1. Introduction

While findings from the Human Genome Project have not yet affected the health care of most individuals directly, the rapid advancements made in the field of genomics over the last decade have ensured that the promise of a revolution in human health remains real.\(^1\)

One of the most significant outcomes of the acceleration in genomic science is the development of personalised medicine. Personalised medicine is defined as:

\textit{‘the capacity to predict disease development and influence decisions about lifestyle choices or to tailor medical practice to an individual’}.\(^2\)

This includes targeted drugs and treatments based on a detailed understanding of the genetic bases of disease. In addition to the promise of improved patient care and disease prevention, personalised medicine has the potential to lower the ever increasing cost of health care.\(^3\) It is expected that the use of personalised medicine will increase into the future.

Scope

The National Health and Medical Research Council (NHMRC) has developed this paper with the assistance of its Human Genetics Advisory Committee (HGAC) to provide an overview of the role of genomics in personalised medicine, and its potential to improve health care. In particular, it highlights the clinical utility of various genetic and genomic tests as it is this often overlooked aspect of testing that determines the likelihood of an improved outcome for the individual. The clinical utility of a test is a measure of whether the result of that test would alter the healthcare decisions consequently made by the requesting health professional or by the patient.\(^3\)

Audience and objectives

The purpose of this Information Paper is to provide health professionals with a source of information on personalised medicine. This paper seeks to support the health professional in understanding the applications, utility and limitations of personalised medicine in clinical care.

Clinical Utility of Personalised Medicine

1. Introduction
2. Background to Personalised Medicine

Disease diagnosis is often based on symptoms that might be indicative of several diseases. It is, however, now possible for the diagnosis of some diseases to be made more easily and in a more timely manner as genetic tests for disease-specific mutations become increasingly available.

Genome studies are revealing a large number of molecular biomarkers relating to specific gene variations. These may confirm the clinical diagnosis in the presence of overt disease. They may also indicate an asymptomatic person’s susceptibility to a specific disease and/or more reliably predict a person’s differential response to treatment. Such biomarkers can serve as the basis of new genomics-based predictive and diagnostic tests, the results of which may be used by a trained health professional to:

- diagnose a disease (and possibly the subtype) in an individual;
- assess an individual’s risk of disease;
- identify whether an individual will benefit from particular interventions; and/or
- tailor dosing regimens to individual variations in metabolic response.

Personalised medicine is the application of genetic information to predict disease development, influence decisions about lifestyle choices, and tailor preventative interventions or medical treatment to the individual needs of each patient. Personalised medicine can allow screening, early intervention and treatment to be concentrated on those who will benefit, reducing expense and side effects for those who are not likely to benefit. It is important to note that the application of personalised medicine goes beyond genetic disease, and can optimise treatment for many diseases including HIV and epilepsy.

Through personalised medicine, it is anticipated that in time, the ‘single-fit-all’ drug will be replaced by more effective drug interventions and treatments that are specifically designed and customised to an individual’s personal genetic profile.

Genetic variations

Genetic variations can be described as single gene or complex. Single gene refers to a variation in a single gene that is sufficient to alter the phenotype (a mutation). However, not all sequence variations in single genes are causally linked; sometimes variants of unknown clinical utility are found and cannot be used in clinical decision making. In contrast, complex interactions involve mutations in many genes, often with small cumulative effects, and interaction with environmental factors. With complex interactions, the nature and contribution of each of the implicated genes and the environment is not yet well understood.

There is currently no single repository of information about the genetic contributions to complex diseases. At present, the dominant research method is to analyse large groups of individuals with and without the disease in question. Using genome sequencing technology, these groups of individuals are analysed for the presence and absence of a finite set of specific genetic variants across the genome through Genome-Wide Association Studies (GWAS). One of the catalogues for such studies is available at http://www.genome.gov/gwastudies/.

Genetic testing

The genetic information required to personalise an individual’s treatment is obtained through genetic testing. Genetic testing can be differentiated into somatic and germ cell genetics, based on the type of DNA mutations involved and their effect on disease. Somatic cell genetics refers to mutations acquired in the DNA of somatic cells some time after conception and are therefore not heritable. Germ cell genetics refers to mutations in the DNA of the germ cells (ova or sperm) and so are heritable. For more information on genetic testing, see Medical genetic testing: Information for health professionals—a resource developed to provide a source of information for use by health professionals involved in genetic testing.*

*See additional resources list, following bibliography.
Evaluation of genetic testing

There is active debate internationally about the best way to evaluate the efficacy of genetic tests. One model involves assessment of the analytical validity, clinical validity, clinical utility, and ethical, legal, social issues associated with a test (ACCE), as described below:

**Analytic validity:** defines the test’s ability to accurately and reliably measure the genotype of interest. This aspect of evaluation focuses on the laboratory component. The four specific elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity, laboratory quality control and assay robustness.

**Clinical validity:** defines the test’s ability to detect or predict the presence or absence of the disease (phenotype) – its sensitivity, specificity, positive and negative predictive values.

**Clinical utility:** is a measure of the health care value provided by the test/technology.

**Ethical, Legal and Social Issues** considers issues associated with the test and its results for the patient.

This paper focuses on the clinical utility and applications of personalised medicine.

3. Applications of Personalised Medicine

Personalised medicine can provide medical practitioners with an additional biological basis with which to categorise some diseases. This will influence genomic based improvements in screening, diagnosis and prognosis. It will also allow for greater optimisation of preventative and therapeutic care.

Personalised medicine can facilitate disease prediction, prevention and treatment strategies by:

- determining if someone is at increased risk of developing a disease, followed by promotion of and support for compliance with available prevention strategies;
- diagnosing disease earlier in development using optimal surveillance, thereby allowing more effective interventions or treatment options;
- enhancing therapeutic efficacy by ensuring the most appropriate drug is used and that the dosing regimen takes into consideration any genetic variants, which may influence metabolism of the drug; and
- avoiding preventable drug related complications and side effects resulting from generic “one size fits all” drug prescribing.

Medical practitioners will be able to provide more tailored prevention and treatment programs for their patients resulting in improved patient outcomes, reduced adverse events, and more cost effective use of health care resources.

Use of personalised medicine is categorised into predictive medicine and treatment optimisation, as outlined below.

Predictive medicine

Genetic information can inform a more accurate prediction of the risk of developing a disease, disease progression, and severity of symptoms, in an individual. This information can be used to tailor prevention and treatment to that individual as well as to make informed choices relating to lifestyle, reproductive matters, screening and preventative treatments. A summary of the clinical utility of predictive medicine for some diseases is included in Table 1.

Treatment optimisation

Many adverse drug reactions are the result of individuals being prescribed the incorrect dosage of medication. In addition to well understood variables such as age, sex, weight and body fat, genetic differences can give rise to differing responses to a given drug. This is because many enzymes involved in drug response have genetic variants that may be associated with an increase or decrease in drug metabolism.
Treatment optimisation refers to pharmacogenetics/pharmacogenomics. Pharmacogenomics aims to match the best available drug or dose to an individual’s genomic profile.8,9

Box 1, below, discusses the clinical utility of DNA genetic testing for the use of the breast cancer drug, Tamoxifen.

Pharmacogenomics can help to inform a tailored dosage regimen allowing for an improved drug response, while managing the risk adverse reactions. Abacavir, used in the treatment of HIV infection, is one such example (Box 2). Serious adverse drug reactions are an important clinical issue and cause of hospital admissions.7 Identifying genetic risk factors for serious adverse drug reactions could decrease the costs of healthcare, and improve patient outcomes.10 A summary of the clinical utility of pharmacogenetic tests for some diseases can be found in Table 2.

**BOX 1: CLINICAL UTILITY OF DNA TESTING PRIOR TO TREATING WITH TAMOXIFEN**

Tamoxifen is a drug used in the treatment of patients with oestrogen-receptor positive breast cancer. Tamoxifen is a pro-drug and must be metabolised to its active product endoxifen before it becomes effective. The enzyme cytochrome P450 2D6 (CYP2D6) is involved in this biotransformation. About a third of women treated with this drug relapse and there appears to be considerable variation in how individuals respond, including their risk of developing side effects. One explanation for this variability is the genetic makeup of the CYP2D6 gene, which demonstrates variable activity seen within and between different populations. This leads to differences in the metabolism of some individuals, who can range from being poor, intermediate, extensive or ultrarapid metabolisers.11 The genetic ability to metabolise drugs that use CYP2D6 is now proposed to explain why some demonstrate poorer efficacy while others have more side effects. This has been tested in clinical trials involving women with breast cancer taking tamoxifen. Some trials have shown a clear distinction based on genetic profiling, while in other trials the distinction is not apparent. Thus the clinical utility of DNA genetic testing to determine the dose and predict the response to tamoxifen remains to be determined.12

**BOX 2: CLINICAL UTILITY OF DNA TESTING PRIOR TO TREATING WITH ABACAVIR**

Abacavir is a drug used for treating HIV infection. However, 5% to 8% of patients can develop a potentially life threatening allergic reaction (Stevens Johnson syndrome) soon after starting this drug. Researchers in Western Australia showed in 2008 that Caucasians with the HLA-B*5701 allele were particularly susceptible to this complication.12 They devised a DNA test to detect those who had this HLA marker. Today, DNA testing for HLA-B*5701 is routinely undertaken before starting Abacavir. The clinical utility of this test is established and it is one of the few DNA genetic tests funded through Medicare. Using this approach, this hypersensitivity reaction has not been eliminated but its frequency is now estimated to be about 3.4%.13 A similar hypersensitivity reaction occurs in Asians that have the HLA B*1502 allele who take carbamazepine, a drug used to treat epilepsy. Again, DNA testing can identify who are at risk so alternative therapies can be introduced.
### Table 1: Clinical utility of predictive medicine

<table>
<thead>
<tr>
<th>Disease</th>
<th>What the test detects</th>
<th>Reason for testing</th>
<th>Comments</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatic cell genetics – single genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukaemia&lt;sup&gt;14,15&lt;/sup&gt;</td>
<td>Minimal residual disease</td>
<td>Patients often relapse after an apparent cure</td>
<td>Has become standard care for acute promyelocytic leukaemia, chronic myeloid leukaemia and Philadelphia chromosome (Ph') positive acute lymphoblastic leukaemia</td>
<td>• Allows for a more accurate prognosis and to identify further treatment needs.</td>
</tr>
<tr>
<td><strong>Germ cell genetics – single genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Presence of adenomatous polyposis coli (APC) gene mutation</td>
<td>APC gene mutation confers almost 100% penetrance&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Individuals with a family history of FAP undergo extensive surveillance which is expensive, invasive and can have side effects.</td>
<td>• Negative test result removes the need for surveillance. Offers reproductive options.</td>
</tr>
<tr>
<td>Huntington disease (HD)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Presence of HD mutation</td>
<td>Mutation confers 100% penetrance and HD is presently incurable</td>
<td>Though presently incurable, preventative therapies are being investigated. HD testing can relieve anxiety for unaffected individuals, and allow affected individuals to make informed life choices.</td>
<td>• Allows for planning for life and long term health decisions, including family planning. May in future allow for protective therapies.</td>
</tr>
<tr>
<td>Lynch Syndrome&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Mutations in the MLH1, MSH2, MSH6, and PMS2 genes</td>
<td>Mutations in these genes increase the risk of developing Lynch syndrome; penetrance is not 100%</td>
<td>In families with Lynch Syndrome, MLH1 and MSH2 account for approximately 90% of detected mutations, MSH6 for approximately 7%-10% and PMS2 for fewer than 5%.</td>
<td>✓ Detection of mutations allows for surveillance which includes colonoscopy with removal of precancerous polyps every one to two years starting at age 25.</td>
</tr>
<tr>
<td><strong>Germ cell genetics – complex diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II diabetes&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Can test for the presence of up to 40 implicated gene mutations</td>
<td>Used in research to understand better the causes of diabetes</td>
<td>Diabetes is the result of not well understood complex interactions of multiple genes and the environment.</td>
<td>× No greater predictive value than risk factors and family history.</td>
</tr>
<tr>
<td>Alzheimer disease&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Type E4 of ApoE gene</td>
<td>Identifying an increased risk allows early intervention and planning</td>
<td>The testing has been used at population level to detect population level risk. The test is not accurate enough to predict individual risk.</td>
<td>× Most cases occur sporadically and do not involve these mutations.</td>
</tr>
</tbody>
</table>

Notes:
- • Used in clinical practice but not formally evaluated
- ✓ Clinically useful
- × Limited clinical utility
- * Penetration describes the proportion of individuals carrying a particular variation of a gene (the genotype) that also express an associated trait (the phenotype).

As indicated in Table 1 above, there are a number of tests currently being performed in clinical practice for which the clinical utility is yet to be formally evaluated. In addition, there is ongoing research to better understand causal factors for disease that are not useful in clinical practice at this time. The clinical utility of many tests are yet to be determined. For some tests the outlook is positive, though others may not prove to be useful in the clinical setting.
As indicated in Table 2, the potential for genetic testing to optimise individual treatment has already been demonstrated by some treatments. Clinical utility remains to be proven in some other areas. Pharmacogenetics and pharmacogenomics have an important role to play in preventing serious adverse events resulting from the administration of prescription pharmaceuticals. However, in many cases the precise nature of this role, beyond informing dosage regimens, remains to be determined.

Table 2: Clinical utility of treatment optimisation

<table>
<thead>
<tr>
<th>Disease and drug/test</th>
<th>Drug/test purpose</th>
<th>Reason for testing</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatic cell genetics – single genes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer Herceptin® (trastuzumab)</td>
<td>Herceptin® is used to treat tumours which overexpress the HER2 protein. HER2 positive breast cancers can be targeted more effectively.</td>
<td>Herceptin has significant side effects and in tumours not over-expressing in HER2 the risks outweigh the potential benefits.</td>
<td>✓ Herceptin®, a costly drug can now be targeted to those most likely to respond and so as well as cost savings, it reduces the risks of complications in those unlikely to respond to it.</td>
</tr>
<tr>
<td>Colon cancer Cetuximab</td>
<td>Cetuximab has little effect if the patient has a mutated KRAS gene.</td>
<td>Patients with wild-type gene are most likely to benefit from Cetuximab.</td>
<td>✓ Improved survival rates for KRAS negative patients. A costly drug is not used in patients unlikely to respond to it.</td>
</tr>
<tr>
<td><strong>Somatic cell genetics – complex interactions (Pharmacogenomic type test)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breast cancer MammaPrint®</td>
<td>Measures the expression profile of 70 genes implicated in endocrine responsive breast cancer. Stratifies patients into high and low risk groups for relapse and metastasis.</td>
<td>This can inform treatment decisions as high risk groups may need further chemotherapy treatment while low risk groups may only require hormone therapy and monitoring.</td>
<td>✓ Clinical utility is to be confirmed. Clinical use may be justified while ongoing studies confirm the role of MammaPrint® in clinical practice. This would assist in decision making particularly for treated early stage breast cancer when it is difficult to predict what type (if any) adjuvant therapy is needed.</td>
</tr>
<tr>
<td><strong>Germ cell genetics – single genes</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease, transplantation, some forms of leukaemia Thiopeurines</td>
<td>The thiopurine methyltransferase (TMPT) gene is important in the metabolism of thiopurines.</td>
<td>Some subtypes rapidly metabolise thiopurines (requiring higher doses) while others metabolise slowly (more likely to develop side effects).</td>
<td>✓ The ability to personalise dosages can reduce the risk of complications, while ensuring effectiveness. This is likely to be clinically useful.</td>
</tr>
<tr>
<td>Clotting problems Warfarin</td>
<td>Warfarin prevents blood clots from forming. Variants in the CYP2C9 and VKORC1 genes influence response to warfarin treatment.</td>
<td>Warfarin can cause bleeding which has the potential to be life threatening. Testing can allow for the starting dose of warfarin to be adjusted so that the correct therapeutic dose can be achieved earlier and with lower risk to the patient.</td>
<td>✓ The FDA recommends DNA testing before warfarin therapy is started. Despite this, the test has not yet impacted on clinical practice.</td>
</tr>
</tbody>
</table>

Notes:
- ✓ Clinically useful
- ▲ Under evaluation

Assessments of the clinical utility of genetic testing to guide medication regimes and improve patient outcomes are ongoing. If these tests are found to be clinically useful, they have the potential to dramatically change how medications are prescribed.

About 10% of labels for U.S. Food and Drug Administration (FDA)-approved drugs, contain pharmacogenomic information. This number is expected to rise. Tests approved by the FDA for use in optimising dosage when prescribing drugs can be found on the FDA website.
Impact on healthcare

Advances in genomics have already found clinical application in the development of new, targeted drugs to treat some cancers and genetic tests that can predict whether individuals would benefit from particular interventions. As advancements and discoveries in genomics continue at an ever increasing rate, the clinical ability to accurately predict disease risk and drug response will continue to improve. It is through the use of such tests that the promise of personalised medicine may be realised.

In addition to the promise of improved patient care and disease prevention, there is potential for personalised medicine to impact on the cost of health care. Health care costs may be lowered by individual genetic test results and/or by analysis of an individual’s full genome sequence (whole genome sequencing) allowing for screening, and the tailoring of drugs and treatments to minimise side effects and improve outcomes. Testing can also rule out individual disease susceptibility where there is an increased risk in the family, reducing the need for costly and sometimes invasive screening and preventative therapy. These functions all play a role in ensuring more targeted and cost-effective health-care into the future.

The benefit of whole genome sequencing as opposed to testing targeted genes is that the one sequence can be interrogated throughout an individual’s lifetime to identify additional genetic markers as required or discovered. In some instances, the cost of genetic testing will be offset by avoiding expensive treatments when they are unlikely to be efficacious and by ensuring that additional treatment for side effects that are unlikely to occur.

Conversely, the development of drugs that are beneficial or of therapeutic use for only a small cohort of patients is often more expensive and pharmaceutical companies may be less inclined to develop them. As a result, the potential to tailor drug treatments may go unfulfilled due to a lack of resources, funding and take up by pharmaceutical companies, leading to unmet expectations.

4. Conclusion

Genetic knowledge has the potential to influence lifestyle choices and decisions about preventative measures as well as medical and surgical treatments to improve patient outcomes. Robust evaluation and sensible regulation of genetic tests are necessary to realise the promise of personalised medicine. This includes consideration of a drug and/or treatment’s efficacy, and genetic test’s analytical and clinical validity, in order to ensure that the test is safe, and performs as intended.

As highlighted in this information paper, equally important is a test’s clinical utility, both in terms of its health and economic implications, when compared to standard care.
References


**Additional Resources**


National Human Genome Research Institute, Catalogue of genome wide association studies* [http://www.genome.gov/27531910](http://www.genome.gov/27531910)

*It is important to note that these sources are not necessarily comprehensive and do not necessarily reflect clinical practice in Australia. Website addresses are correct as at: 5 November 2010.*