, J-Y, 1996, 'Long term follow-up patients with Crohn's disease treated with azathiopurine or 6-mercaptopurine' *Lancet*, 347: 215-219; Lemann, M., Zenjari, T., Bouhnik, Y., et al, 2000, 'Methotraxate in Crohn's disease: Long term Efficacy and toxicity', *Am J Gastroenterol*, 95(7): 1730-1734.

62 *Ibid.*

63 *Ibid.*

64 Based on a $NZ exchange rate of $1.2. See Reserve Bank of Australia, 2008, Exchange Rates, 1 September 2008.

65 *Ibid.*

Table 3.1: Costs to treat azathiopurine side effects

Adverse effect	Cost	Description
Neutropenia – life threatening	$16,620	7 days ICU, 5 days general ward, antibiotics and G-CSF
Neutropenia – severe	$6,210	Average 6 days general ward, antibiotics and G-CSF
Neutropenia – moderate	$388	2 GI clinics, 2 FBCs
Hypersensitivity	$212	GI clinic, FBC, LFT
GI disturbance	$158	GI clinic
Hepatitis	$350	2 GI clinics, 2 LFTs
Opportunistic infection	$230	GI clinic + drugs
Pancreatitis	$158	GI clinic
Pneumonitis	$7,168	Hospital admission, corticosteroids, antibiotics, CT scan and lung biopsy

Source: Priest, V.L., et al, 2006, *op. cit.* with some prices based on MBS fees. Not FBC = Full Blood Count; G-CSF = Granulocyte Colony Stimulating Factor; ICU = Intensive Care Unit; LFT = Liver Function Test.

This intolerant group could be anticipated by routine measurement of TPMT activity in order to allow for lower doses of AZA to be provided to TPMT-deficient patients. The 2006 study found that have approximately 11.5 per cent of Caucasian patients are at risk of neutropenia (nine per cent moderate and 2.5 per cent either severe and life threatening). PGx testing was expected to identify 90 per cent of the TMPT deficient population, and therefore current testing technology was assumed to have a 90 per cent sensitivity.[66]

The test was assumed to cost $50.[67] In Australia, approximately 30,850 patients are on azathiopurine. Approximately 37 per cent, or 11,415 patients, are 'new patients' where they are either just starting therapy or switching from an alternate therapy. To test all new Caucasian patients before prescribing would cost approximately $502,000 each year. Without testing, it would be expected that approximately 904 patients would develop moderate neutropenias, while 251 would experience more severe side effects in the form of severe or life threatening neutropenias.[68] Given the above adverse drug reaction treatment costs, testing for new Caucasian patients (assuming the patient population mirrors the broader population) would result in savings of $2.7 million each year. The economic benefits would therefore exceed the costs, with net savings of $2.1 million expected each year.

More importantly, doctors can be more active in prescribing azathiopurine knowing the most severe adverse drug reactions can be controlled for their patient. For every 1,000 patients cost savings of $1.3 million would be expected due to the use of azathiopurine compared to methotrexate. While the proportion of doctors prescribing methotrexate to patients to avoid potential risks of neutropenia are not known, where doctors may perhaps in the past avoided azathiopurine to minimise patient risk, they can now prescribe the drug and improve the probability of IBD going into remission.

3.5 Improving outcomes for patients with HIV

HIV and AIDS is perhaps the greatest challenge of modern medicine. In Australia 998 people are diagnosed with HIV infection each year, and 197 people are diagnosed with AIDS. Approximately 80 people die annually from the disease in Australia. In 2006, it was

[66] This is based on the phenotype testing evidence.

[67] The test in NZ was reported to cost NZ$57, see Priest, V.L., Begg, E. J., Gardiner, S.J., Frampton, C. M.A., Gearry, R. B., Barclay, M. L., Clark, D.W.J., and Hansen, P., 2006, *op. cit.*

[68] General population data shows that a patient is four times as likely to experience a severe neutropenia compared with a life threatening neutropenia.

estimated that 16,400 people were living with HIV/AIDS in Australia. Of the diagnoses observed in 2006, the average age was 38.[69]

Abacavir, a nucleoside reverse-transcriptase inhibitor (NRTI) and an important antiretroviral treatment against infection with the human immunodeficiency virus (HIV), is an effective first line treatment for HIV. Abacavir works by slowing the spread of HIV infection in the body.

In white populations, however, between five per cent and eight per cent of patients on abacavir will have a serious hypersensitivity reaction characterized by fever, rash, and symptoms in the gastrointestinal tract, other organ systems, or both. The cost of treating this hypersensitivity has been estimated in Australia to be between $212 per patient for a moderate reaction to $15,800 for an episode requiring hospitalisation.[70] Research has shown that approximately 60 per cent of hypersensitivity reactions are mild and 40 per cent are severe enough to need hospitalisation. Approximately 0.7 per cent are fatal.[71]

In 2002, a major discovery was made by researchers that the HLA-B*5701 biomarker is highly associated with hypersensitivity reactions to abacavir. These findings encouraged clinicians in Australia to carry out prospective HLA-B*5701 genotyping between 2002 and 2005, which was able to show that HLA-B*5701 explained all of the variation in Caucasian patients. PGx testing for the HLA-B*5701 biomarker now enables clinicians to avoid the hypersensitivity side effect, improving the safety and quality of care for patients.

Assuming ethnicity distribution matches Australian ethnicity distribution, 88 per cent of newly diagnosed patients would be considered at risk (Caucasian). Testing these patients at a cost of $41.50 per test (MBS fee) costs just over $36,000 per year. Research[72] shows that approximately 70 persons that would have developed the hypersensitivity reaction are able to avoid the reaction, with 42 experiencing a moderate reaction and 28 persons experiencing a severe reaction. In total, avoided expenditure on hypersensitivity treatment would be more than $450,000 per annum. Besides the clear improvements in patient safety, there is a net saving to Australia of around $415,000 per annum.

Importantly, however, the test would also be critical to improving patient compliance. Research in British Columbia found that the major reason for stopping abacavir early (< 6 weeks) was due to concern for hypersensitivity.[73] The study showed that 12 per cent of patients discontinued abacavir early. This finding has been confirmed by a number of other studies.[74]

Stopping early was shown to be associated with a significantly longer time to Visceral Leishmaniasis (VL), a disease where patients present with fever, enlargement of lymph nodes, enlargement of the liver, enlargement of the spleen, cytopenias or enzymatic profiles: patients that could not tolerate abacavir (and had to be put on alternative therapies) on average developed VL within 131 days of diagnosis, while patients that could tolerate abacavir reached VL at an average of 81 days. As a consequence, patients stopping abacavir early were more likely to seek care from emergency physicians or specialists with higher costs for services within first 60 days of starting abacavir.

---

69 National Centre in HIV Epidemiology and Clinical Research (NCHECR), Australian Surveillance Update April 2007 and Annual Surveillance Report 2007.

70 This is based on the average cost per adverse event in 2003-04 indexed to $2008.

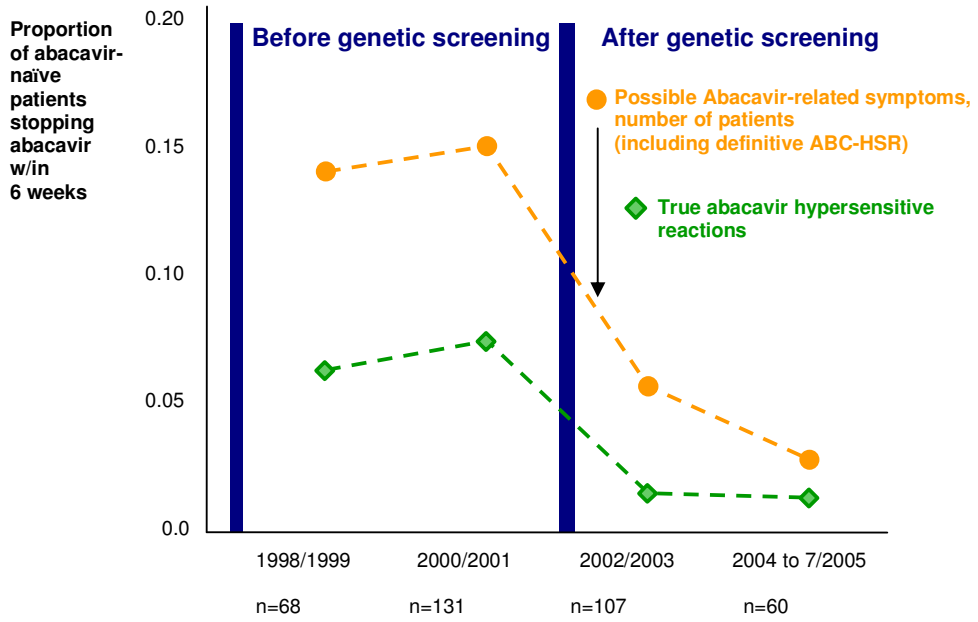
71 Cairns, G., 2008, *Hypersensitivity testing for abacavir slightly more cost-effective than tenofovir use, if both drugs equally potent*, AIDSmap, September, http://www.aidsmap.com/en/news/EDE2BB5D-B7BA-4DB7-9B11-460D7374CDC8.asp [September 2008].

72 Mallel, 2008, op. cit.

73 Phillips E. EACS Dublin 2005: PE9.7/9, quoted in Mallel, 2008, op. cit.

74 Trottier et al, 2007, 'Abacavir early discontinuation decreased from 13.6% to 5.6% after screening', *IAS*, abstract MOPEB002); +HLA-B*5701 + HSR from 12.2% to 0%, Zucman et al JAIDS 2007; epub March 8); ^ABC HSR 6.5% historically to 0% post screening, Reeves et al HIV Medicine March 2006, all quoted in Mallel, S., 2008, *op. cit.*

Figure 3.2: Improvement in patient compliance by all abacavir patients



Source: Mallel, S., 2008, *op. cit.*

There is currently an MBS item number for HLA-B*5701 testing to improve prescribing of abacavir. This is one of only a few PGx tests available. The MBS item number also serves as a general category for other genetic testing.

3.6 Improving care for patients with depression

Clinical depression is a serious medical condition. It significantly affects the way a person feels, causing a persistent lowering of mood. Depression is often accompanied by a range of other physical and psychological symptoms that can interfere with the way a person is able to function in their everyday life.

Worldwide the World Health Organisation estimates that more than 121 million people are depressed. Depression is the leading cause of disability and the fourth leading contributor to the global burden of disease. By the year 2020, depression is projected to reach second place for the global burden of disease.[75]

In Australia, around one in five people will experience a depressive illness at some time in their lives and around six per cent will experience a more severe form of the illness.[76] If inadequately treated, depression can result in suicide, a common cause of death. Treatment for depression is expensive and protracted. Depression is the fourth largest burden of disease on the Australian population and the largest non-fatal burden of disease.[77]

Approximately one third of depressed patients are on medications, with Serotonin Selective Reuptake Inhibitors (SSRIs) being the first line of treatment. While there is evidence of a positive effect of SSRIs for patients with depression and anxiety disorders, FDA data has

[75] World Health Organisation, 2008, *Depression*, http://www.who.int/mental_health/management/depression/definition/en/

[76] Sane Australia, 2008, *Depression*, http://www.sane.org/images/stories/information/factsheets/0701_info_depression.pdf [September 2008]

[77] AIHW, 2003, *op. cit.*

shown that *the response rate for these drugs is only 60 per cent to 70 per cent*,[78] meaning that between three and four people in ten are not receiving therapeutic benefits from pharmaceuticals — but still are exposed to the side effects of the drugs, which can be severe. Similarly, another class of antidepressants, tricyclic antidepressants, are shown to be *effective in between 50 to 80 per cent of patients*.[79] This defines a large group of patients with difficult-to-treat depression.

There are a wide range of biomarkers being examined to better target pharmaceutical treatments of depression, including a number of CYP450 enzymes (CYP2D6 and CYP2C19), and other biomarkers, such as 5-HTT.[80] With current spending on antidepressants of approximately $458 million each year,[81] and depression significantly affecting one in five Australian's health, wellbeing and ability to participate in the community, improving the efficacy and efficiency of this spending holds the potential to significantly improve the quality and safety of care as well as economic outcomes.

3.7 Improving care for patients with breast cancer

Breast cancer was the most common newly diagnosed cancer among females in 2001 (11,791 new cases diagnosed). It is projected that there was projected that there would be 13,261 women diagnosed with breast cancer in 2006 and 14,818 in 2011. Breast cancer in males is rare. A woman's risk of dying from breast cancer before the age of 85 has been declining, from a 1 in 29 risk in 1983 to a 1 in 36 risk in 2004. There were 2,641 female deaths and 20 male deaths due to breast cancer in 2004. Australia's death rate from breast cancer is lower than the rates for New Zealand, the United Kingdom, Canada and the United States of America. The average age of first diagnosis was 60 years for a woman and 66 years for a man in 2002. In 2003-04, approximately 18 per cent of women that presented to hospital for treatment of breast cancer were under the age of 50. [82]

Treatment of breast cancer varies by patient and the progression of the cancer, and can include surgery to remove the cancer, mastectomy, and chemotherapy. In 2003-04, the most common procedures for female patients with a principal diagnosis of breast cancer were 'excision of lesion of breast' with 8,930 separations, followed by 'simple mastectomy' with 4,817 separations and chemotherapy administration with 1,913 separations. Total expenditure on breast cancer was $241 million in 2000-01. Of this, $96 million was spent on population screening mammography, $72 million on hospital admitted patients, $21 million on out-of-hospital medical costs and $27 million on pharmaceuticals requiring a prescription. Breast cancer was reported to have an estimated lifetime treatment cost of $11,897.[83]

Approximately a quarter of all women diagnosed with breast cancer are prescribed tamoxifen.[84] Tamoxifen works by interfering with the activity of the hormone oestrogen, which feeds the growth of many, but not all breast cancers. Tamoxifen's metabolites bind to the oestrogen-receptor sites in breast cells and prevents oestrogen from binding to them.

---

78 Scheffer, R., 2008, *Treating pediatric psychiatric illness with selective serotonin reuptake inhibitors*, http://www.chw.org/display/PPF/DocID/33996/router.asp September 2008]

79 Koumantakis, G., 2008, *One size does not fit all*, GAP Forum, July.

80 Weizman, A., and Weizman R., 2000, 'Serotonin transporter polymorphism and response to SSRIs in major depression and relevance to anxiety disorders and substance abuse', *Pharmacogenomics*, 1(3): 335-341.

81 Total spending for psychoanaleptics as reported in Department of Health, 2008, *op. cit.*

82 The number of new cases of breast cancer in males per year increased from 43 in 1983 to 84 in 2002. See AIHW, 2006, *Breast Cancer in Australia 2006*, Australian Government Canberra.

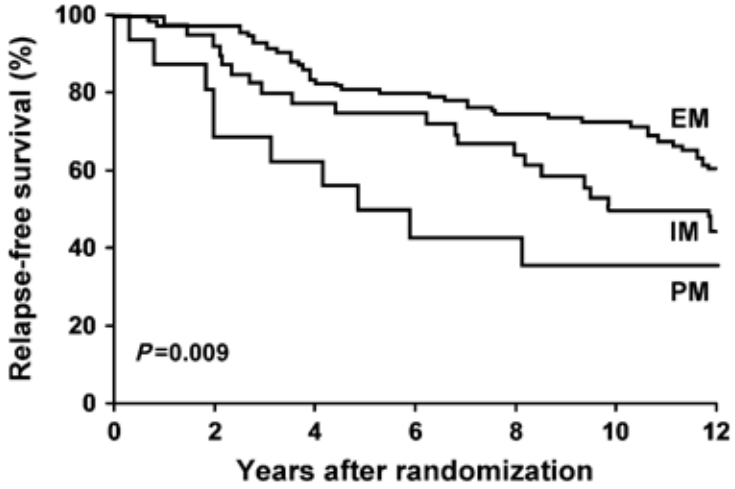
83 AIHW, 2006, *op. cit.*

84 For women who have not had breast cancer but are at high risk (women who carry a mutation in the breast cancer genes BRCA1 or 2, women who have a significant family history of breast cancer, and women who have precancerous lesions including atypical ductal and lobular hyperplasia and lobular carcinoma in situ) tamoxifen can be used to reduce their chance of developing the disease.

Because tamoxifen works against the effects of oestrogen in the breast, it functions as an 'anti-oestrogen' in breast tissue. For people with advanced breast cancer, tamoxifen is used to slow or stop the growth of cancer cells that are present in the body. For people with early stage breast cancer, tamoxifen is used as an additional treatment (adjuvant therapy). It helps prevent the original breast cancer from returning, and it helps prevent the development of new breast cancers. Tamoxifen has had a major impact on breast cancer, reducing recurrence by about 40 per cent in tens of thousands of women participating in hundreds of clinical trials, and has also been used to prevent cancer from occurring in the first place in women who have a higher risk of breast cancer.[85]

Tamoxifen is only effective, however, if the body can properly metabolise it. Recent research on tamoxifen has shown that up to seven to ten per cent of Caucasian women with breast cancer may not receive the full medical benefit from taking tamoxifen, because they are poor metabolisers of CYP2D6. Because of this biomarker, the effectiveness of tamoxifen is reduced and women's chance of breast cancer recurrence increases. Research undertaken by the Comprehensive Cancer Centre and the Mayo Clinic has found that poor metabolisers of CYP2D6 were twice as likely to see their breast cancer return (Figure 3.3).[86]

Figure 3.3: Percentage of patients expected to relapse following tamoxifen treatment depending on their CYP2D6 status



Source: Goetz, M.P., Kamal, A., and M.M. Ames, 2007, Tamoxifen Pharmacogenomics: The Role of CYP2D6 as a Predictor of Drug Response, Clinical Pharmacology & Therapeutics (2008) 83, 160–166.

Recently, a PGx test has been developed that can identify patients that will not respond to tamoxifen as a therapy, enabling their doctors to provide them with other, better therapies. This PGx test evaluates a woman's CYP2D6 function to indicate whether she is likely to be a poor metaboliser or not. The FDA has required the labelling of tamoxifen to indicate that CYP2D6 poor metabolisers who take tamoxifen have a higher risk for breast cancer recurrence, and that PGx testing is available.

Testing patients for the CYP2D6 biomarker has been reported to cost $200.[87] If testing for all newly diagnosed Caucasian patients (approximately 2,300 in 2007-08) were undertaken, this would cost between $460,000 each year.

[85] http://www.cancer.gov/clinicaltrials/results/anastrozole0805

[86] James Rae, Ph.D., at the University of Michigan Comprehensive Cancer Center and Matthew Goetz, M.D

[87] Joan Arehart-Treichel, 2005, Psychiatric News , 'Gene Testing Could Help Predict Drug Responses', *American Psychiatric Association*, 40(10).

If between seven and ten per cent of women are poor metabolisers, between 161 and 230 women will be at risk that tamoxifen is ineffective, and 60 per cent will be at risk of a relapse within ten years time (between 93 and 132 patients). If these patients could be prescribed alternative therapies that would increase their probability of survival to be in line with extensive metaboliser groups, between 32 and 46 patients could be expected to avoid relapse through improved therapy.

From a health outcome, this is significant improvement in relapse free survival rates for patients. From an economic perspective, the benefits would accrue in the form of avoided costs of treatment in the ten years following therapy. Based on 2001 cost data, and indexing these costs to $2008, the potential benefits of avoided relapse could range from $543,000 to $776,000 each year depending on the rate of poor metabolisers in the female population, the potential improvement in health outcomes through alternative therapies, and the costs of treatment for relapsed patients.

In addition, there would be economic benefits if some women were able to return to work. Assuming that the age distribution of the poor metaboliser cohort matches that of the wider breast cancer population, then approximately 18 per cent of women that would avoid relapse would be under age 50 (between 6 and 8 women). Applying a conservative wage rate to value their economic contribution of $40,000 per year, and assuming they would be able to return to work once their cancer was in remission, this would result in additional benefits of up to $2.4 million to $3.2 million over the ten years of remission.

3.8 Improving health outcomes for patients on statins

Statins are a type of lipid-lowering drug in common use in Australia. Statins may be prescribed to help lower levels of LDL-cholesterol[88] in the blood, for example in the treatment of hypercholesterolemia. This in turn can reduce the risk of diseases such as coronary heart disease.[89]

Statins work by blocking the action of an enzyme called HMG-CoA reductase, which is the enzyme that controls the rate of cholesterol production in the body. By doing this, the availability of cholesterol is reduced. Statins also increase production of the receptor for 'bad' LDL-cholesterol, which helps clear LDL-cholesterol from the circulation; and help liver cells take up more LDL cholesterol from the blood as it passes through. The resulting effect is a reduction of total cholesterol, LDL cholesterol and triglyceride fats. Statins can reduce the level of LDL-cholesterol in the blood by 30 to 63 per cent.[90] Higher doses of statin drugs reduce the risk of cardiovascular disease, but may also be associated with side effects in some people.

Statins are the most commonly prescribed drugs in Australia. In 2006, more than 17 million scripts were filled (10 per cent of all PBS scripts), at a cost to government of $940 million (17 per cent of the total cost to government of the PBS) and a total cost to the community (patients and governments) of $1.1 billion (18 per cent of total PBS spending by the

[88] Low-density lipoproteins, sometimes referred to as 'bad' cholesterol.
[89] Virtual Medical Centre, 2008, *Statins*.
[90] *Ibid.*

community).[91] Within this group, simvastatin and pravastatin are among the most prescribed in Australia;[92] in 2006:

- 5.9 million simvastatin scripts (35 per cent of all statin scripts) were filled, at a cost of $308 million to the government and $360 million to the community; and
- 1.8 million pravastatin scripts (11 per cent of all statin scripts) were filled, at a cost of $95 million to the government and $111 million to the community.

Research, however, has shown that their efficacy across a large population could be enhanced by evaluating inter-individual differences; it has been estimated that between ten and 60 per cent of patients do not respond to statins. At a total cost of $940 million to the government, improvements in prescribing could result in significant savings to the community.

There may also be opportunities to control side effects and improve patient compliance. While statins are considered one of the safest classes of lipid-lowering drugs and are well tolerated in the short term, common side-effects include headache, nausea and vomiting, constipation, diarrhoea, or rash. More severe side effects, in the form of muscle pain and break down of muscle tissue, known as myopathy, may also occur. Patients at increased risk of developing muscle problem associated with statin therapy are those with kidney failure, thyroid problems and liver disease.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group identified a genetic risk factor for myopathy in patients who were being treated with simvastatin. This study showed that patients with the SLCO1B1 biomarker had a higher risk of developing myopathy if they were prescribed higher doses of simvastatin (80mg compared to 40mg). The study showed that 60 per cent of all cases of myopathy were explained by the SLCO1B1 biomarker and that this outcome could be avoided by modifying the dose for these patients.

Further investigation is required to identify the optimal therapeutic approach. Nevertheless, the potential for a major breakthrough in such a high volume drug would produce significant health benefits for Australians.

3.9 Exploring the full economic impact

The case studies show that over time potential applications for PGx will be wide and varied, impacting potentially all medicines currently listed on the PBS. Given that more than half of all medicines are influenced by a handful of biomarkers, tests that analyse multiple biomarkers for patients, such as microarray technologies (‘genome chips’) or genome scans, will enable better prescribing for a wide range of diseases. For example, testing for the CYP2D6 biomarker using microarray technologies that map all CYP450 biomarkers can enable better prescribing for not only breast cancer drugs, but potentially a range of other medicines, including over time statins, anti-depressants, warfarin and other drugs given more than half of all medicines are influenced by these biomarkers. Similarly, PGx tests for the TPMT biomarker will enable better treatment of not only IBD, but potentially other cancers as well.

It is expected that the number of tests will increase exponentially over the next five to ten years, with PGx becoming a major component of medical practice by the end of ten years.

---

91 Pharmaceutical Benefits Division, 2007, Expenditure and prescriptions twelve months to 30 June 2006, Department of Health and Ageing, Australian Government Canberra, http://www.health.gov.au/internet/main/publishing.nsf/Content/3CC2D4DF821FE5ADCA2570F40005B9B1/$File/Full%20book%202005-06.pdf [September 2008].

92 Four statins are currently available in Australia: atorvastatin, fluvastatin, pravastatin and simvastatin. Atorvastatin (Lipitor®) is the most prescribed.

PGx technologies will be added to the Australian health system on a case by case basis, and clearly the most important impact for the community will be the potential to improve patient safety — this has been the chief focus of the few MBS items that have been listed today, while the PBS conditions of listing have been implemented to improve the cost effectiveness of PBS items. When fully implemented, however, the full economic impact of PGx is likely to be significant, although the total value to Australia is difficult to determine with precision today. The reasons for this are several, including:

- the evidence base is continuing to emerge;
- there are generally multiple causes of adverse drug response or ineffectiveness, including not only genetic factors but also age, co-morbidities, diet and other environmental factors;
- test efficacy is variable; and
- the benefits of PGx (avoided adverse events, improved effectiveness, improved compliance) will vary by disease, which vary in severity by disease.

Nevertheless, exploring the full economic impact once PGx is likely to be common medical practice by taking a top down, macro estimate of the potential benefits is useful, particularly when the government may need to consider investments in additional resourcing for health technology assessment bodies, or to support education and training initiatives among clinicians. We consider the potential macro benefits of PGx technologies once 'fully implemented' (assuming in approximately ten years time) in terms of their ability to:

- reduce ADRs;
- reduce wasted expenditure on ineffective drugs; and
- improve patient quality of life and in turn, their utilisation of the healthcare system.

3.9.1 Avoided adverse drug reactions

A 2003 review of literature and reports from data collections of the Australian Bureau of Statistics, Institute of Health and Welfare, Council for Health Care Standards and Patient Safety Foundation[93] found that two to four per cent of all hospital admissions (7.6 million in 2006-07)[94] are medication-related (ADRs); up to three-quarters were found to be potentially preventable, leaving 25 per cent that might have been reduced through improvements in technology.

Genetic biomarkers are a major contributor to both preventable and non-preventable ADRs. For this study it was assumed that most drug-drug interactions and a majority of environmental factors influencing drug safety are known, and potentially preventable with better medication management. It was also assumed that 'non-preventable' ADRs are due to unexpected drug sensitivities, arising in the main from currently unknowable biomarker profiles, and to a lesser extent from other environmental factors, including age, co-morbidities, and diet. For this study, it was conservatively assumed that between 0.5 per cent (based on 38,000 in 2007) and one per cent (76,000 in 2007) of all hospital admissions are due to currently non-preventable ADRs that could be avoided through improved PGx technology. *In reality, PGx will likely enable some 'preventable' ADRs to be avoided as well and in practice it will likely be that not all 'non-preventable' ADRs will be able to be avoided as a result of PGx.* In the absence of better data at this time, this approach provides an 'order of magnitude' estimate: is likely to capture the majority of additional ADRs that

[93] Runciman, W.B., Roughead, E.E., Semple, S.J., Adams, R.J., 2003, *op. cit.*
[94] AIHW, 2008, *op. cit.*

are likely to be avoided with PGx while also excluding the ADRs that could be prevented with fewer medical errors.

Although Australia is a strongly multicultural society, census data shows that from an ethnicity perspective it is more homogenous than expected. In 1999 Australian census ethnicity data showed that nearly 95 per cent of all Australians are either Caucasian[95] (88 per cent) or East Asian[96] (5 per cent).[97] These ethnicities have been shown to be poor metabolisers of approximately half of all prescriptions in Australia. Poor metabolisers are at higher risks of adverse events. If patients were screened before being prescribed medicines where they have a higher risk of an adverse outcome, then potentially approximately half of the population (approximately 12.2 million)[98] would need to be screened at a cost of approximately $205 per test.[99] The total cost in Year 1 would be $2.4 billion.

On the benefits side, adverse events were estimated in 2003-04 to cost $14,027 on average per hospital admission.[100] Indexing this cost by three per cent to 2018, if these adverse events (between 38,000 and 76,000) could all be avoided using PGx technologies,[101] the potential benefits from the avoided costs of ADRs would be between $1.0 billion and $1.6 billion in Year 1 (2018).

From a net benefits perspective, if the tests were able to reduce the number of adverse events by only 76,000 ADRs (one per cent), there would be a net cost of $781 million in Year 1. If only 38,000 ADRs (0.5 per cent) could be prevented, there would be a net cost to Australia of $1.4 billion in Year 1. In Year 2, however, the net benefits to the community would be positive, because half the population's biomarker profile would be known. If a further ten per cent of the population required testing in the following year, the total cost at $206 per test would be $246 million. On the benefits side of the equation, however, the number of adverse events would similarly be expected to be reduced by between 0.5 and one per cent as a result of historic testing. The benefit to Australia in Year 2 would be between $1.1 billion and $1.7 billion. In Year 2, there would be net benefits of between $812 million to $1.5 billion. By Year 5, 16.7 million Australians (63 per cent of the population) would have had their PGx profile defined, which will guide prescribing for the rest of their lives. The net benefits would therefore continue to rise while the total cost to the community would decline. Once fully implemented the benefits from avoided adverse events is likely to reduce total healthcare expenditure by approximately one per cent.

Over a five year horizon, net benefits of between $2.1 billion and $5.5 billion would be expected if all of the ADRs not due to medical error could be avoided through PGx technologies.

Sensitivity analysis

Given the multitude of factors that may lead to an ADR, however, it was then assumed that only 40 per cent of the current 'unpreventable' ADRs could be explained by genetic

95 Anglo-celtic (70%), North and West European (7%), Southern European (7%), East European (4%), Jewish (0.66%).

96 South East Asian (2.5%) and North East Asian (2.7%).

97 Other ethnicities included West Asian and North African (2.5%), South Asian (1.3%), Pacific (0.5%) and African (0.1%).

98 ABS, 2008, Cat. No. 3201.0 - Population by Age and Sex, Australian States and Territories, Jun 2002 to Jun 2007, Australian Government Canberra. In the 12 months to 30 June 2007, the Australian population increased by 317,162 people, reaching 21,015,042. The annual growth rate for the year ended 30 June 2007 (1.53%) was higher than that recorded for the year ended 30 June 2006 (1.49%). This population was projected forward ten years at the growth rate for 2007 to get the cost in ten years' time.

99 This was the $2008 price that was indexed at three per cent per annum to 2018 prices – the cost being $270.

100 Jonathon P Ehsani, Terri Jackson and Stephen J Duckett, 2006, The incidence and cost of adverse events in Victorian hospitals 2003, MJA 2006; 184 (11): 551-555. [In 2003-04] the mean cost of all admitted episodes without an adverse event was $2,181 (95% CI, $2,171 – $2,190) compared with $14,027 (95% CI, $13,865 – $14,187) for an episode with an adverse event.

101 The costs of adverse events were indexed by a conservative 3 per cent per annum to 2018 prices.

variation[102] and avoided through PGx testing. This would reduce the number of ADRs that might be avoided to between approximately 19,000 (0.2 per cent) and 38,000 (0.4 per cent) ADRs in Year 1 (2018).

Applying the same assumptions as above, in Year 1 there would be a net cost to Australia of between $1.6 and $2.1 billion if PGx technologies only explained 40 per cent of non-preventable events (and less than 0.5 per cent of all ADRs in that year). By Year 2, however, the benefits under both scenario would be positive, generating benefits of between $177 million and $600 million. Over a five year horizon, the total cost to Australia would be $1.2 billion in the low case (only 0.2 per cent of ADRs avoided). There would be a net benefit of $1 billion in the high case of 0.4 per cent of all ADRs being avoided.

3.9.2 Avoided wastage

Related to the improvement in the quality of care, doctors will be able to avoid current 'trial and error' methods of prescribing. Currently more than half of all medicines require the presence of particular biomarkers that between five and ten per cent of the population lack. If PGx were able to improve prescribing to reduce the number of scripts provided that would not work, this would enable patients and governments to avoid wasting expenditure on drugs that won't work.

In 2006-07, 168.5 million PBS scripts were filled[103] at an average price of $32 to the government and $6.50 to the patient. Assuming that approximately 20 per cent of all scripts are new scripts, and that for half of all scripts between five and ten per cent will be either unsafe or ineffective, the potential benefits of avoided wastage would be between $53 million and $105 million (one per cent of total PBS spending) by 2018. Over a five year period, this could add a further $360 million to $720 million in additional benefits, bringing the total net potential benefit to Australia from reduced healthcare costs (avoided adverse events and avoided wasted medicine expenditure) to between $2.5 billion and $6.2 billion.

3.9.3 Improvements in quality and effectiveness of care

In addition, PGx would enhance the effectiveness of prescribing and the quality of care, by enabling doctors to target the right dose for a patient. On top of cost savings from avoided adverse events and wasted drug expenditure, Australian quality of life would improve, leading to lower utilisation of healthcare resources and higher labour force participation. It is difficult to credibly quantify the potential benefits from improved quality of life that would be derived from PGx technologies today. Nevertheless, the case studies provide examples of how improved quality of life translates into lower healthcare utilisation and labour force participation:

- For example, in the case of warfarin, more effective prescribing would reduce utilisation of the healthcare system by reducing the incidence of stroke, saving the community between $219 million to $680 million each year. In ten years time, this could add a further $5.7 billion in savings on top of avoided ADRs and wasted expenditure.
- In the case of tamoxifen, more effective prescribing would reduce recurrence of breast cancer, avoiding expenditure of between $543,000 to $776,000 each year

[102] This estimated using data from Miller, G.C., Britt, H.C., and Valenti, L., 2006, 'Adverse drug events in general practice', *Medical Journal of Australia*, 184(7):321-324, which identified the different causes of adverse drug events. Causes that were potentially preventable by PGx technologies were identified to be drug sensitivity (upper bound 14.9%), allergy (upper bound 13.7%), overdose (upper bound 2.5%), other (upper bound 4%) and don't know (upper bound 6.8%).

[103] 234 million scripts were filled in total, including PBS and non-PBS scripts.

through lower rates of recurrence. Indexing this to 2018, this could provide an additional $6.5 million in reduced healthcare costs over a five year horizon.

In addition, there would be economic benefits if some women were able to return to work; this could result in additional benefits of $2.4 million to $3.2 million over the ten years of remission.

3.9.4 Summary impact

The net economic benefits from avoided ADRs and unnecessary pharmaceutical spending are estimated to be approximately $2.5 billion to $6.2 billion over five years time once fully implemented, which would represent an approximate one per cent reduction of total health care expenditure. On top of this, the burden of many diseases would likely be reduced through more effective care, which would lead to significant improvements in patients' quality of life and leading to further reductions in healthcare resources over time. Considering only the savings from safer and more effective care with warfarin and tamoxifen would add more than $6 billion to the total potential savings expected over the same time period, bringing the total benefits to more than $12 billion (two per cent of total healthcare spending).[104] This ignores potential improvements in the effectiveness of care for other major categories of PBS spending, including cardiovascular medicines and antidepressants.

With government spending on health care projected to grow from nine per cent today to an estimated 16 to 20 per cent of GDP by 2045, and with Australia facing a growing crisis in the shortage of skilled medical professionals, any ability to constrain growing health care costs will directly support the future sustainability of the Australian health care system.

[104] This additional $6 billion captures some of the 'preventable' ADRs that were not included in the avoided ADR calculation.

4 Barriers to pharmacogenomics uptake

PGx technologies will bring new opportunities for improved patient care but also challenges for regulatory and reimbursement systems that have been developed on the basis of separate technology platforms and a 'one size fits all' model of drug development. Government will need to invest in the systems and resources required to ensure it is able to optimise the uptake of cost effective technologies that improve the quality use of medicines.

This chapter considers some of the current challenges and barriers to the optimal uptake of PGx over the next five to ten years, including regulatory, reimbursement, clinical, privacy, ethical and infrastructure issues.

4.1 Regulatory challenges

The current regulatory model, while robust in its basic foundations, will be challenged by PGx. The essential areas of concern arise from:

- the fragmented or 'siloed' nature of the regulatory bodies that have been developed on historically separate technology platforms (pharmaceuticals and diagnostics);
- the inadequate resourcing of evaluation bodies (MSAC, PBAC) to cope with the growth in demand for their services;
- the potential for poor regulation of product quality where products are not listed on the MBS; and
- poor mechanisms for identifying technologies that would improve the quality use of medicines where there is not a private incentive to bring that product to market.

From a safety and quality of care perspective, these regulatory challenges create risks for poor equity of access to the safest care possible (where a product is not listed on the MBS), sub-optimal use of medicines, wasted expenditure and poor health outcomes. From an administrative perspective, these challenges create risks for poor process consistency, predictability, and transparency. These issues have been recognised by the Department of Health and Ageing, PBAC and MSAC as requiring action to improve the regulatory environment in the context of these emerging technologies. Stakeholder consultations have also indicated that these bodies have recognised the potential for significant benefits to the community through improved quality use of medicines, avoidance of ADRs, and more effective therapy.

4.1.1 Regulatory silos

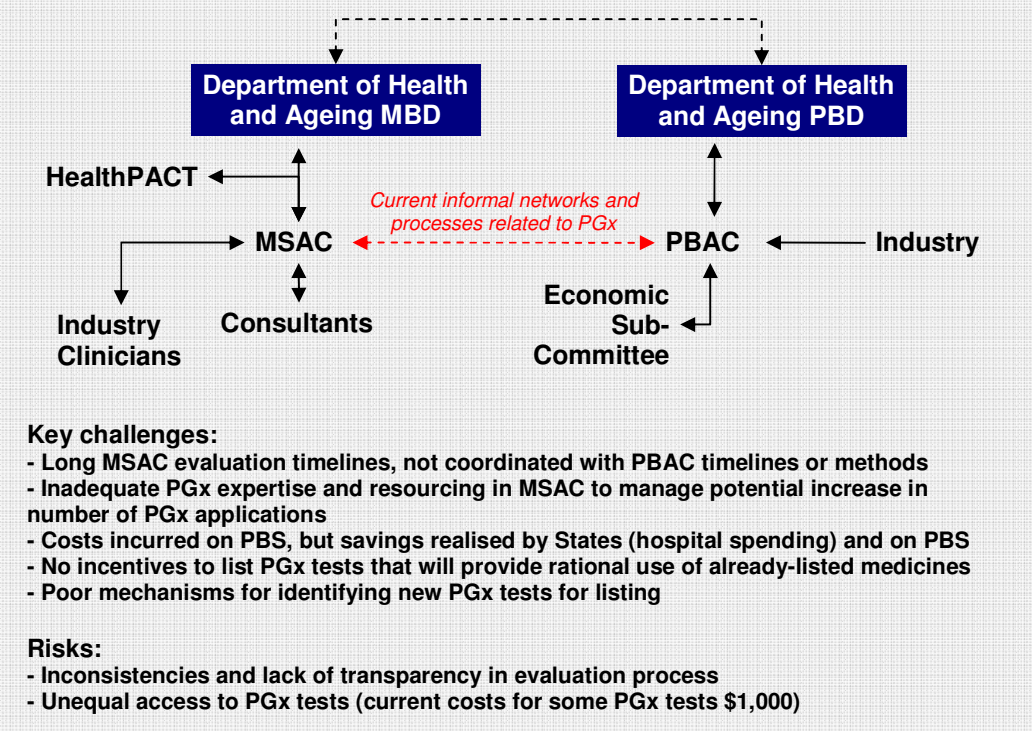
PGx represents the convergence of previously separate technology platforms: pharmaceuticals and diagnostics. This is a growing feature of modern healthcare and technology, and creates challenges for regulatory bodies that were set up on the basis of a particular technology focus, such as PBAC, which evaluates the effectiveness and cost effectiveness of pharmaceuticals (for listing on the PBS), and the Medical Services Advisory Committee (MSAC), which evaluates the effectiveness and cost effectiveness of medical procedures, including diagnostic tests (for listing on the MBS). Newer health technologies

that require assessment of a number of combined technologies, which may reduce overall costs of healthcare, can fall between the limits of these bodies.

To date, there have been only a handful of PGx technologies requiring review. These have been evaluated on an 'exceptional' basis, through collaboration between the respective divisions of the Department of Health and their key advisory bodies, PBAC and MSAC (Figure 4.1).

Where the test has originated from the PBAC process, the outcome has been that the PBAC has implemented a condition of listing, which requires a PGx test to be conducted before the pharmaceutical can be prescribed (trasutuzmab, gefitinib). In no case has there been a 'companion listing' on the MBS for the PGx test where a PBS condition of listing has been implemented: the PGx test has either been funded by the pharmaceutical company or it has been left to the patient to fund the test. The lack of a 'companion listing' potentially creates risks for equality of patient access to care: stakeholders have indicated the cost of some PGx tests can exceed $1,000.

Figure 4.1: Current evaluation framework for pharmacogenomics – no formal processes for coordination between MSAC and PBAC



Separately there have also been listings of some PGx technologies on the MBS (see Table 2.2 in Chapter 2) but these have been initiated by clinicians through the MSAC process; it is not clear that PBAC was consulted in the listing of these technologies.

While the current approach to PGx has generally worked for these initial 'test case' listings, this disjointed process creates risks for potential gaps in the controls on PBS spending and access to technologies through the MBS. Moreover, MBS item number or numbers will be an important enabler for the uptake of PGx. The absence of MBS or PBS listing can suggest deficiencies in the adequacy of evidence of efficacy or cost-effectiveness. This in turn will tend to create an obstacle to the optimal dissemination and uptake of a service, even though

the biomarker may in fact be valid. Clinicians may have limited access through some public hospitals and some private pathology providers in the case of these diagnostic tests, but practice will be inconsistent across clinicians.

Without reform to the current regulatory arrangements, risks will arise due to the 'chicken and egg' situation between MSAC and PBAC:

- Under current arrangements, PBAC is routinely asked to assess a product with respect to PGx data where there was no diagnostic test supported by the MBS, no obvious cost of that test to build into the assessment, and no certainty that either or both these elements would be forthcoming within a reasonable timeframe, if at all. It is conceivable that an MSAC assessment of the validity of the test would differ from a PBAC assessment of the effectiveness and cost-effectiveness of a drug; a single test could relate to more than one drug, but PBAC applications would relate to a single drug.
- On the other hand, a difficulty for MSAC is that a test that may have relevance to the metabolism of a number of drugs, some known and some not yet known, requires an understanding of drug utilisation in order to form a precise estimation of the potential utilisation of the test.
- MSAC does not routinely review pharmaceuticals and although it is no doubt within the competence of its members, the expertise in this area lies more within the PBAC. The cost effectiveness of the diagnostic tests is directly related to the cost-effectiveness of the pharmaceuticals to which the test is relevant, and how any conditions of use of a drug or drugs are based on this testing. Only then can one take into account all of the cost of the pharmaceuticals, estimation of any expectation of improved clinical outcomes and then take the cost of the diagnostics into account.

In the US, the FDA responded to the challenge of converging technologies by creating the Office of Combination Products. Similarly, in Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with advice about the effectiveness and efficiency of all health technologies, including drugs, devices and diagnostics. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing national guidance on the use of new and existing medicines, treatments and procedures and clinical practice. These centralised structures ensure the costs and benefits are considered from a community perspective as opposed to a single portfolio perspective, which minimises the risks that a technology may not be considered because it does not provide savings within the same technology portfolio. They also provide mechanism for consistency, predictability, and transparency of the technology assessment process.

Australia has not implemented any reforms to provide for the convergence of pharmaceuticals and other technologies. Nevertheless, PBAC has been dealing with the assessment of evidence relating to PGx for some time and PGx has been recognised as an important, emerging tool for the improved quality use of medicines. It is clear that PBAC and MSAC, however, currently lack the resources to undertake timely reviews of evidence of linked technologies and there is no *formal, standardised means to coordinate assessments between PBAC and MSAC*. A concurrent health economic assessment with a relevant pharmaceutical would greatly simplify the assessment of the PGx test. The review of other aspects of the assessment such as accuracy or specificity would not need to differ greatly from existing assessment processes within MSAC, except that as the number of tests requiring review increases, the reviews may need to involve reviews of evidence dossiers

(prepared by sponsor companies) as opposed to all reviews being undertaken by MSAC (or some other HTA body).

4.1.2 Long MSAC evaluation timelines

When MSAC was established in 1998 it was assumed that the majority of applications would originate from clinicians and professional medical associations. Given that medical professionals were expected to have caseloads that would prevent them from devoting the time and resources to prepare full reviews of the evidence for an MSAC submission, MSAC has a responsibility to undertake its own reviews of the evidence (through consultancies) for an MBS listing. MSAC therefore has a very different process and level of review required to approve a technology for MBS listing than PBAC, which reviews dossiers of evidence prepared by pharmaceutical companies.

In the past ten years, MSAC has approved on average 14 new item numbers each year, which is significantly less than the more than 100 new PBS listings each year on average. The current time to list a service on the MBS is between two and three years, compared to an average time of approximately 18 months for the PBS.[105] With respect to PGx, MSAC has generally lacked the resources and expertise to rapidly progress reviews of PGx tests, and very few have been submitted for listing. In the past 10 years, MSAC has on average added one genetic test every two years.[106] Although the average time to listing on the MBS is two to three years, there has been a recent example of a four year wait for a PGx application.[107]

These timelines are only likely to lengthen as more PGx technologies enter the Australian market. Extending the National Medicines Policy to PGx, this creates risks for timely access to technologies required to provide high quality, rational use of medicines. Moreover, any benefits from potential improvements to streamline the TGA and PBAC evaluation and listing processes will be eliminated if parallel processes and timetables can not be developed for MSAC as well.

In order to promote the quality use of medicines, there is a clear need to harmonise MSAC's reviews of PGx technologies with PBAC review timelines.

The Department of Health and Ageing has been exploring options to triage or fast-track applications on the basis of risk to reduce the time to listing for PGx technologies. As the number of technologies requiring assessment increases, however, there is also a clear need for *additional resources to be funded* for the review of PGx. Multiple government department and agency representatives indicated that both PBAC and MSAC are currently at the limit of their resource capabilities and unable to take on any more responsibility without additional funding. While fast track reform options for HTA in Australia should be pursued, additional personnel and funding will also be required to harmonise MSAC and PBAC timelines and processes, which is critical to the development of a long run, sustainable framework for PGx.

4.1.3 Poor regulation of quality

The advent of PGx will have the effect of shifting the burden of quality and safety from the clinic to the lab. Currently accreditation of laboratory facilities through National Association of Testing Authorities (NATA) is only required if MBS funding is sought. If PGx tests are not funded by the government, under current legislation no accreditation required. This could

---

105 O'Malley, S., 2006, *op. cit.*

106 Royal College of Pathologists, 2008, *Genetic Testing in the 21st Century: Are We Ready?*

107 The drug imatinib targets a specific biomarker known to cause chronic myeloid leukaemia. Imatinib was listed on the PBS in 2004, with benefits restricted to patients who had taken a PGx test to show that the drug would be effective for them, similar to the HER2 testing for trasutuzmab. It took four years for an assay to be evaluated by MSAC and listed on the MBS. See Royal College of Pathologists, 2008, *op. cit.*

result in poor quality testing, with patients making healthcare decisions based on inaccurate results.

Australia either needs to implement an information campaign to alert consumers to these risks, or it could consider regulation of private market testing. The former is likely to be a lower cost mechanism for ensuring patients make decisions based on accredited laboratory evidence. In addition, given the potential for consumers to purchase tests from overseas labs, a regulatory approach for Australian labs would probably not achieve the desired outcome (and would be impossible to monitor).

4.1.4 Poor mechanisms for improving rational use of already-approved and listed medicines

As a result of the fragmented system, no systematic reviews of evidence are being undertaken, as are currently conducted in the US and Europe. No guidelines for clinical practice have been developed, and significant inconsistencies exist in clinical settings, which create concerns for patient equity. Moreover, no body has a role to recommend revised labelling requirements for already-listed medicines to the TGA.

Consequently, while it remains within the power of MSAC to recommend either temporary item number/s, conditional inclusion on the MBS for testing for certain conditions, use of certain drugs, etc, or both, there are significant risks that technologies that might strongly improve the safety, quality and cost effectiveness of care in Australia will not be listed on the MBS or widely disseminated in clinical practice.

There is a need to create a responsibility in Australia for the review of PGx evidence as it emerges, particularly for currently listed pharmaceuticals (e.g. warfarin) in order to modify indications or restrictions to take into account this new evidence.

4.2 Reimbursement challenges

The complexity of the regulatory structures also presents a challenge for the funding of PGx technologies: the costs of PGx will be incurred on the MBS, while the savings will be realised by other portfolios. Moreover, generally-applied offset requirements for listing on the MBS potentially provide a significant disincentive for private firms to list new PGx tests. Test providers will not list their technologies on the MBS if it contributes to the further erosion of the price paid for other technologies, or does not reflect the value of the test.

PGx technologies represent a new technology and should be considered in the context of reductions in overall health expenditure beyond the MBS and improvements in health outcomes. It would be less relevant with respect to seeking balance across other testing already listed on the MBS.

To provide appropriate incentives for listing, PGx should be reimbursed on a cost-effectiveness basis, similar to the method by which pharmaceuticals are priced (costs per QALY gained). The reasons for this are two-fold:

- *Variability in test costs* — There is likely to be significant variability in the price of different tests depending on the equipment and personnel required. Some tests may require specialised, high cost equipment or personnel while others may be based on high throughput (and lower cost) technologies. Clinician and company interviews indicated that prices on the private market currently range from $50 to several thousand dollars per test.
- *Variability in test benefits* — Different tests will provide very different health and economic benefits to Australia. For example, a microarray test for a CYP450

biomarker or biomarkers could improve health outcomes for a range of therapies, potentially saving Australia millions of dollars and generating significant QALY benefits each year. Other tests will be more focused and produce benefits for smaller patient groups. If these benefits are inadequately valued, there will be a disincentive for the test to be listed on the MBS. The test may be provided on the private market, but will create risks for equality of access to the technology.

There would not appear to be an inherent obstacle to reimbursing PGx on the MBS on this basis. Implementing this reform will require concurrent HTA assessments of pharmaceuticals and PGx technologies, which will require much greater formal coordination of MSAC and PBAC than is currently the case.

4.3 Barriers to research translation

4.3.1 Poor clinician knowledge

Poor clinical uptake of valid PGx tests in Australia is due in the main to poor clinician understanding of PGx and its potential to improve patient outcomes, as well as a lack of decision support tools to interpret PGx test results.

In the US, the FDA updates quarterly a list of valid PGx tests, which provides advice for clinicians on whether the test is 'mandatory' or 'recommended' and for what populations with links to medical literature. The FDA also requires updates to medicine labels to ensure consistency of advice to clinicians.

No advisory body undertakes these roles in Australia. There are currently no algorithms available to guide clinical practice, or processes to update labels for already-listed drugs. Australia needs general guidelines to improve clinical practice as well as drug specific guidelines to ensure appropriate interpretation and revisions of therapy.

4.3.2 Improving the evidence base

For PGx to significantly enhance the quality use of medicines, the evidence base around the clinical utility of biomarkers needs to be improved. There is a need to validate biomarker tests and to support the uptake of these tests, but also to ensure that medical practice does not 'get ahead' of the science.

Consideration of PGx evidence has not been a mandatory component of the assessment processes for pharmaceuticals to date. This may have contributed to the relative paucity of evidence currently available on PGx in Australia. Until PGx evidence forms a routine part of assessments by the TGA and PBAC, it is likely that clinical pharmacological research would continue to follow existing patterns and formats, and that pharmaceutical company funding would equally follow the same sort of patterns.

The National Health and Medical Research Council is the biggest funder of health research in Australia. Its history in funding translational research – examining the appropriateness, manner, effectiveness and even cost-effectiveness of putting scientific knowledge into clinical practice – suggests that it would not be prudent to expect that it would independently determine that research in this area is required in order to determine how best to achieve benefits for health outcomes and health expenditure related to this fairly new science. It is unlikely that the NHMRC would divert funding from current streams to 'invest' in PGx research without government direction.

There are no other likely major sources of funding in Australia.

Therefore, to direct funding to the expansion of knowledge in this field, and to focus on areas likely to be of most direct benefit to health systems, government and the community, the government would need to commit specified funds to this as a priority area.

It is preferable that this be over and above current allocations for NHMRC, at least for a limited period, and that it be specifically designated for this field of research. Even so, it may be that NHMRC could be tasked to manage this as a priority program. However, a strategy to achieve these aims from within current NHMRC allocations is likely to be significantly delayed by existing grant allocation cycles, reviews to determine what might be sacrificed to allow for this new priority, and probably some degree of pushback from existing stakeholders that might perceive some disadvantage to themselves that might result from the changed priorities.

Given the link to improving the quality use of medicines, it would be optimal for the National Medicines Policy Executive to have input into determining a research strategy in relation to PGx.

4.4 Privacy, legal and ethical issues[108]

Despite the potential benefits of PGx, experience shows that a critical threshold issue for community participation in activities involving the collection of sensitive health information is the extent to which people are confident that their personal privacy will be protected. The question is how to ensure people feel in control and confident while allowing the necessary information to be collected and used in clinical, research and other relevant settings.

Significant as they are, privacy issues affecting individuals are only one part of the picture. Health service providers are also likely to have questions about their privacy, ethical and legal obligations and risks in recommending or providing PGx testing.

While PGx does not necessarily raise new privacy, legal or ethical issues, these issues are nevertheless likely to have implications for health service providers' and the community's support for PGx and the cost and timelines for any implementation. This section considers privacy, legal and ethical issues for the community associated with a systematic implementation of PGx in Australia.

4.4.1 Privacy issues

PGx: special case of sensitive health information

Many of the inquiries and discussions about PGx both in Australia and overseas recognise that patients, health service providers and the broader community will expect that PGx testing is conducted in a way that takes account of privacy issues. Most people consider any health information to be highly personal (Box 4.1), and therefore expect and need to be confident that their privacy will be protected whenever they use a health service. This is recognised, for example, in the fact that health information is included in the definition of sensitive information in the *Privacy Act 1988 (Cth)* (the Privacy Act) and is currently the subject of specific health privacy laws in NSW and Victoria.[109]

Box 4.1: Community concerns for health information — a case study

Some useful insights about possible community views of PGx can be gained from a recent study of community reactions to process of screening newborn babies for certain conditions. The report which was prepared for the NSW Genetic Services Advisory Committee in 2006 found amongst other things

[108] This section has been prepared by Information Integrity Solutions.

[109] Section 6 of the Privacy Act provides that ***'sensitive information'*** means….(b) health information about an individual see www.austlii.edu.au/au/legis/cth/consol_act/pa1988108/s6.html

that:

- the concept of the current testing was highly supported;
- when participants were advised about the practice of storage and further use of NBS Sample Cards they found this 'surprising and even shocking' and looked for high levels of transparency on such issues;
- while participants were generally supportive of research uses of the samples and were happy for decisions about research to be handled by due process, they expected to have a choice if the samples were personally identifiable;
- participants indicated areas of research that they considered unacceptable or concerning including research uses that might lead to discrimination by insurers or employers, and some felt strongly that use by pharmaceutical and biotechnology companies was also unacceptable.

Source: Information Integrity Solutions, 2008, *Privacy, Ethical and Legal Issues in PGx Testing* and Ian Muchamore, Luke Morphett and Kristine Barlow-Stewart, 2006, *Community Views and Perspectives of Newborn Screening*, The Centre for Genetics Education NSW Genetics Service, February, www.genetics.edu.au/pdf/nbs_commview.pdf [September 2008].

Information about a person's genetic makeup, whether used to improve drug prescribing or otherwise, is considered to be very sensitive information. Amongst other things it can be predictive of health conditions, it can reveal information not only about the individual concerned but also about other family members, and it can be obtained easily as it is present in every cell, or stray hair, of an individual.[110] The 2003 Australian Law Reform Commission's (ALRC) and the Australian Health Ethics Committee's (AHEC) report into the protection of genetic information clearly suggests that there are difficult and complex issues to be considered. In the case of screening for drug treatment, the ALRC and AHEC identified that these risks could include:

- denial of treatment that could still be of assistance or discrimination in treatment or in the individual's interactions with the health system;
- misuse or mishandling of genetic information, particularly if in wide circulation or included in an electronic health record; and
- as in the Australian HIV/AIDS experience, obligations or pressure to provide the test results in other contexts such as employment or insurance, opening up the possibility of discrimination or increased charges.

Following the 2003 inquiry, the Privacy Act was amended to make it clear that the extra protections applying to sensitive information should also apply to genetic information. [111]

With respect to PGx testing, a key question is whether the PGx testing process or the results of such tests raises the need for particular caution in its implementation beyond other sensitive information. There are varying views on the question of the sensitivity of PGx information generally. For example, one fact sheet notes that some argue that PGx testing results are less sensitive because they do not examine disease specific genes but rather 'drug related polymorphisms' while others see that it as at least as sensitive or more sensitive as other health information because of the extent of testing and because the results may be

[110] Paragraph 3.16, Australian Law Reform Commission and Australian Health Ethics Committee Report *Essentially Yours: The Protection of Human Genetic Information in Australia* Government Response to Recommendations www.alrc.gov.au/inquiries/title/alrc96/agd.htm

[111] See section 6 of the Privacy Act which provides that sensitive information included genetic information about an individual that is not otherwise health information.

passed more freely amongst health services.[112] Another paper observes that 'PGx test results might reveal susceptibility to certain cancers'.[113]

The level of predictive information that may be revealed by PGx will vary by test; some will have a low risk of revealing broader information about a person's health, while others may result in providing more information than intended. Critically, some information that is not sensitive today may become sensitive tomorrow. 'Junk DNA' was once thought to be useless; it is now thought to be a vital part of the control machinery surrounding the expression of particular genes. Thus, it is critical that a precautionary principle is adopted and all information is considered sensitive. This is in keeping with the current rules and regulations set out in the legal framework for health information. The Privacy Act now treats all health and genetic information as sensitive and regardless of the characterisation of the test results. In terms of the implementation of PGx, in general PGx should be seen as only one example of a wide range of sensitive information that is protected by the current privacy and legal framework for health information.

The current regulatory framework for individual privacy and the protection of sensitive information

Privacy laws generally aim to give individuals control over their personal information. They do this by establishing information handling standards that regulated bodies, including agencies and business and not-for-profit organisations, must apply when handling personal information. The standards vary slightly from law to law but generally contain principles governing collection, use, storage and disclosure of personal information and also provide a right of access to personal information.

Box 4.2: The Privacy Act – Treatment of sensitive information

The federal Privacy Act is the key source of privacy protection in Australia. In summary, and noting that both health information and genetic information are defined as sensitive information under the Privacy Act, the framework for the collection and use of personal information in the context of PGx testing would require that:

- individuals consent to the collection of sensitive information unless an exception applies (National Privacy Principle ten (NPP 10);
- individuals must be advised of certain matters including the purpose for which personal information is collected, to whom it may be disclosed and so on, at or before the collection (NPP 1.3);
- organisations are limited to using or disclosing personal information for the purpose for which it was collected unless exceptions, including for health research in specific circumstances, apply (NPP 2);
- individuals must be given access to personal information about them unless an exception applies (NPP 6); and
- organisations must take reasonable steps to make sure that personal information is accurate for the purpose for which it is to be used and is held securely.

Source: Information Integrity Solutions, 2008, Privacy, Ethical and Legal Issues in PGx Testing

The Privacy Act forms the foundation for the protection of individuals and their sensitive information; this Act would govern the uptake of PGx in Australia as well. Major elements related to PGx include rules for *consent*, *the security and storage of records* and *secondary uses and disclosures*:

[112] Katherine Morley *Pharmacogenetics & Pharmacogenomics Fact Sheet 6 – September 2002* Office of Public Policy and Ethics Institute for Molecular Bioscience, The University of Queensland Australia www.uq.edu.au/oppe/PDFS/Pharma.pdf

[113] Report of the Secretary's Advisory Committee on Genetics, Health, and Society May 2008 *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges* Department of Health and Human Services USA page 72

- *Consent*[114] — Under the Privacy Act individual consent is needed for the collection of both health and genetic information, unless an exception applies. Consent is also introduced in other privacy principles, for example to authorise use or disclosure or other actions that would otherwise be inconsistent with principles.

  In the context of PGx testing, consideration of issues such as the nature of the information needed to ensure consent is properly informed will be important. For example, there are questions surrounding whether people will need to be advised of matters such as:

  - the possible consequences for treatment availability;
  - the possible interest of insurers or employers; or
  - the possibility that tests reveal information of relevance to family members;

  It will be important to consider both from an ethical and privacy perspective whether individuals would be asked to consider research uses of test results and the choices that would be available here. Experience is that the approach to consent and the management of consent could have a significant impact on the positive uptake of initiatives such as PGx testing. Health service providers will need to consider their approach to consent and may be looking for advice and guidance.

- *Security and storage of records* — The need for careful and appropriate storage of records will be important in the context of PGx testing. However, this is not a new issue and the Privacy Act already imposes security obligations on all agencies and organisations that handle personal information. These provisions will apply to private sector health practitioners, pathology labs and other health service providers. There are existing challenges, including whether organisations' security practices currently meet requirements and the different standards/obligations between state public bodies and private sector. There will also be increasing challenges arising as the number of players in the system expand and from the possible overlay of electronic health records (EHR).

  The issue for the storage of information associated with PGx is less likely to be what security standards should apply. Rather the important issue could be ensuring that security standards are being applied. While Australia has not yet had a major security incident made public it is not clear that practices are sound. The ALRC's recent privacy report brings a particular sharpness to this issue. It is recommending the introduction of data breach notification requirements similar to those now operating in many states in the United States and contemplated in the United Kingdom, New Zealand and other countries. The rules would require organisations to tell individuals of security or other data breaches that could have a significant impact for them.

  Security failures could have a very significant impact on public confidence in the process and so raises questions about the current practices. What is needed to build trust and confidence is careful attention to processes and evidence that use,

[114] In common usage, consent means to 'express willingness, give permission, agree' the Privacy Act does not define consent other than to say 'consent means express consent or implied consent'. However, the key elements for consent are usually considered to include that: it is voluntary; it is adequately informed; and the individual must have the capacity to understand, provide and communicate their consent.
The concept of consent carries the sense that the individual is in charge or in control and it is therefore an important element in privacy discussions. However, the concept only works in this way where individuals have real choice. It can be overused or mask the fact that individuals in fact have little control, for example where they have to proceed with a transaction because they need a particular service and there are no other options.

disclosure and security issues are very well addressed through such processes as strong governance procedures going to accountability and transparency.

- *Secondary uses and disclosures* — A key challenge to the notion of individuals being in control of personal information about them is the use or disclosure of personal information for purposes other than the original purpose of collection, either by the collecting organisation or a third party. Some further uses or disclosures are likely to be expected and accepted. They may be familiar common practices, for example billing or quality management, or individuals may have been advised of the proposed use or disclosure at the time of collection. Secondary uses are more likely to be an issue where they are unexpected or where individuals have little choice in the matter. Some of the possible secondary uses which may raise issues in the PGx testing context are mentioned below.
    - *Employment* — While the possibility of discrimination or other adverse treatment should an individual be asked or required to disclose the results of a PGx test to an employer, either in pre-employment checking or in the context of managing an illness, is often raised as concern, there is currently little experience available to indicate how real the issue is. The ALRC/AHEC 2003 report found little use of genetic information by employers at that time. However, it did anticipate that the use of genetic information was likely to increase as the costs of testing fall and the accuracy, reliability and range of tests increases. In this regard, the ALRC noted that employers' collection and use of genetic information was largely unregulated. This is still the case. The ALRC in 2003, and again in its 2008 report on privacy, recommended that the current exemption for employee records be removed. As noted earlier the Government is currently considering its response to the later report. In terms of PGx testing the risks may be even less. However, in taking testing proposals forward it is likely to be important to recognise this as an area of community concern and which may need to be addressed at least in communication strategies.
    - *Insurance* — Similar concerns exist in the relation to the possibility of discrimination or increased costs should individuals need to disclose PGx test results when applying for insurance. It is also useful to look at the ALRC/AHEC report on this issue. It concluded that 'there is no justification at present for departing from one of the fundamental principles that governs voluntary, risk-rated rated insurance—i.e., full disclosure and equality of information between the applicant and the insurer'. The report did identify a number of issues where it considered action was needed, by the Government and the insurance sector. The message for PGx testing seems to be that while there may be little impact at this point stakeholders will need to monitor insurance interest in this area of testing.
    - *Disclosures to family members* — While the PGx testing is unlikely to of itself reveal information about genetic makeup, as noted earlier, there may be conclusions that can be drawn about susceptibility to diseases that may have implications for individual's family members. Given this it is possible that at some point health service providers will need to consider if they need to inform relevant family members of the implications of a set of test results for their own health, with or without the consent of the individuals concerned. While this is a complex area raising both legal and ethical issues, it is worth noting in this regards that the Privacy Act was recently amended to allow the use or disclosure of an individual's genetic information, without

> consent, where necessary to lessen or prevent a serious threat to the life, health or safety of a genetic relative of the individual, subject to guidelines issued by the National Health and Medical Research Council and approved by the Privacy Commissioner.

The Privacy Act is not the only law that will have a bearing on PGx testing. Australia has a complex array of laws aimed at protecting privacy and particularly the privacy of health information. Both the Australian government and each State and territory have legislation or administrative guidelines in this area. In addition to 'general information' privacy legislation, New South Wales, Victoria and the ACT also have specific laws on the handling of health information, which apply to state public sector agencies and private sector organisations.[115] This means that private health services (including not-for-profit health services) may be covered by the federal Privacy Act as well as by specific State or territory health privacy legislation. Health services that operate across State and territory borders may have to comply with multiple laws, each with different requirements.

Moreover, where new approaches to health are being developed, privacy is considered one of the critical factors and is being given serious attention. For example, the National E-health Transition Authority, which is funded by all Australian governments and which is charged with establishing a framework which will allow Australia to take up e-health opportunities, has adopted detailed and specific privacy 'blueprints' for its key initiatives.[116]

Future privacy reform developments

The adequacy and appropriateness of the current legal framework governing patient privacy in the context of PGx was recently (2003) considered by an Australian Legal Reform Council and Australian Health Ethics Committee. The inquiry examined in detail the current framework, including the Privacy Act, for the handling of sensitive health information and made a range of recommendations. The inquiry made recommendations for:

- a national 'harmonised' set of laws protecting privacy and health information;
- strong ethics consideration of the issues; and
- coverage of tissue samples by the privacy framework.

The Australian Government accepted some but not all of the recommendations. Its view in response was that existing legislation, including the Privacy Act and the *Disability Discrimination Act 1992,* with some modifications, provided an appropriate framework to protect genetic information. The Government recognised that there were a range of matters where further thinking and policy development was needed, including in relation to insurance and employment and research approaches.

A more recent (2008) ALRC inquiry into the extent to which the Privacy Act and related laws continue to provide an effective framework for the protection of privacy in Australia is also relevant. This review again identified the complexity, overlap and fragmentation of the privacy framework, in particular in the health sector as a major area of concern. The report recommended that the Privacy Act be the key source of privacy protection for health information via a set of 'unified privacy principles' addressing the general handling of personal information and proposed new *Privacy (Health Information) Regulations* that would contain requirements that are different or more specific than provided for in the

[115] A list of laws relating to the handling of personal information prepared by the Office of the Victorian Privacy Commissioner at www.privacy.vic.gov.au/dir100/priweb.nsf/download/8219B55BB38A8CBBCA256F8C00209B48/$FILE/Privacy%20and%20related%20legislation%20in%20Australia%20at%2018%20October%202007.pdf

[116] Information about NEHTA's privacy approach is available at www.nehta.gov.au/index.php

general principles.[117] The ALRC has also recommended that an intergovernmental agreement should be developed to ensure that the privacy regulation of health information (including relevant definitions) is harmonised across all sectors, including State health systems. The Australian Government is now considering its response to this report.

Key findings for privacy issues related to pharmacogenomics in Australia

For the purposes of this report the conclusions to be drawn regarding PGx privacy issues are as follows:

- PGx is a subset of broader concerns for the protection of health information, *all of which is considered sensitive in Australia*;
- Australia's current privacy framework provides a base level protection for health information and has the advantage of applying to most contexts in which sensitive health information might be collected and used;
- this framework is not without difficulties, however; it is complex, overlapping and both health service providers and individuals can find it hard to understand their obligations and rights;
- there are strong and divergent views about whether this basic framework is sufficient in addressing privacy issues for health information and is sufficient on its own to promote community confidence in adopting health innovations; and
- the Government's response to ALRC report and if the recommendations are adopted, the implementation process, are likely to be very significant to all Australian health innovations.

4.4.2 Ethical issues

The ALRC/AHEC 2003 report defines ethics as 'an accumulation of values and principles that address questions of what is good or bad in human affairs. Ethics searches for reasons for acting or refraining from acting; for approving or not approving conduct; for believing or denying something about virtuous or vicious conduct or good or evil rules.' The report includes an extensive discussion of ethical issues that may arise in the context of genetic testing. The report notes that predictive tests raise greater ethical and social concerns than testing conducted for immediate clinical reasons requiring among other things:

- careful thought about whether testing ought to performed where no treatment is available, or where the patient is a child;
- much more care in interpretation, both by health professionals and the individuals concerned;
- considerably more attention to collateral uses, and the possibility of breaches of privacy or unfair discrimination; and
- the provision of adequate pre- and post-test counselling and support services.

The Centre for Genetics Education suggests a similar list of issues that may give rise to ethical issues including:

- the shared nature and ownership of genetic information;
- limitations of genetic testing;

[117] The ALRC Report 108 For Your Information: Australian Privacy Law and Practice, Part H available at www.austlii.edu.au/au/other/alrc/publications/reports/108/

- the potential for discrimination; and
- setting boundaries in applications of the genetics technology.[118]

While PGx testing may not be predictive in the same sense, these discussions are a useful indicator of the issues that may also need to be considered by individuals' health service providers, the industry or government policy makers if wide use of such testing proceeds.

Awareness of the issues, ethics education, and appropriate frameworks and advice are likely to be approaches that head off risks to the possible business case for PGx testing. Australia currently has no guidelines developed for clinicians to guide them on when PGx testing should be undertaken, how the results should be interpreted and communicated or how patients should be supported and counselled through the process. These gaps create significant risks and/or barriers to the uptake of PGx testing in Australia.

4.4.3 Legal issues

A recent report by the United States Department of Health and Human Services canvasses the legal issues that may arise in the context of PGx. It notes that the fact that the PGx is in early stages poses a particular risk from a legal perspective. The accepted 'standards of care', labelling guidelines etc are not yet in place, making it unclear whether decisions about the testing process and following treatment were appropriate or where liability may fall if things go wrong.

It also notes that as the use of PGx tests expands there may also be liability issues if an individual suffers an ADR that could have been avoided should an appropriate test had been ordered or where a patient is prescribed a drug that is indicted for a specified test result without first having undergone such a test. A further issue the paper identifies is the possible conflict between the clear need for education and training for clinical practitioners and the impact this may have on their malpractice risk; the final responsibility to warn patients of risks may shift to the practitioner from the drug manufacturer as the practitioners' expertise rises.

Similar issues are likely to arise in the Australian context. In 2002, Katherine Morley of the University of Queensland noted that 'currently, no countries have regulations specifically relating to [PGx]'. She suggests that if testing becomes widely used there will be a range of legal and regulatory issues to consider. In particular, she identifies a need for labelling and prescription guidelines and for the regulation of PGx tests including the 'permissibility of 'off label' uses of PGx drugs'.

The way forward will need careful consideration of these and other legal issues.

4.4.4 Conclusions

There are a wide range of privacy, ethical and legal issues for Australia in the implementation of PGx.

With respect to privacy concerns, PGx is currently being considered in the context of broader reforms to improve the privacy of individuals with respect to health information.

Overall, the larger areas of focus specific to PGx for Australia lie in the ethical and legal issues associated with PGx implementation.

- In the absence of guidance for clinicians regarding which patients should be tested, when they should be tested and how they should be counselled regarding that information, there are currently risks patients receive inconsistent advice or care,

[118] Fact Sheet 23 Some Issues in Human Genetics available at www.genetics.edu.au/factsheet/fs23.html

leading to substandard health outcomes or poor quality of care. Without adequate counselling support, some patients may develop 'stigma' issues over PGx data that are not warranted. There will need to be patient support so that issues of 'disorder' can be managed appropriately so that patients do not feel and are not labelled.

- Moreover, while current rules for limitation and consent of medical information would be expected to apply to PGx, there are potentially unforeseen outcomes that patients will also need to be advised to consider. For example, what may not appear to be sensitive information today may be perceived to be sensitive in the future as research continues. From a legal perspective issues of liability are largely untested and this may slow the uptake of PGx technologies in the community.

Australia needs a plan for how information is shared and stored, and critically needs to deliver training to clinicians and further develop guidelines to help clinicians provide best practice care to their patients.

4.5 ICT infrastructure

Australia currently lacks the ICT infrastructure to optimally share PGx information and provide for best practice in the clinic, and this represents a major barrier to optimising the uptake of PGx in Australia.

To minimise the risk of unnecessary duplication of testing and to maximise the safety of patients across care settings, there needs to be the infrastructure to ensure that PGx data can be stored and shared in a way that is easy for both the patient and their carers. Moreover, the individual healthcare consumer has potentially the greatest stake in maximising the efficacy of treatment and avoiding adverse outcomes. Readily accessible patient information will encourage informed decision making and will encourage consumers to raise the prospective use of testing to improve outcomes with their treating health professionals.

Because of the large volume of data (potentially a whole genome scan), the development of an E-Health record will facilitate the sharing of patient data effectively across providers. The development of electronic decision support tools will also help clinicians implement PGx.

- *Electronic Health Records* — As the tests relate to genetically determined individual metabolism of certain drugs, and normally of relevance to more than one drug, the information may retain relevance to both ongoing medical treatment as well as unrelated medical treatments over many years. PGx information is complex, and so unlike say a 'blood type' or 'allergy' is unlikely to be remembered by the individual. Therefore safe and accessible storage of information would be of use. This report is not advocating specific investment in electronic health records simply to accommodate PGx, however, it is important to note that this infrastructure will be important in the effective uptake and use of PGx in the future. PGx represents another facet of healthcare that would be made more effective when secure EHRs become readily available.
- *Decision support tools* — The relationship between genetic information and drug metabolism can be complex. Additionally PGx is not yet well understood by the majority of clinicians. Thus, implementation and application would probably be extremely slow until the study of PGx becomes part of the medical school curriculum and a routine part of prescribing. Uptake would be far more rapid and less prone to errors of interpretation if electronic decision support tools could be made available to clinicians, preferably available within desktop applications already in use.

5 Implementing pharmacogenomics in Australia: a roadmap for Australian governments

This chapter presents a roadmap for supporting the optimal use of PGx in Australia over the next five to ten years. The key elements include reform to the regulatory and reimbursement frameworks governing PGx diagnostics and the establishment of a lead authority to support investments in education and training of medical professionals.

5.1 Creating a framework for pharmacogenomics uptake in Australia: overview of recommendations

The Australian Government has committed itself to the quality use of medicines and timely access to those medicines.

PGx technologies hold the promise of substantially improving the rational, quality use of medicines in Australia, and delivering potentially significant reductions in the total costs of care to the community through safer care. With government spending on health care projected to grow from nine per cent today to an estimated 16 to 20 per cent of GDP by 2045, and with Australia facing a growing crisis in the shortage of skilled medical professionals, any ability to constrain growing health care costs will directly support the future sustainability of the Australian health care system.

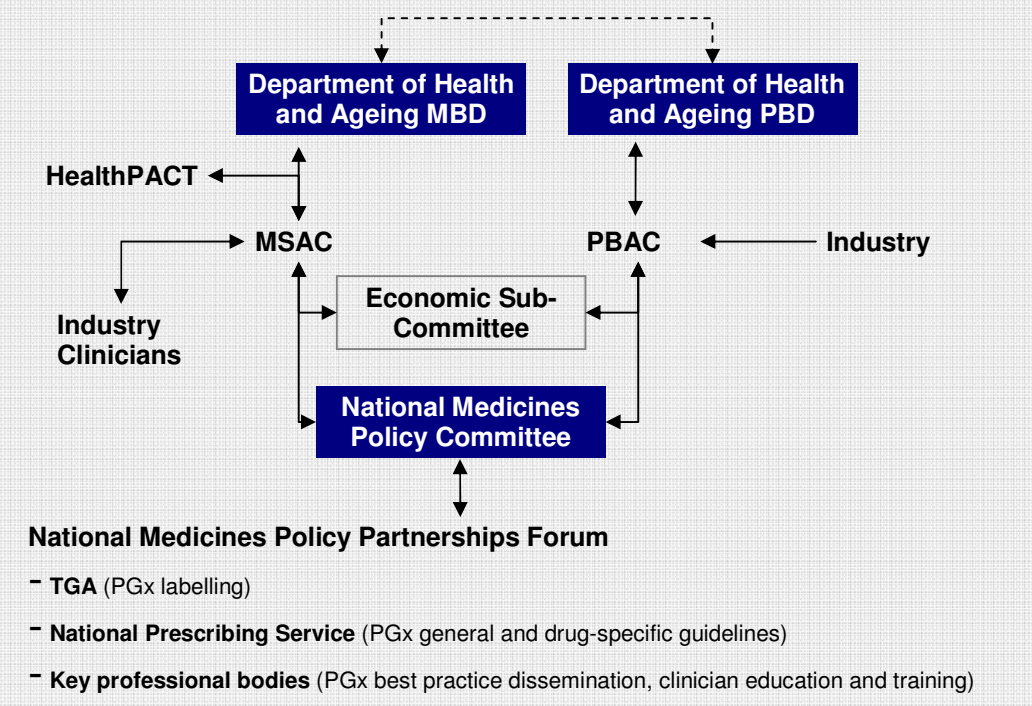
PGx technologies have only begun to emerge, and their clinical utility is being established in to help guide therapy in a number of disease areas. In ten years time, PGs will likely be a common medical practice, with potentially hundreds of tests available to clinicians to better target medicines. Microarray and other genome scanning technologies that provide comprehensive PGx profiles for patients in particular will deliver significant value to the community.

The transition from 'trial and error' medicine today to a more targeted approach in five to ten years time will require the system to ensure that patients have timely access to PGx technologies as they become available, at a cost the community can afford.

While the National Medicines Policy is a sound foundation for optimising the uptake of PGx in Australia, PGx does not sit neatly within this policy framework, nor within the broader regulatory structures. To date PGx recommendations have been made on an exceptional or 'case by case' basis by a range of bodies. This approach has been broadly acceptable to date; however, with the expected increase in the number of PGx technologies and their potential clinical application this approach is unsustainable and ineffective, creating growing risks for system inconsistencies, patient inequity and wasted expenditure.

It is proposed that the government establish a national framework for PGx. This would involve establishing new responsibilities for PGx among current stakeholders and the creation of a health technology assessment (HTA) body that would have sole authority to provide all advisory opinions on the therapeutic value and the cost-effectiveness of PGx.

Figure 5.1: A National Framework for Pharmacogenomics



The implementation of a national PGx policy would involve:

- recognition that PGx is an *emerging, core pillar of the National Medicines Policy* and an essential tool for the rational, quality use of medicines;
- the clear enunciation that the *National Medicines Policy Executive should oversee policy development related to all technologies, including PGx*, that will improve the quality use of medicines in Australia;
- *enhanced horizon scanning* by HealthPACT to ensure that new PGx technologies are identified, particularly for drugs that are already listed on the PBS;
- *reviews of PGx evidence* to be commissioned by the National Medicines Policy Executive and Committee;
- *applications to be brought by the Government* (via MSAC) where there is no private incentive to list a test on the MBS;
- *the creation of a new HTA advisory body* that will have sole authority to evaluate the cost effectiveness of PGx technologies with responsibilities to make recommendations to both MSAC and PBAC;
- *reimbursement for PGx testing to be provided on the basis of cost effectiveness analysis*, outside current price volume caps for diagnostic tests, to provide incentives for innovation and to encourage the listing of items on the MBS;

- *the development of general and drug specific guidelines* by the National Prescribing Service to ensure standardised, equitable PGx practice;
- *the development of decision support tools* to help clinicians implement best practice in pharmaceutical therapy on the basis of PGx testing; and
- *the roll out of education and training programs*, with priority given to clinicians in fields where tests are mandatory or recommended.

In total seven key recommendations are made to provide a framework for PGx in Australia.

5.2 Recommendation 1: Enhance horizon scanning and reporting requirements

HealthPACT currently undertakes horizon scanning on behalf of MSAC and AHMAC's Clinical, Technical and Ethical Principal Committee (CTEPC) for a range of technologies, including diagnostic technologies. HealthPACT has a number of Sub-Committees with particular areas of focus, such as highly specialised surgeries.

Given the rapid developments in PGx technologies expected to occur over the next five to ten years, a further committee should be created under HealthPACT focused on PGx to identify new technologies that could improve the rational use of medicines. In particular, the committee should focus on the emergence of new technologies that might improve the quality use of medicines that are already listed on the PBS, where there may not be a private sector incentive to apply for a PGx test listing on the MBS.

Reporting should be provided not only to MSAC and AHMAC but also the newly formed National Medicines Policy Executive and Committee (via MSAC), which has terms of reference to commission research that would improve the functioning of the National Medicines Policy. This will strengthen the role of the National Medicines Policy Executive as the key body to drive the quality use of medicines in Australia.

5.3 Recommendation 2: Expand the responsibilities of the National Medicines Policy Executive to include pharmacogenomics recommendations

The newly created National Medicines Policy Committee is required to:

- provide advice on medicines policy related issues to the National Medicines Policy Executive, the Government and other bodies as requested;
- consult with the National Medicines Policy Executive to determine work plan and priorities;
- conduct, oversee or consider medicine policy related projects and/or research identified by the National Medicines Policy Executive; and
- refer to the National Medicines Policy Executive, where appropriate, specific medicines policy issues that could be considered for research/project funding.

The National Medicines Policy Executive and Committee should receive quarterly reports from HealthPACT and have a responsibility to commission reviews (on authority of the National Medicines Policy Executive) of the evidence.

The National Medicines Policy Executive should also:

- commission the development of education and training programs for medical professionals as appropriate to ensure equal access to therapies;
- liaise with key professional bodies through the National Medicines Policy Partnerships Forum to promote best practice in PGx therapy; and
- as a long term objective, provide recommendations to the Therapeutic Goods Administration (TGA) to update labelling requirements for pharmaceuticals as the evidence base evolves.

5.4 Recommendation 3: Create a pharmacogenomics advisory body

The National Medicines Policy requires not simply access to new medicines, but *timely access* to new medicines, facilitated by *streamlined* regulatory processes.

The current time required to achieve MBS listing takes an average of two to three years, and there are recent examples of MSAC assessments for a PGx test taking more than four years. This is due in part to the requirement for MSAC to evaluate the evidence as well as limited expertise available to MSAC to undertake the assessment. Currently, MSAC reviews approximately 19 submissions each year, compared to PBAC's review of more than 100 dossiers annually.

As PGx technologies emerge, MSAC's case load will begin to look more like that of the PBAC and less like the historical MSAC submission profile. The current time to listing raises significant concerns for patient access, and to some extent may encourage item creep or the non-listing of PGx technologies on the MBS. The increase in the number of potential evaluations required will only exacerbate the current delays in the system. The delays to MBS listing may create inequalities for some patients or frustrate the National Medicines Policy quality use of medicines objective where conditions of PBS listing have been applied. Moreover, the potential benefits of reforms to streamline the current TGA and PBAC listing processes (recommended in the recent Productivity Commission *Annual Review of Regulatory Burdens on Business*) would be reduced, as diagnostic testing becomes more widespread.

The current regulatory structure is inadequately resourced and lacks the skills to evaluate PGx technologies on a timely basis. Mechanisms need to be created to:

- increase clarity and consistency of PGx evaluation processes across PBAC and MSAC; and
- reduce the time required to evaluate PGx technologies.

There are a number of models that could formally improve collaboration between MSAC and PBAC, which would also be expected to reduce the time to listing for PGx technologies:

- Option 1 — Require the Economic Sub-Committee to serve both PBAC and MSAC with respect to PGx;
- Option 2 — Create a new PGx Sub-Committee in MSAC; or
- Option 3 — Increase resourcing to MSAC to fund an approved panel of PGx experts that serve both MSAC and PBAC.

Option 1 would formally link the activities of PBAC and MSAC by creating a single economics advisory body for linked pharmaceuticals and PGx technologies. Such an

approach could be extended over time so that a single body would perform HTA for all medical technologies as occurs in other markets, such as Canada (CADTH), the United Kingdom (NICE) and the US (FDA Office of Combination Products). The clear advantages of the pharmaceuticals and PGx HTA body are that:

- PGx would be clearly recognised as a tool to improve the quality use of medicines in Australia;
- the body would harness synergies with the pharmaceuticals evaluation committee which will be essential for evaluating the costs and benefits of a PGx test;
- the body would be able to take a comprehensive view of both the costs and benefits to the community of the pharmaceutical and companion PGx test, and provide appropriate recommendations to inform the reimbursement of each; and
- this would provide a platform for the potential further reform to HTA in Australia.

This option represents the most significant break from the status quo and would not be without its hurdles. PBAC is a statutory advisory body and MSAC is a Ministerial Advisory Committee, which creates administrative barriers to its implementation in the short run. The current PBAC Economic Sub-Committee is also already short of the required resources to review new applications for PBAC listing; there is a concern in government that expanding the requirements for this Committee would compromise its ability to meet its obligations for timely reviews of applications. Clearly, however, if such an approach were considered, *there would need to be a complete review of the resourcing of the body* to ensure it had adequate skills and funding to undertake timely reviews of technologies. This would require a several year commitment to evaluate the resourcing strategy for the body in order to identify more effective and sustainable operating protocols and more funding to attract, develop and retain the appropriate skills within the organisation. However, given the potential benefits to the community through safer care and rational use of medicines, this would appear to be a prudent investment by the community.

While the creation of a single HTA authority for PGx and pharmaceutical medical technologies would provide a natural, long run solution, a move to rationalise the number of HTA bodies in Australia may be seen as more effectively considered as part of a larger government strategy to respond to the broader trend of medical technology convergence. It is also likely that the number of PGx applications is going to be uneven over the next five years (though likely increasing thereafter), which would indicate that a less formal arrangement could be developed in the short run to ensure the efficient review of PGx technologies while minimising the reform burden to existing agencies. Options 2 and 3 would not place additional demand on the PBAC system, although each would require additional resourcing and funding than is currently provided to MSAC to attract, develop and retain the appropriate skills to provide a national HTA services for PGx. Option 2 provides for a formal Sub-Committee to be created in MSAC to evaluate and fast track PGx technology listings. Option 3 represents an ‘enhanced status quo option, and provides effectively the same outcome as Option 2 but through a less formal panel arrangement, which is how MSAC currently undertakes reviews: through the commissioning of consultant medical professionals.

The advantages of Options 2 and 3 are that they offer the possibility of a phased approach, and would enable action to be taken on PGx without a major revision to the HTA system in Australia. Clarifying the roles and responsibilities and processes for PGx assessment will reduce risks arising from the current system for PGx review, and provide a mechanism for harmonising listings on the PBS and MBS. Given the current trends towards medical technology convergence, however, these approaches represent only half-measures towards a long run solution and would likely be rationalised under a broader reform agenda.

Overall it is recommended that Option 1 is pursued as this would provide for the greatest collaboration between MSAC and PBAC, and would more clearly cement PGx as a major tool for improved quality use of medicines. The HTA authority would be able to establish conditions for the fast tracking of evaluations through the development of levels of review required depending on a risk-impact assessment. It should also commit to fast tracking MBS listing reviews where companies provide PGx data as part of its PBAC submission.

5.5 Recommendation 4: Reform reimbursement for pharmacogenomics tests

PGx technologies are not the same as other diagnostic tests; there is likely to be significant differences between:

- the costs of tests (depending on technologies/personnel involved, and the size of potential patient populations); and
- the potential benefits provided to the community in terms of improvements in the quality of life and avoidance of wasted expenditure on the PBS.

PGx technologies will provide significant savings to the PBS, similar to the introduction of new PBS items that deliver health outcomes more cost effectively. Where some tests are able to provide significant value in terms of controlling spending across a wide range of pharmaceuticals, there should be incentives for the technology to be listed so that spending on the PBS can be controlled. The current MBS offsets approach to diagnostics does not allow government access to these more sophisticated pricing tools and as a result, items may not be MBS listed. To the extent that technologies are not listed on the MBS that improve patient safety and the cost-effectiveness of care, patient access will be compromised and allocative inefficiencies would be expected to arise.

It is proposed that reimbursement for PGx be provided outside current price-volume arrangements and based on a cost-effectiveness (cost per QALY) basis, similar to the evaluation of PBS technologies, with the principles of cost effectiveness applied with equal rigor to PGx technologies.

5.6 Recommendation 5: Develop pharmacogenomics clinical guidelines

The National Prescribing Service should be required to develop general and disease specific guidelines to support ethical use and equitable access to PGx in collaboration with appropriate clinical groups. Specialised clinical bodies should be involved in the development of drug-specific guidelines, which the National Prescribing Service would disseminate while the National Prescribing Service would develop the general guidelines for PGx to support clinician uptake. Guidelines should provide for standardised use of PGx, interpretation of results and therapy algorithms. Where biomarkers have been shown to be valid, testing should be indicated as mandatory.

As a long run objective, the National Prescribing Service Guidelines should be harmonised with TGA labels.

5.7 Recommendation 6: Develop ICT decision support tools and privacy standards

ICT infrastructure and solutions will be an important enabler of better healthcare over the next decade, including PGx solutions. The need to invest in better ICT is not driven by PGx; nevertheless, to ensure the benefits of PGx and E-Health investments can be maximised, it is important that considerations are made for imminent technological change in medicines.

In particular, the development of decision support tools will enable clinicians to implement best practice prescribing, which increasingly will involve PGx. Decision support tools will help guide better dosing of patients, reducing wastage and side effects while also improving compliance.

Patients will increasingly have significant volumes of personal data that will need to be kept private. Critically, some patient data that may not appear to be sensitive today may become sensitive information in the future as technology improves. To reduce duplication of testing and improve health outcomes, solutions (such as an IEHR) should be developed to facilitate the appropriate sharing of patient PGx data across providers.

5.8 Recommendation 7: Invest in education and training for healthcare providers and the public

Stakeholder consultations and literature reviews have shown there are very significant differences in education levels among clinicians, with current PGx technologies being provided *ad hoc* and inconsistently to patients.

The National Medicines Policy Executive and Committee should work with the National Medicines Policy Partnership Form to ensure that where tests are required, education and training for medical professionals (specialists and GPs) is developed and provided. The Executive should also, through the National Medicines Policy Partnership Forum, engage with professional colleges, journals and other therapeutic guideline groups to disseminate best practice guidelines among professional communities. Professional colleges should also engage with undergraduate medical schools to ensure teaching integrated into curricula.

Patients also need to be educated about PGx technologies and the ethical, legal and social issues that may be associated with PGx. Patients need to be informed about NATA accreditation, so that they can be confident of the quality and accuracy of the test, and their options. In the development of education and training for professionals, materials should also be developed and distributed to patients.

Appendix A

References

ABS, 2008, 3201.0 - Population by Age and Sex, Australian States and Territories, Jun 2002 to Jun 2007. In the 12 months to 30 June 2007, the Australian population increased by 317,162 people, reaching 21,015,042. The annual growth rate for the year ended 30 June 2007 (1.53%) was higher than that recorded for the year ended 30 June 2006 (1.49%).

Ansell, J., et al., 2001, 'Managing Oral Anticoagulant Therapy,' *Chest*, 119:22S-38S.

Aspinall, M.G., Hamermesh, R.G., 2008, 'Realising the Promise of Personalised Medicine', *Harvard Business Review*, Boston, August.

Australian Institute for Health and Welfare, 2006, *Health Expenditure Australia 2005-06*, Australian Government, Canberra.

Australian Treasury, 2007, *Intergenerational Report 2007*, Part 3: Long Term Fiscal Projections, http://www.treasury.gov.au/documents/1239/HTML/docshell.asp?URL=04_Part_3.htm [August 2008]

Bauduin, L.M., Langman, L.J., and O'Kane, D.,J., 2007, 'Translation of Pharmacogenetics into Clinically Relevant Testing Modalities', *Nature*, 82(4), October.

Begg S., Vos T., Barker B., Stevenson C., Stanley L., Lopez A.D., 2007, *The burden of disease and injury in Australia 2003*, Australian Institute of Health and Welfare, Australian Governement, Canberra, PHE 82.

Berger, J., 2001, 'Economic Impact of a Diabetes Disease Management Program in a Self-Insured Health Plan: Early Results,' *Disease Management*, 4: 2, 65-73

Bouchie, A., 2008, 'The Jury is No Longer Out', *BioCentury*, 16(25), 9 June.

Britt, H., Miller, G.C., Charles, J., Bayram, C., Pan, Ying, P., Henderson, J., Valenti, L., O'Halloran, J., Harrison, C., Fahridin, S., 2008, *Bettering the Evaluation and Care of Health: General Practice Activity in Australia 2006-07*, Australian Institute of Health and Welfare and University of Sydney, Cat. No. GEP 21, Australian Government, Canberra, January.

Cady, R.C., 1998, 'Sumatriptan Injection Reduces Productivity Loss During a Migraine Attack: Results of a Double-Blind, Placebo-Controlled Trial,' *Archives of Internal Medicine*,158

Cancer Council, 2007, Colorectal Cancer, http://www.cancer.org.au/Healthprofessionals/cancertypes/colorectalcancer.htm

Cockburn, I.M., 1999, 'Loss of Work Productivity Due to Illness and Medical Treatment,' *Journal of Occupational and Environmental Medicine*, 41: 11, 948-953

Collins, F.S., 2008, 'Genomic Research and Personalised Medicine: An Expert Interview', *Medscape*, August.

Cowper, P.A., 2004, 'Economic Effects of Beta-Blocker Therapy in Patients with Heart Failure,' *The American Journal of Medicine*, 116: 2, 104-111.

Deloitte, 2007, Targeted Therapies: Navigating the Business Challenges of Personalised Medicine, Deloitte Centre for Health Solutions, p 6.

Department of Health and Ageing, 2000, *National Medicines Policy*, Australian Government, http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-objectives-policy.htm/$FILE/nmp2000.pdf [September 2008], Canberra.

Department of Health and Human Services, 2008, *Realising the Potential of Pharmacogenomics: Opportunities and Challenges*, Report of the Secretary's Advisory Committee on Genetics, Health and Society, Washington DC, May.

Department of Premier and Cabinet, Victoria, 2008, *Next Steps in Australian Healthcare Reform: the Proposals of the Victorian Premier*, Victorian Government, Melbourne, June.

Deverka, P.A., Doksum, T., Carlson, R.J., 2007, 'Integrating Molecular Medicine into the US Healthcare System: Opportunities, Barriers, and Policy Challenges', *Nature*, 82(4), October.

Dewey H.M., Thrift A.G., Mihalopoulos C., Carter R., Macdonell R.A.L., McNeil J.J., and G.A. Donnan, 2003, 'Lifetime Cost of Stroke Subtypes in Australia: Findings From the North East Melbourne Stroke Incidence Study (NEMESIS)', *Stroke*, 34: 2502-2507.

European Medicines Agency, 2008, *Reflection Paper on Pharmacogenomics in Oncology*, Committee For Human Medicinal Products, European Medicines Agency, April.

Evans, W.E.., and McLeod, H.L., 2003, 'Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects', *NEJM*, 348:538-549.

Feld, R., Sridhar, S.S., Shepherd, F.A., Mackay, J.A., and Evans, W.K., 2006, *Use of the Epidermal Growth Factor Receptor Inhibitors, Gefitinib (Iressa®) and Erlotinib (Tarceva®), in the Treatment of Non-small Cell Lung Cancer: A Clinical Practice Guideline*, Cancer Care Ontario, January.

Forum on Patient Compliance 2002 (Center for Business Intelligence).

Gardiner, S.J, Gearry, R.B., Begg, E.J., Zhang, M., and Barclay, M.L., 2008, 'Thiopurine Dose in Intermediate and Normal Metabolizers of Thiopurine Methyltransferase May Differ Three-Fold', *Clinical Gastroenterology and Hepatology*, 6:654–660.

Gardiner, S.J., and Begg, E.J., 2005, 'PGx for Drug Metabolising Enzymes: Is It Happening in Practice?', Pharmacogenetics and Genomics, 15:365-369.

Garrison, L.P., and Austin, M.J.F., 2006, 'Linking Pharmacogenetics-based Diagnostics and Drugs for Personalised Medicine', *Health Affairs*.

Goetz, M.P., Kamal, A., and Ames, M.M., 2008, 'Tamoxifen Pharmacogenomics: The Role of CYP2D6 as a Predictor of Drug Response', *Nature*, 83(1), January.

Goetz, M.P., Kamal, A., and M.M. Ames, 2007, Tamoxifen Pharmacogenomics: The Role of CYP2D6 as a Predictor of Drug Response, Clinical Pharmacology & Therapeutics (2008) 83, 160–166

Greenberg, P.E., 2003, 'The Economic Burden of Depression in the United States: How Did It Change Between 1990 and 2000?', Journal *of Clinical Psychiatry*, 64: 1465-1475.

Hill, J.W., 2002, 'The Effect of Donepezil Therapy on Health Costs in a Managed Care Plan,' *Managed Care Interface*: 63-70

Hughes CM. Medication non-adherence in the elderly: how big is the problem? Drugs Aging 2004;21(12):793-811

Ingelman-Sundberg, M., 2008, 'PGx Biomarkers for Prediction of Severe Adverse Drug Reactions', *NEJM*, 358:637-639.

Ingelman-Sundberg, M., and Rodriguez-Antona, C., 2005, Pharmacogenetics of drug-metabolizing enzymes: implications for a safer and more effective drug therapy, Philos Trans R Soc Lond B Biol Sci. 2005 August 29; 360(1460): 1563–1570.

Joan Arehart-Treichel, 2005, Psychiatric News , 'Gene Testing Could Help Predict Drug Responses', Volume 40 Number 10, American Psychiatric Association, p. 33

Jonathon P Ehsani, Terri Jackson and Stephen J Duckett, 2006, The incidence and cost of adverse events in Victorian hospitals 2003, MJA 2006; 184 (11): 551-555.

Joyce H .S. You et al., 'The Potential Clinical and Economic Outcomes of Pharmacogenetics-Oriented Management of Warfarin Therapy – A Decision Analysis.' Thromb Haemost. 2004; 92:590-597.

Kennedy, M., 2008, *Pharmacogenomics in an Era of Personal Genomes, Carney Centre for Pharmacogenomics*, Christchurch School of Medicine and Health Sciences, University of Otago.

Kirchheiner, et. al, ACTA Psychiatry, Scandanavia, 2001, 104:173-192.

Kleinke, J. 2001 'The Price of Progress: Prescription Drugs in the Health Care Market', *Health Affairs*, 20(5), Sept-Oct.

Lacana, E., Amur, S., Mummanneni, H.Z., Frueh F.W., 2007, 'The Emerging Role of Pharmacogenomics in Biologics', Nature, 82(4), October.

Lemann, M., Zenjari, T., Bouhnik, Y., et al, 2000, 'Methotraxate in Crohn's disease: Long term Efficacy and toxicity', *Am J Gastroenterol*, 95(7): 1730-1734.

Lichtenberg, F., 1996, 'Do (More and Better) Drugs Keep People Out of Hospitals?,' *American Economic Review* 86, May, 1996, 384-388.

Lowrance, W., 'The Promise of Human Genetic Databases' (2001) 322 *British Medical Journal* 1009.

Mallel, S., 2008, *Clinical Applications of Pharmacogenetics in HIV*, Symposium: Clinical Applications of Pharmacogenetics in HIV, Ritz Carlton Hotel, Isla Verde, Puerto Rico, 7 September.

Mallal, S., Phillips, E., Carosi, G., Molina, J.M., Workman, C., Tomažič, J., Jägel-Guedes, E., Rugina, S., Kozyrev, O., Flores J., Hay, P, Nolan, D., Hughes, S., Hughes, A., Ryan, S., Fitch, N., Thorborn, D., and Benbow, A., 2008, 'HLA-B*5701 Screening for Hypersensitivity to Abacavir', *NEJM*, 358:568-579.

McWilliam, A., Lutter, R., and Nardinelli, C., 2006, *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin*, AEI-Brookings Joint Centre for Regulatory Studies, Working Paper 06-23.

Medical Services Advisory Committee, 2005, *Guidelines For the Assessment of Diagnostics Technologies*, Australian Government, Canberra.

Medicines Australia, 2005, *Medicines Australia Submission to the Productivity Commission Inquiry Impact of Advances in Medical Technology on Healthcare Expenditure in Australia*, Canberra, pp 80-88.

Medicines Australia, 2005, Medicines Australia, 2005, *Submission to the Productivity Commission Inquiry: Impact of Advances in Medical Technology on Healthcare Expenditure in Australia*, Medicines Australia, Canberra.

Meropol, N. J., 2005, 'Epidermal Growth Factor Receptor Inhibitors in Colorectal Cancer: It's Time to Get Back on Target', *Journal of Clinical Oncol*ogy, 23(9):1792-1793.

Meyerhardt, J.A.., and Mayer, R.J., 2005, 'Systemic Therapy for Colorectal Cancer', *NEJM*, 352:476-487.

Miller, G.C., Britt, H.C., and Valenti, L, 2006, Adverse Drug Events in General Practice Patients in Australia, Medical Journal of Australia, 184(7):321-324.

Morris, M., Iacopetta, B., and Platell, C., 2007, 'Comparing survival outcomes for patients with colorectal cancer treated in public and private hospitals', *MJA*, 186 (6): 296-300.

Nakamura, Y., 2008, 'Pharmacogenomics and Drug Toxicity', *NEJM*, 359:856-858.

National Cancer Institute, 2005, Anastrozole After Tamoxifen Better for Early Breast Cancer than Tamoxifen Alone, US Natinoal Institutes of Health, http://www.cancer.gov/clinicaltrials/results/anastrozole0805.

National Centre for Biotechnology Information, 2008, *One Size Does Not Fit All: The Promise of Pharmacogenomics*, National Centre for Biotechnology Information, August.

National Centre in HIV Epidemiology and Clinical Research (NCHECR), Australian Surveillance Update April 2007 and Annual Surveillance Report 2007.

National Committee for Quality Assurance, 2003, *State of Health Care Quality: 2002*

National Comprehensive Cancer Network, 2008, *NCCN Updates Guidelines for Colorectal Cancer*, National Comprehensive Cancer Network, http://www.nccn.org/about/news/newsinfo.asp?NewsID=194 [3 November 2008].

O'Malley, S., 2006, 'The Australian Experiment: The Use of Evidence Based for the Reimbursement of Surgical and Diagnostic Procedures', *Australian New Zealand Health Policy*, v. 3, May.

Osterberg, L., Blaschke, T., 2005, 'Adhereence to medication', New England Journal of Medicines, vol. 353, 487-497.

Owen, R.P., Klein, T.E., Altman, R.B., 2007, 'The Education Potential of the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB)', *Nature*, 82(4), October.

Paxton, A., 2008, *Things Heat Up for Personalised Testing*, College of American Pathologists, August.

Pearson, D.C., May, G.R., Fick, G., et al, 2004, Azathiopurine for maintenance of remission in Crohn's disease, Cochrane Library; Bouhnik, Y., Lemann, M., Mary, J-Y, 1996, 'Long term follow-up patients with Crohn's disease treated with azathiopurine or 6-mercaptopurine' *Lancet*, 347: 215-219

Pharmaceutical Benefits Division, 2007, Expenditure and prescriptions twelve months to 30 June 2006, Department of Health and Ageing, Australian Government Canberra, http://www.health.gov.au/internet/main/publishing.nsf/Content/3CC2D4DF821FE5ADCA2570F40005B9B1/$File/Full%20book%202005-06.pdf [September 2008].

Pharmaceuticals Benefits Advisory Authority, 2007, *Annual Report*, Australian Government, Canberra.

Phillips, K.A., Van Bebber, S., Issa, A.M., 2006, 'Diagnostics and Biomarker Development: Priming the Pipeline', *Nature*, 5:463-469.

President's Council of Advisers on Science and Technology, 2008, *Priorities for Personalised Medicine*, President's Council of Advisers on Science and Technology, Washington DC, September.

Price, C., 2000, 'Australian Population: Ethnic Origins', *People and Place*, 7(4):12-16.

PricewaterhouseCoopers, 2005, *Personalised Medicine: the Emerging Pharmacogenomics Revolution*, http://www.pwc.com/techforecast/pdfs/pharmaco-wb-x.pdf [September 2008].

Priest, V.L., Begg, E. J., Gardiner, S.J., Frampton, C. M.A., Gearry, R. B., Barclay, M. L., Clark, D.W.J., and Hansen, P., 2006, 'Pharmacoeconomic Analyses of Azathiopurine, Methotrexate and Prospective Testing for the Management of Inflammatory Bowel Disease', *Pharmacoeconomics*, 24(8): 767-781.

Rieder, M.J., Reinder, A.P., et al,, 2005, 'Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose', *New England Journal of Medicine*, 352(22):2285-93.

Royal College of Pathologists Australasia, 2008, *Genetic Testing in the 21st Century: Are We Ready?*, Royal College of Pathologists Australasia, Sydney.

Runciman, W.B., Roughead, E.E., Semple, S.J., Adams, R.J., 2003, 'Adverse Events and Medication Errors in Australia', *International Journal for Quality in Health Care*, 15:i49-i59.

Shih, T., and Pusztai, L., 2006, 'Do PGx Tests Provide Value to Policy Makers?', *Pharmacoeconomics*, 24(12): 1173-1177.

Shurin, S.B., and Nabel, E.G., 2008, 'Pharmacogenomics — Ready for Prime Time?', *NEJM*, 358:10, March 6.

Stroke Foundation, 2008, *Facts, figures and stats*, http://www.strokefoundation.com.au/facts-figures-and-stats

US Food and Drug Administration, 2008, Critical Path Initiative Warfarin Dosing, Department of Health and Human Services, Washington DC, http://www.fda.gov/oc/initiatives/criticalpath/warfarin.html [September 2008].

US Food and Drug Administration, 2008, *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels*, Department of Health and Human Services, http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm [September 2008].

US National Centre for Biotechnology Information, 2008, *One Size Does Not Fit All: the Promised of Pharmacogenomics*, http://www.ncbi.nlm.nih.gov/About/primer/pharm.html [September 2008]

Vallance, P., and Levick, M., 2007, 'Drug Discovery and Development in the Age of Molecular Medicine', *Nature*, 82(4), October.

Virtual Medical Centre, 2008, *Statins*.

Wagner, E.H., 2001, 'Effect of Improved Glycemic Control on Health Care Costs and Utilization,' *Journal of the American Medical Association*, 285: 2, 182-189.

Wall Street Journal, 2008, 'Genetic Research May Help Pick Patients' Best Cancer Drugs', *The Wall Street Journal*, New York, 2 June.

Wilson, R., Runciman, W.B., Gibberd R.W., *et al*., 1995, 'The Quality in Australian Health Care Study', *Medical Journal of Australia,* 163(458-471).

Woodcock, J., 2007, 'Molecular Medicine: How, What and When?', *Nature*, 82(4), October.

World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva; 2003.

Vegter, S., Boersma, C., Rozenbaum, M., Wilffert, B., Navis, G., and Postmal, M.J., 2008, Pharmacoeconomic Evaluations of Pharmacogenetic and Genomic Screening Programmes:A Systematic Review on Content and Adherence to Guidelines, *Pharmacoeconomics,* 26(7): 569-587.